HIV Molecular Immunology 2009

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Contents

Preface

Scope and purpose of the HIV molecular immunology database

HIV Molecular Immunology is a companion volume to *HIV Sequence Compendium*. This publication, the 2009 edition, is the PDF version, suitable for printing, of the web-based HIV Immunology Database (`http://www.hiv.lanl.gov/content/immunology/`). The web interface for this relational database has many search options, as well as interactive tools to help immunologists design reagents and interpret their results.

In the HIV Immunology Database, HIV-specific B-cell and T-cell responses are summarized and annotated. Immunological responses are divided into three parts, CTL, T helper, and antibody. Within these parts, defined epitopes are organized by protein and binding sites within each protein, moving from left to right through the coding regions spanning the HIV genome. We include human responses to natural HIV infections, as well as vaccine studies in a range of animal models and human trials. Responses that are not specifically defined, such as responses to whole proteins or monoclonal antibody responses to discontinuous epitopes, are summarized at the end of each protein section. Studies describing general HIV responses to the virus, but not to any specific protein, are included at the end of each part.

The annotation includes information such as cross-reactivity, escape mutations, antibody sequence, TCR usage, functional domains that overlap with an epitope, immune response associations with rates of progression and therapy, and how specific epitopes were experimentally defined. Basic information such as HLA specificities for T-cell epitopes, isotypes of monoclonal antibodies, and epitope sequences are included whenever possible. All studies that we can find that incorporate the use of a specific monoclonal antibody are included in the entry for that antibody. A single T-cell epitope can have multiple entries, generally one entry per study.

Finally, maps of all defined linear epitopes relative to the HXB2 reference proteins are provided. Alignments of CTL, helper T-cell, and antibody epitopes are available through the search interface on our web site at `http://www.hiv.lanl.gov/content/immunology`.

Only responses to HIV-1 and HIV-2 are included in the database. CTL responses to SIVs are periodically summarized in our review section by Dr. David Watkins and colleagues. Dr. Christian Brander and colleagues annually provide a concise listing of optimally defined CTL epitopes. Reviews from previous years can be found at `http://www.hiv.lanl.gov/content/sequence/HIV/REVIEWS/reviews.html`.

Questions regarding the database can be sent via email to `immuno@lanl.gov`.

About the data

At the time of this publication, the HIV Immunology Database contained over 4900 CTL/CD8+ epitopes, over 1000 Helper/CD4+ epitopes, over 1400 unique antibody epitopes, and a total bibliography of over 2100 references (Figure 1). To illustrate the distribution of the epitopes, we have plotted them by position in the HIV proteome (Figure 2).

For T-cell epitopes, the density of epitopes by position reflects the density of defined epitopes in the database, which in turn roughly reflects the density of responses, as judged by EliSpot assays from natural infection. Both CTL/CD8+ T-cell (maroon) and Helper/CD4+ T-cell (green) responses are most commonly detected in Gag and Nef, and the database has the highest density of epitopes captured from the literature in these regions.

In contrast, the antibody epitope database density (blue) is less meaningfully captured in this graph, because only continuous epitopes are included. Many antibody responses defined in the database are to discontinuous epitopes, or are defined regionally or by competition experiments, and other database entries are polyclonal responses with multiple antibodies binding to multiple regions; these are not included in this map. The database entries have other biases in frequency. For example, the database is based on retrieval of information from the literature, and so a region like the V3 loop of HIV-1, which is of particular interest to investigators, has been studied with great intensity, and this high level of interest accounts for the large spike of antibody entries in gp120.

Citing the database

This publication may be cited as

HIV Molecular Immunology 2009. Karina Yusim, Bette T. M. Korber, Christian Brander, Barton F. Haynes, Richard Koup, John P. Moore, Bruce D. Walker, and David I. Watkins, editors. Publisher: Los Alamos National Laboratory, Theoretical Biology and Biophysics, Los Alamos, New Mexico.

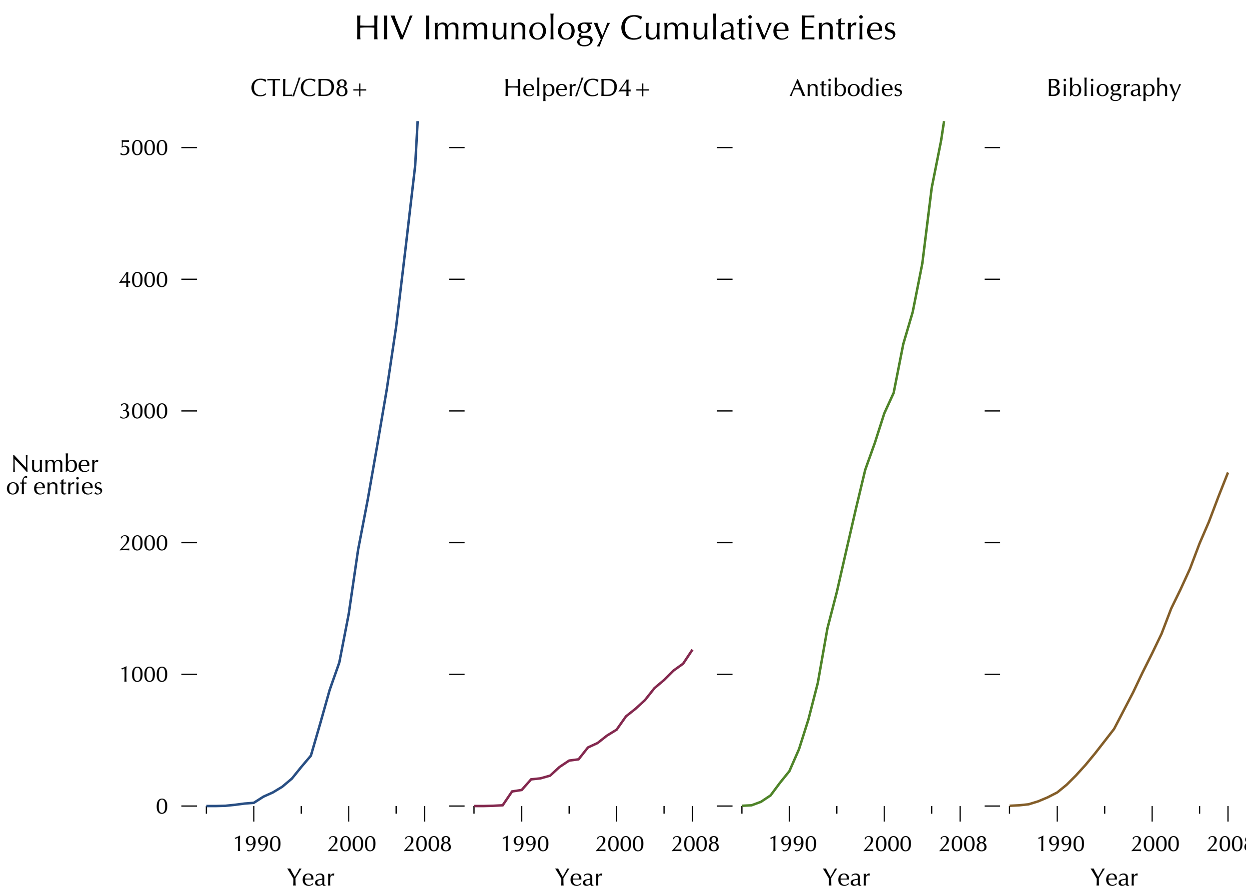


Figure 1: HIV immumology database cumulative entries. The CTL, T Helper and Antibodies plots show the total number of epitope entries described in the database at the denoted point in time. If an epitope is described in 5 papers then it is considered to be 5 entries. Thus the number of unique epitopes is lower than the plotted number. Although all 4 plots begin at 1985, the earliest CTL and Helper epitopes were described in 1987.

About the PDF

The complete *HIV Molecular Immunology 2009* is available in Adobe Portable Document Format (PDF) from our website, `http://www.hiv.lanl.gov/content/immunology`. The PDF version is hypertext enabled and features ‘clickable’ table-of-contents, indexes, references and links to external web sites.

This volume is typeset using LaTeX. The immunology data tables and epitope maps are produced automatically from the SQL database by a series of Perl programs.

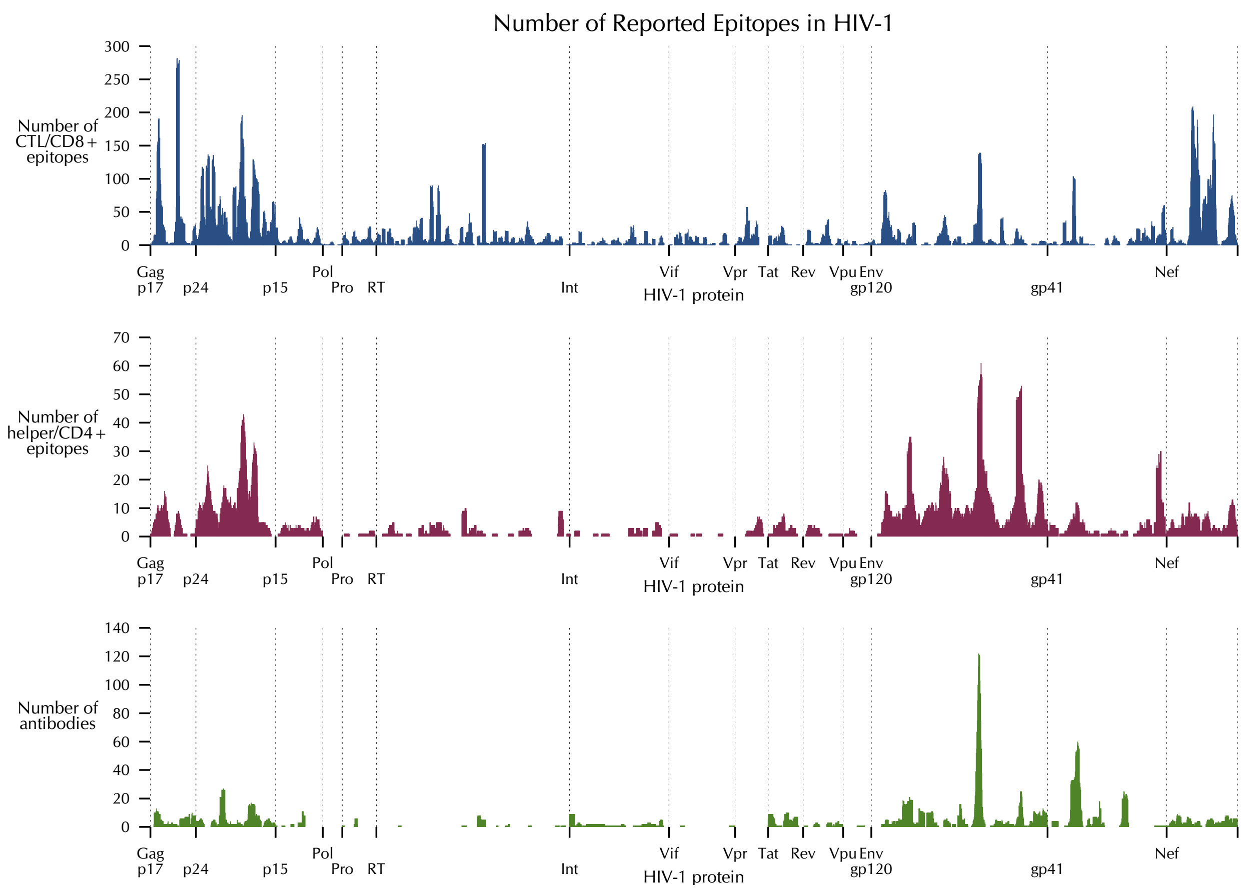
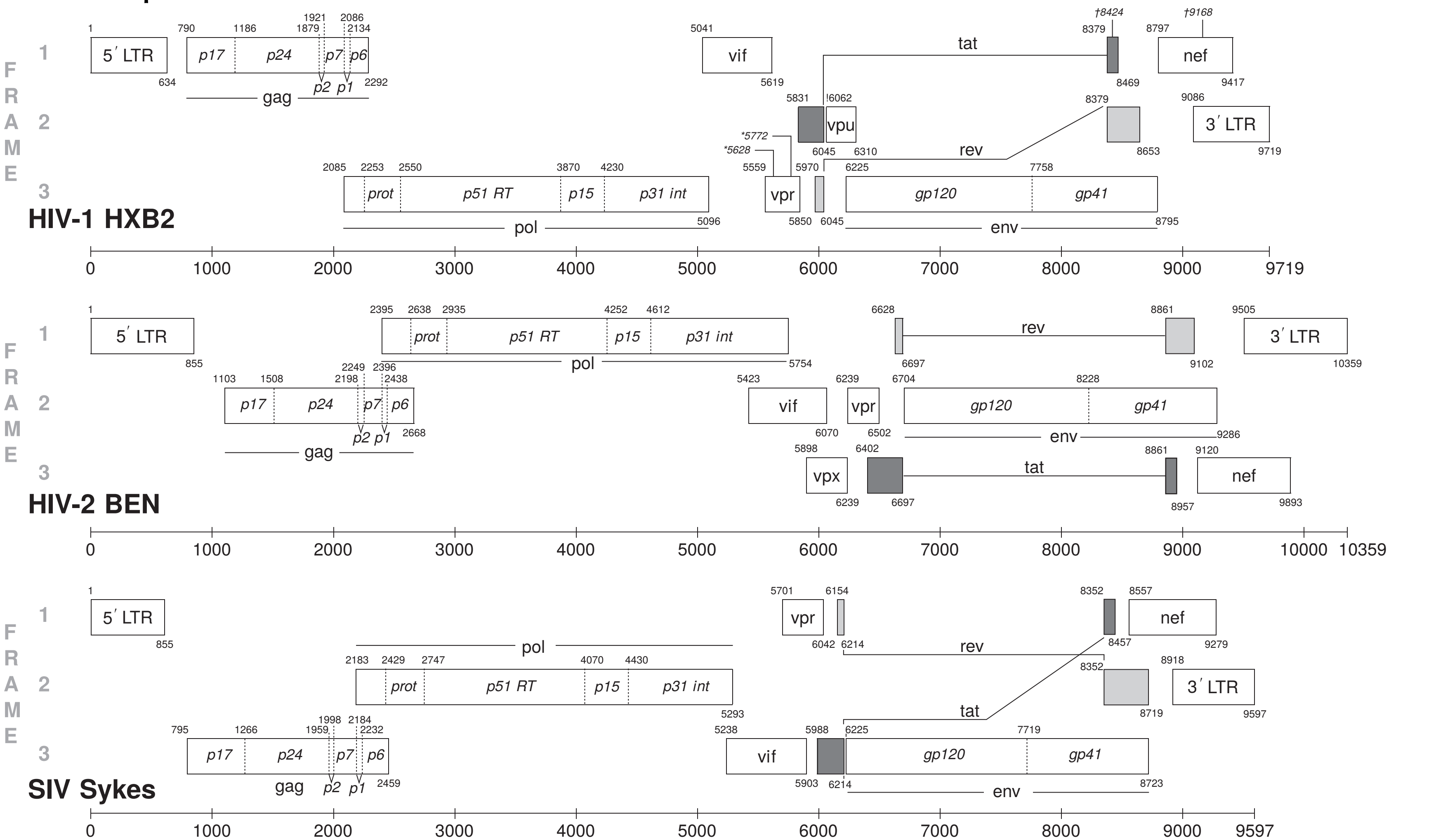


Figure 2: The number of unique epitopes included in the database that span each position in the HIV proteome.

Genome maps



Landmarks of the HIV-1, HIV-2, and SIV genomes. The gene start, indicated by the small number in the upper left corner of each rectangle, normally records the position of the `a` in the `atg` start codon for that gene while the number in the lower right records the last position of the stop codon. For *pol*, the start is taken to be the first `t` in the sequence `ttttttag` which forms part of the stem loop that potentiates ribosomal slippage on the RNA and a resulting −1 frameshift and the translation of the Gag-Pol polyprotein. The *tat* and *rev* spliced exons are shown as shaded rectangles. In HXB2, *5628 and *5772 mark positions of frameshifts in the *vpr* gene; !6062 indicates a defective `acg` start codon in *vpu*; †8424 and †9168 mark premature stop codons in *tat* and *nef*. See Korber *et al.*, Numbering Positions in HIV Relative to HXB2CG, in *Human Retroviruses and AIDS*, 1998, p. 102. Available from `http://www.hiv.lanl.gov/content/sequence/HIV/REVIEWS/HXB2.html`

HIV/SIV proteins

Name	Size	Function	Localization
Gag MA	p17	membrane anchoring; env interaction; nuclear transport of viral core (myristylated protein)	virion
CA	p24	core capsid	virion
NC	p7	nucleocapsid, binds RNA	virion
	p6	binds Vpr	virion
Protease (PR)	p15	gag/pol cleavage and maturation	virion
Reverse Transcriptase (RT)	p66, p51	reverse transcription	virion
RNase H	(heterodimer)	RNAse H activity	virion
Integrase (IN)		DNA provirus integration	virion
Env	gp120/gp41	external viral glycoproteins bind to CD4 and chemokine co-receptors	plasma membrane, virion envelope
Tat	p16/p14	viral transcriptional transactivator	primarily in nucleolus/nucleus
Rev	p19	RNA transport, stability and utilization factor (phosphoprotein)	primarily in nuleolus/nucleus shuttling between nucleolus and cytoplasm
Vif	p23	viral infectivity factor, inhibits minus-strand viral DNA hypermutation	cytoplasm (cytosol, membranes), virion
Vpr	p10-15	promotes nuclear localization of preintegration complex, inhibits cell division, arrests infected cells at G2/M	virion nucleus (nuclear membrane?)
Vpu	p16	promotes extracellular release of viral particles; degrades CD4 in the ER; (phosphoprotein only in HIV-1 and SIVcpz)	integral membrane protein
Nef	p27-p25	CD4 and class I downregulation (myristylated protein)	plasma membrane, cytoplasm, (virion?)
Vpx	p12-16	Vpr homolog present in HIV-2 and some SIVs, absent in HIV-1	virion (nucleus?)
Tev	p28	tripartite tat-env-rev protein (also named Tnv)	primarily in nucleolus/nucleus

Abbreviations

Abbreviations and acronyms used in this database.

Abbrev.	Meaning
AA	amino acid
AAV	adeno-associated virus
Ab	antibody
ACTG	AIDS clinical trial group
ADC	AIDS dementia complex
ADCC	antibody-dependent cell-medicated cytotoxicity
ADE	antibody-dependent enhancement
ADRA	Antiviral Drug Resistance Analysis: a program that analyzes your sequences for mutations known to confer drug resistance and links to the records in the database
AIDS	acquired immunodeficiency syndrome
ANN	artificial neural networks
APC	antigen presenting cell
ARC	AIDS related complex
ART	anti-retroviral therapy
AZT	azidothymidine
BIMAS	BioInformatics and Molecular Analysis Section
BIV	bovine immunodeficiency virus
BLAST	Basic Local Alignment Search Tool
CAEV	caprine arthritis/encephalitis virus
CD4BS	CD4 binding site
CD4i	antibody that has enhanced binding to gp120 in the presence of SCD4 (CD4 induced)
CDC	Centers for Disease Control and Prevention
CDR	complementary determining regions
CFA	complete Freund's adjuvant
CHI	Center for HIV Information
CMI	cell-mediated immunity
CMV	cytomegaliovirus
CNS	central nervous system
CP	canary pox
CRF	circulating recombinant form
CsA	cyclosporine A
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocyte
CTLe	CTL effector
CTLp	CTL precursor
CyPA	cyclophilin A
DC	dendritic cell
DDDP	DNA-dependent DNA polymerase
DHH	U. S. Department of Health and Human Services
dMM	deopymannojirimycin
dpc	days post challenge
DTT	dithiothrietol

Abbrev.	Meaning
EIA	enzyme immuno assay
EIAV	equine infectious anemia virus
ELF	Epitope Location Finder
ELISA	Enzyme Linked ImmunoSorbent Assay
ER	endoplasmic reticulum
Fabs	fragment antigen binding-univalent antibody fragment
FATT-CTL	Fluorescent antigen-transfected target cell–CTL
FIV	feline immunodeficiency virus
FP	fowl pox
FSW	female sex worker
GALT	gut-associated lymphoid tissues
GDE format	Genetic Data Environment
gp	glycoprotein
GRIV	genetic resistance to HIV
HAART	highly-active anti-retroviral therapy
HCV	hepatitis C virus
HEPS	HIV-exposed persistently seronegative
HIV	human immunodeficiency virus
HIVD	HIV-1 dementia
HLA	human leukocyte antigens
HLA-MHC	human leukocyte antigens-major histocompatibility complex
HMM	hidden Markov models
IAVI	International AIDS Vaccine Initiative
IDE	immunodominant epitope
IE genes	immediate early genes
IFA	incomplete Freund's adjuvant
IFN	interferon
IG format	IntelliGenetics format
Ig	immunoglobulin
IL	interleukin
INHI	immunologically normal HIV-infected
iscom	immunostimulating complex
KLH	keyhole limpet hemocyanin
LANL	Los Alamos National Laboratory
LDA	limiting dilution assay
LN	lymph node
LPR	lymphoproliferative response
LT	labile enterotoxin
LTNP	long-term non-progressor
LTR	long terminal repeat
LTS	long term survivor
mAb	monoclonal antibody
MBL	mannose-binding lectin
MCMC	Markov chain Monte Carlo
MDP	muramyl dipeptide
MEI	multiple epitope immunogen
MHC	major histocompatibility complex
MHR	major homology region
ML	maximum likelihood
MLV	murine leukemia virus

Abbrev.	Meaning
MP	maximum parsimony
mpc	months post challenge
MPER	membrane-proximal external region
MRC	Medical Research Council, UK
MSF	multiple sequence alignment format of the GCG sequence analysis package
MV	measles vector
MVA vector	modified vaccinia virus Ankara
Nab	neutralizing antibody
NCBI	National Center for Biotechnology Information
NIAID	National Institute of Allergies and Infectious Diseases
NIBSC	National Institute for Biological Standards and Control, UK
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
NJ	neighbor joining
NLS	nuclear localization signal
NRP	non-rapid progressor
NSI	non-synctium-inducing
p	protein
PB	peripheral blood
PBL	peripheral blood lymphocyte
PBMC	peripheral blood mononuclear cell
PCOORD	principal coordinate analysis
PCR	polymerase chain reaction
PERV	porcine endogenous retrovirus
PHYLIP	Phylogeny Inference Package
PL	proteoliposome
RAC	ricin A chain
RDDP	RNA-dependent DNA polymerase
rec/r	recombinant
RIP	Recombinant Identification Program: a program for detecting evidence of inter-subtype recombination
RIPA	Radio Immuno Precipitation Assay
RP	rapid progressor
RRE	Rev-responsive element
rsgp160	recombinant soluble gp160
RSV	Rous sarcoma virus
SAM	Sequence Alignment and Modeling program
SAP	sequential antigen panning
sCD4	soluble CD4
scFv	single-chain variable fragment
SDS	sodium duodecyl sulfate
SFV	Semliki Forest virus
SI	synctium inducing
SIV	simian immunodeficiency virus

Abbrev.	Meaning
SIVE	SIV encephalitis
SLE	systemic lupus erythhermatosis
SNAP	synonymous-nonsynonymous analysis program
STI	supervised treatment interruption (also seen as structured treatment interruption and standard treatment interruption)
TCLA	T cell line adapted
TCR	T-cell receptor
Th	T-helper cell
TNF	tumor necrosis factor
VEE	Venezuelan equine encephalitis
VESPA	Viral Epidemiology Signature Pattern Analysis
VIP	vasoactive intestinal peptide
VL	viral load
VLP	virus like particle, assembled from p55 gag
VSV	vesicular stomatitis virus
VV	vaccinia virus
WB	Western Blot

Amino Acid Codes

A	Alanine
B	Aspartic Acid or Asparagine
C	Cysteine
D	Aspartic Acid
E	Glutamic Acid
F	Phenylalanine
G	Glycine
H	Histidine
I	Isoleucine
K	Lysine
L	Leucine
M	Methionine
N	Asparagine
P	Proline
Q	Glutamine
R	Arginine
S	Serine
T	Threonine
V	Valine
W	Tryptophan
X	unknown or “other” amino acid
Y	Tyrosine
Z	Glutamic Acid or Glutamine
.	gap
-	identity
$	stop codon
#	frameshift

Reviews

Part I

Review Articles

I-A

How to Optimally Define Optimal Cytotoxic T Lymphocyte Epitopes in HIV Infection?

Anuska Llano[a], Nicole Frahm[b], Christian Brander[a,c]

I-A-1 The evolution of the optimal CTL epitope list at Los Alamos HIV Immunology database

T-cell responses to HIV infection were first described in 1987, when Walker *et al.* [1987] and Plata *et al.* [1987] independently showed CD8 T-cell reactivity against viral proteins. Soon after, the first epitopes were identified using short synthetic peptides, allowing for ever-increasingly detailed assessments of HIV-specific immune responses and HIV evolution analyses [Kawashima *et al.*, 2009; Nixon *et al.*, 1988]. To date, more than 1200 individual HLA class I-restricted HIV-1 epitopes have been identified, with 276 of these characterized in detail and defined to their minimal or optimal length. With the initiation of large international cohorts of individuals who are in very early stages of infection or who have superior ability to control viral replication, the establishment of multi-national research consortia, and the development of sophisticated viral genome sequencing and analysis tools, many epitopes have been assessed for their relative contribution to the natural control of HIV infection and potential suitability as vaccine immunogens. While many studies take advantage of the detailed description of previously identified and oftentimes immunodominant epitopes, a number of recent studies highlight the importance of subdominant responses, T-cell activities to variable targets, and responses present at the very earliest time points after infection, as these factors may play a crucial role in viral control [Bansal *et al.*, 2005; Frahm *et al.*, 2006; Goonetilleke *et al.*, 2009]. By nature, these responses have not been identified frequently, and in some cases have not undergone the extensive work-up that has been given to the immunodominant responses restricted by frequent HLA class I alleles. The description of such responses poses a challenge to those who strive to provide the HIV community and T-cell immunologist with a reliable resource of well-defined T-cell epitopes. In our attempt to maintain such a resource at the Los Alamos National Laboratory HIV database, we face this challenge frequently, and the following sections outline some of the considerations that shape our product of the "optimal" CTL epitope list.

This year's update of the Los Alamos HIV Immunology Database CTL epitope listing marks the 15th year since we initiated this online list, which has proven a useful tool for the HIV community at large. Based on a few in-house criteria, we have over the years created what we refer to as the "A-list", which contains only those epitopes for which we are fairly confident that they have been defined to their optimal length and for which restriction by a specific HLA class I allele has been indisputably demonstrated. At the same time, we have included in the general section of the database a "B-list" of all T-cell epitopes that have been described in the literature. Thus, within the Los Alamos HIV Immunology database, all studies describing specific T-cell responses to either short peptides or longer segments are included. In addition, search tools on the web site allow rapid searches for these T-cell targets and the retrieval of summarized details about the study in which these responses were defined. As a consequence, any reported T-cell response to HIV should be accessible at LANL, whether it was identified in natural infection or vaccination, including responses defined in individuals with or without specifically defined HLA alleles and with or without a known level of disease control. This information is retained with the epitopes in the full "B-list" database, which can be accessed using a web-based search interface (`http://www.hiv.lanl.gov/content/immunology/ctl_search`). We highlight this fact to encourage anyone accessing the database to go beyond the epitopes given in the A-list whenever the specific study warrants inclusion of less well-defined CTL activities. Including a broader range of epitopes may help to ascertain one's own findings, and potentially allow one to infer, for instance, a potential HLA restriction in a given subject for whom only limited samples are available

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and who thus needs to be analyzed in a less full-blown approach.

I-A-2 Why should we bother with a list of optimally defined epitopes?

As mentioned above, the "optimal/A-list" of HIV epitopes is based on a number of in-house, arbitrary criteria, which we have regularly reviewed over the years. In brief, these criteria include the unequivocal experimental demonstration of restriction by a specific HLA class I allele and the definition of the optimal epitope length. The latter is defined as the peptide truncation that, in its shortest version, elicits a maximal functional response. While in earlier years, serial truncations were often used at decreasing concentrations in cytotoxicity (Cr51 release) assays, more recent studies often use the EliSpot or flow-cytometry based detection of effector functions including cytokine release or expression of CD107. Although these different effector functions have been shown to be subject to variable activation (i.e., peptide concentration) thresholds [Betts *et al.*, 2004], we have not seen or heard of an example in which one or the other marker would have identified different optimal epitope lengths. Aside from HLA restriction and optimal epitope definition, there are no other criteria that we consider for inclusion in the A-list. This practice has sometimes appeared to be overly strict, and a reasonable case can be made for diverging views. While we regularly discuss the input we receive from investigators in the field, our consensus remains to base our selection on the above criteria and to include only the very best defined epitopes in this listing. The major rationale for this is to keep the list free of epitopes that have been defined based on incomplete HLA restriction assays, (mis)interpretation of the data, insufficient arrays of peptide truncations tested or, in a few cases, pure speculation regarding epitope length and HLA restriction. The B list includes essentially all of the epitopes as defined in the published literature by primary authors, thus these less well-defined epitopes are captured in the database as well.

As our optimal epitope list has served as a training set for several epitope prediction algorithms (`http://www.syfpeithi.de/`, `http://atom.research.microsoft.com/bio/epipred.aspx`), we also feel that epitopes that are characterized based on HLA prediction tools should not be included in the A-list. Otherwise, the risk exists that an algorithm may use a training set that contains data that are the product of its own predictions. While this may not be a big issue for those alleles for which many epitopes have been described, cases such as epitopes presented on HLA-B63 (B*1516, B*1517) indicate that existing tools would not have been able to identify the true breath of the allele-specific binding motifs and would have in some cases led to the wrong prediction of optimal epitope length [Frahm *et al.*, 2005]. The prediction of possible HLA restriction is also complicated by the fact that most HIV epitopes can be presented in the context of several different HLA class I alleles [Frahm *et al.*, 2007]. Thus, while the individual response in a single subject will likely provide reliable data, the issue of incorrect, or at least incomplete HLA restriction assignment becomes a real problem in individuals expressing multiple alleles that can present the epitope under study. Apart from the well-described epitope sharing between alleles in the same locus and HLA supertype, such as A3/A11 or B57/B58, individuals mounting, for instance, a response to the known HLA-B37 and B57 `YFPDWQNYT` epitope in Nef, could mount these responses through HLA-A29, -B35, or -C06 [Frahm *et al.*, 2007]. If two or more of these alleles are expressed in a given individual, only a detailed functional HLA restriction analysis could provide reliable HLA restriction information. While this example may seem far-fetched, it only highlights one situation where experimental proof for presentation in the context of at least five alleles has been published. Similar examples exist for HCV epitopes and, in cases where alternatively presenting alleles are encoded by more or less frequent haplotype combinations, will certainly distort immunodominance analyses and have an impact on viral evolution analyses [Niu *et al.*, 2009]). In addition, it is also possible that individuals make responses to a single epitope on more than one of their alleles. This has been analyzed only for a few epitopes and mainly in the context of well-described allele pairs in the same supertype; thus the consequences of a potential "functional homozygosity" (i.e., presentation of a limited set of epitopes on several HLA alleles with similar epitope binding motifs) on viral control *in vivo* and immune evasion of the virus is unknown. Finally, it is also important not to rely on "defining" individual 4-digit typing by inference from larger HLA data sets from unrelated populations and ethnicities. Although haplotype frequencies for well-studied populations have been fairly well established, the ongoing expansion of HIV-related studies and vaccine trials into populations for which these data are limited, introduces a considerable risk of predicting incorrect subtypes. While this may be a particular issue for HLA-B15 and A68 alleles (for which subtypes fall into separate HLA supertypes and thus present vastly different epitopes), the case of HLA-B35 and others (A2, B44, etc.) clearly illustrates that high-resolution typing should be employed for the best definition of HLA restriction [Sidney *et al.*, 2008].

Similar to detailed HLA restriction analyses, there are several reasons why definition of optimal epitope length should be based on experimental analysis rather than binding motif predictions or only partial truncations. While some hints from available epitope sequences may be helpful in the experimental design of truncation studies or overlapping peptide synthesis (such as the elimination of possible rare ("forbidden") C-terminal residues; `http://www.hiv.lanl.gov/content/sequence/PEPTGEN/peptgen.html`), only a systematic approach will clarify the identity of the targeted sequence. An older example of how this may affect epitope response patterns is the case of two embedded B57 epitopes, where one shorter version is fully contained in a longer epitope sequence [Goulder *et al.*, 2000c]. As shown in our own analyses on promiscuous epitope presentation, embedded epitopes can also be presented on different HLA molecules, again highlighting that HLA restriction and fine mapping approaches need to go hand in hand [Frahm *et al.*, 2007]. Importantly, shorter is not necessarily better, as has been shown in a number of cases where bulged epitopes were presented in the context of alleles such as HLA-B35 and its subtypes [Burrows *et al.*, 2006]. Existing prediction algorithms, trained on existing data of mostly 9–10mer epitope sequences, could not possibly predict these epitopes and their HLA restrictions. Rather, the mapping analyses ideally start from the full-length peptide that initially elicited the detected response (often an overlapping peptide of 15-18 amino acids in length). The ever-decreasing cost for peptide synthesis and the development of collaborative studies among laboratories where many peptide truncations already exist will hopefully enable many more research groups to conduct such additional analyses.

While we strive to collect all well-characterized CTL epitopes in our list of optimally defined CTL epitopes, we are also trying to strike a balance between including as much information and as many epitopes as possible while avoiding the potential detrimental effects of including epitopes that are not conclusively defined. Since most epitopes represent correctly defined optimal targets in a clinically-relevant setting [Goonetilleke *et al.*, 2009], they do put us in the difficult position of either relaxing the inclusion criteria or asking for additional analyses to be conducted. We however also feel that their inclusion in the comprehensive listing (B-list) of the HIV Immunology Database will make such information readily accessible to the wider research community, in the end providing a benefit for all involved in the definition of protective immune responses, T-cell immunity and viral evolution. At the same time, we remain open to suggestions on how we could improve the A-list so that it meets the changing needs of the community. For any comments, please contact us.

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I-A-3 Table of optimal HIV-1 CTL epitopes

Table I-A.1: Best defined HIV CTL epitopes.

HLA	Protein	AA	Sequence	Reference
A*0101 (A1)	gp160	787–795	RRGWEVLKY	Cao, 2002
A2	RT	127–135	YTAFTIPSV	Draenert *et al.*, 2004b
A*0201 (A2)	p17	77–85	SLYNTVATL	Johnson *et al.*, 1991; Parker *et al.*, 1992, 1994
A*0201 (A2)	p2p7p1p6	70–79	FLGKIWPSYK	Yu *et al.*, 2002b
A*0201 (A2)	Protease	76–84	LVGPTPVNI	Karlsson *et al.*, 2003
A*0201 (A2)	RT	33–41	ALVEICTEM	Haas *et al.*, 1998; Haas, 1999
A*0201 (A2)	RT	179–187	VIYQYMDDL	Harrer *et al.*, 1996a
A*0201 (A2)	RT	309–317	ILKEPVHGV	Walker *et al.*, 1989; Tsomides *et al.*, 1991
A*0201 (A2)	Vpr	59–67	AIIRILQQL	Altfeld *et al.*, 2001a,b
A*0201 (A2)	gp160	311–320	RGPGRAFVTI	Alexander-Miller *et al.*, 1996
A*0201 (A2)	gp160	813–822	SLLNATDIAV	Dupuis *et al.*, 1995
A*0201 (A2)	Nef	136–145	PLTFGWCYKL	Haas *et al.*, 1996; Maier & Autran, 1999
A*0201 (A2)	Nef	180–189	VLEWRFDSRL	Haas *et al.*, 1996; Maier & Autran, 1999
A*0202 (A2)	p17	77–85	SLYNTVATL	Goulder, 1999
A*0205 (A2)	p17	77–85	SLYNTVATL	Goulder, 1999
A*0205 (A2)	gp160	846–854	RIRQGLERA	Sabbaj *et al.*, 2003
A*0205 (A2)	Nef	83–91	GAFDLSFFL	Rathod, 2006
A*0207 (A2)	p24	164–172	YVDRFYKTL	Currier *et al.*, 2002
A*0301 (A3)	p17	18–26	KIRLRPGGK	Harrer *et al.*, 1996b
A*0301 (A3)	p17	20–28	RLRPGGKKK	Goulder *et al.*, 1997b; Culmann, 1999; Lewinsohn & Riddell, 1999; Wilkes & Ruhl, 1999
A*0301 (A3)	p17	20–29	RLRPGGKKKY	Goulder *et al.*, 2000b
A*0301 (A3)	RT	33–43	ALVEICTEMEK	Haas *et al.*, 1998; Haas, 1999
A*0301 (A3)	RT	73–82	KLVDFRELNK	Yu *et al.*, 2002a
A*0301 (A3)	RT	93–101	GIPHPAGLK	Yu *et al.*, 2002a
A*0301 (A3)	RT	158–166	AIFQSSMTK	Threlkeld *et al.*, 1997
A*0301 (A3)	RT	269–277	QIYPGIKVR	Yu *et al.*, 2002a
A*0301 (A3)	RT	356–366	RMRGAHTNDVK	Yu *et al.*, 2002a
A*0301 (A3)	Integrase	179–188	AVFIHNFKRK	Yu *et al.*, 2002a
A*0301 (A3)	Vif	17–26	RIRTWKSLVK	Altfeld *et al.*, 2001a; Yu *et al.*, 2002a
A*0301 (A3)	Vif	28–36	HMYISKKAK	Yu *et al.*, 2002a
A*0301 (A3)	Vif	158–168	KTKPPLPSVKK	Yu *et al.*, 2002a
A*0301 (A3)	Rev	57–66	ERILSTYLGR	Addo, 2002; Yu *et al.*, 2002a
A*0301 (A3)	gp160	37–46	TVYYGVPVWK	Johnson *et al.*, 1994
A*0301 (A3)	gp160	770–780	RLRDLLLIVTR	Takahashi *et al.*, 1991
A*0301 (A3)	Nef	73–82	QVPLRPMTYK	Koenig *et al.*, 1990; Culmann *et al.*, 1991
A*0301 (A3)	Nef	84–92	AVDLSHFLK	Yu *et al.*, 2002a

Table I-A.1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
A*1101 (A11)	p17	84–91	TLYCVHQK	Harrer *et al.*, 1998
A*1101 (A11)	p24	217–227	ACQGVGGPGHK	Sipsas *et al.*, 1997
A*1101 (A11)	RT	158–166	AIFQSSMTK	Johnson & Walker, 1994; Zhang *et al.*, 1993; Threlkeld *et al.*, 1997
A*1101 (A11)	RT	341–350	IYQEPFKNLK	Culmann, 1999
A*1101 (A11)	RT	520–528	QIIEQLIKK	Fukada *et al.*, 1999
A*1101 (A11)	Integrase	179–188	AVFIHNFKRK	Fukada *et al.*, 1999
A*1101 (A11)	Integrase	203–211	IIATDIQTK	Wang *et al.*, 2007
A*1101 (A11)	gp160	199–207	SVITQACPK	Fukada *et al.*, 1999
A*1101 (A11)	Nef	73–82	QVPLRPMTYK	Buseyne, 1999
A*1101 (A11)	Nef	75–82	PLRPMTYK	Culmann *et al.*, 1991
A*1101 (A11)	Nef	84–92	AVDLSHFLK	Culmann *et al.*, 1991
A23	gp160	585–593	RYLKDQQLL	Cao *et al.*, 2003
A*2402 (A24)	p17	28–36	KYKLKHIVW	Ikeda-Moore *et al.*, 1998; Lewinsohn, 1999
A*2402 (A24)	p24	162–172	RDYVDRFFKTL	Dorrell *et al.*, 1999; Rowland-Jones, 1999
A*2402 (A24)	gp160	52–61	LFCASDAKAY	Lieberman *et al.*, 1992; Shankar *et al.*, 1996
A*2402 (A24)	gp160	585–593	RYLKDQQLL	Dai *et al.*, 1992
A*2402 (A24)	Nef	134–141	RYPLTFGW	Goulder *et al.*, 1997a; Ikeda-Moore *et al.*, 1998
A*2501 (A25)	p24	13–23	QAISPRTLNAW	Kurane & West, 1999
A*2501 (A25)	p24	71–80	ETINEEAAEW	Klenerman *et al.*, 1996; van Baalen *et al.*, 1996
A*2501 (A25)	gp160	321–330	EIIGDIRQAY	Liu *et al.*, 2006
A*2601 (A26)	p24	35–43	EVIPMFSAL	Goulder *et al.*, 1996a
A*2601 (A26)	RT	449–457	ETKLGKAGY	Sabbaj *et al.*, 2003
A29	Nef	120–128	YFPDWQNYT	Draenert *et al.*, 2004a
A*2902 (A29)	p17	78–86	LYNTVATLY	Masemola *et al.*, 2004
A*2902 (A29)	gp160	209–217	SFEPIPIHY	Altfeld, 2000
A30	p17	34–44	LVWASRELERF	Masemola *et al.*, 2004
A*3002 (A30)	p17	76–86	RSLYNTVATLY	Goulder *et al.*, 2001
A*3002 (A30)	RT	173–181	KQNPDIVIY	Goulder *et al.*, 2001
A*3002 (A30)	RT	263–271	KLNWASQIY	Goulder *et al.*, 2001
A*3002 (A30)	RT	356–365	RMRGAHTNDV	Sabbaj *et al.*, 2003
A*3002 (A30)	Integrase	219–227	KIQNFRVYY	Sabbaj *et al.*, 2003; Rodriguez *et al.*, 2004
A*3002 (A30)	gp160	310–318	HIGPGRAFY	Sabbaj *et al.*, 2003
A*3002 (A30)	gp160	704–712	IVNRNRQGY	Goulder *et al.*, 2001
A*3002 (A30)	gp160	794–802	KYCWNLLQY	Goulder *et al.*, 2001
A*3101 (A31)	gp160	770–780	RLRDLLLIVTR	Safrit *et al.*, 1994a,b
A*3201 (A32)	RT	392–401	PIQKETWETW	Harrer *et al.*, 1996b
A*3201 (A32)	gp160	419–427	RIKQIINMW	Harrer *et al.*, 1996b

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Table I-A.1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
A33	Nef	133–141	TRYPLTFGW	Cao, 2002
A*3303 (A33)	gp160	698–707	VFAVLSIVNR	Hossain *et al.*, 2001
A*3303 (A33)	gp160	831–838	EVAQRAYR	Hossain *et al.*, 2001
A*3303 (A33)	Vpu	29–37	EYRKILRQR	Addo *et al.*, 2002
A66	RT	438–448	ETFYVDGAANR	Rathod, 2006
A*6801 (A68)	Tat	39–49	ITKGLGISYGR	Oxenius *et al.*, 2002
A*6801 (A68)	Vpr	52–62	DTWAGVEAIIR	Sabbaj *et al.*, 2004
A*6802 (A68)	RT	436–445	GAETFYVDGA	Rathod & Kiepiela, 2005
A*6802 (A68)	Protease	3–11	ITLWQRPLV	Rowland-Jones, 1999
A*6802 (A68)	Protease	30–38	DTVLEEWNL	Rowland-Jones, 1999
A*6802 (A68)	Vpr	48–57	ETYGDTWTGV	Rathod & Kiepiela, 2005
A*6802 (A68)	gp160	777–785	IVTRIVELL	Wilkes, 1999
A*7401 (A19)	Protease	3–11	ITLWQRPLV	Rowland-Jones, 1999
B7	p24	84–92	HPVHAGPIA	Yu *et al.*, 2002a
B7	RT	156–164	SPAIFQSSM	Linde & Faircloth, 2006
B7	Rev	66–75	RPAEPVPLQL	Yang, 2006
B*0702 (B7)	p24	16–24	SPRTLNAWV	Lewinsohn, 1999
B*0702 (B7)	p24	48–56	TPQDLNTML	Wilson, 1999; Wilkes *et al.*, 1999; Jin *et al.*, 2000; Wilson *et al.*, 1997
B*0702 (B7)	p24	223–231	GPGHKARVL	Goulder, 1999
B*0702 (B7)	Vpr	34–42	FPRIWLHGL	Altfeld *et al.*, 2001a
B*0702 (B7)	Vif	48–57	HPRVSSEVHI	Altfeld *et al.*, 2001a
B*0702 (B7)	gp160	298–307	RPNNNTRKSI	Safrit *et al.*, 1994b
B*0702 (B7)	gp160	843–851	IPRRIRQGL	Wilkes & Ruhl, 1999
B*0702 (B7)	Nef	68–77	FPVTPQVPLR	Haas *et al.*, 1996; Maier & Autran, 1999
B*0702 (B7)	Nef	68–76	FPVTPQVPL	Bauer *et al.*, 1997; Frahm & Goulder, 2002
B*0702 (B7)	Nef	71–79	TPQVPLRPM	Goulder, 1999
B*0702 (B7)	Nef	77–85	RPMTYKAAL	Bauer *et al.*, 1997
B*0702 (B7)	Nef	128–137	TPGPGVRYPL	Culmann-Penciolelli *et al.*, 1994; Haas *et al.*, 1996
B8	gp160	848–856	RQGLERALL	Cao, 2002
B*0801 (B8)	p17	24–32	GGKKKYKLK	Reid *et al.*, 1996; Goulder *et al.*, 1997d
B*0801 (B8)	p17	74–82	ELRSLYNTV	Goulder *et al.*, 1997d
B*0801 (B8)	p24	128–135	EIYKRWII	Sutton *et al.*, 1993; Goulder *et al.*, 1997d
B*0801 (B8)	p24	197–205	DCKTILKAL	Sutton *et al.*, 1993
B*0801 (B8)	RT	18–26	GPKVKQWPL	Walker *et al.*, 1989; Sutton *et al.*, 1993
B*0801 (B8)	gp160	2–10	RVKEKYQHL	Sipsas *et al.*, 1997
B*0801 (B8)	gp160	586–593	YLKDQQLL	Johnson *et al.*, 1992; Shankar *et al.*, 1996
B*0801 (B8)	Nef	13–20	WPTVRERM	Goulder *et al.*, 1997d
B*0801 (B8)	Nef	90–97	FLKEKGGL	Culmann-Penciolelli *et al.*, 1994; Price *et al.*, 1997

Table I-A.1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
B13	p24	3–11	VQNLQGQMV	Honeyborne *et al.*, 2007
B13	p24	94–104	GQMREPRGSDI	Honeyborne *et al.*, 2007
B13	p2p7p1p6	66–74	RQANFLGKI	Honeyborne *et al.*, 2007
B13	Protease	57–66	RQYDQILIEI	Honeyborne *et al.*, 2007; Mueller *et al.*, 2007
B13	RT	333–341	GQGQWTYQI	Honeyborne *et al.*, 2007
B13	Nef	106–114	RQDILDLWI	Harrer *et al.*, 2005; Honeyborne *et al.*, 2007
B*1302 (B13)	Nef	106–114	RQDILDLWV	Gray *et al.*, 2009
B14	p2p7p1p6	42–50	CRAPRKKGC	Yu *et al.*, 2002b
B*1401 (B14)	RT	142–149	IRYQYNVL	Rathod, 2006
B*1402 (B14)	p24	166–174	DRFYKTLRA	Harrer *et al.*, 1996b
B*1402 (B14)	gp160	584–592	ERYLKDQQL	Johnson *et al.*, 1992
B*1501 (B62)	p24	137–145	GLNKIVRMY	Johnson *et al.*, 1991; Goulder, 1999
B*1501 (B62)	RT	260–271	LVGKLNWASQIY	Johnson, 1999
B*1501 (B62)	RT	309–318	ILKEPVHGVY	Johnson *et al.*, 1991; Johnson, 1999
B*1501 (B62)	Nef	117–127	TQGYFPDWQNY	Culmann, 1999
B*1503 (B72)	p24	24–32	VKVIEEKAF	Honeyborne & Kiepiela, 2005
B*1503 (B72)	p24	164–172	YVDRFFKTL	Masemola *et al.*, 2004
B*1503 (B72)	Protease	68–76	GKKAIGTVL	Rathod & Bishop, 2006
B*1503 (B72)	RT	496–505	VTDSQYALGI	Sabbaj *et al.*, 2003
B*1503 (B72)	Integrase	135–143	IQQEFGIPY	Honeyborne & Kiepiela, 2005
B*1503 (B72)	Integrase	185–194	FKRKGGIGGY	Honeyborne, 2003
B*1503 (B72)	Integrase	263–271	RKAKIIRDY	Cao *et al.*, 2003
B*1503 (B72)	Tat	38–47	FQTKGLGISY	Novitsky *et al.*, 2001
B*1503 (B72)	Nef	183–191	WRFDSRLAF	Cao, 2002
B*1510 (B71)	p24	12–20	HQAISPRTL	Day, 2005
B*1510 (B71)	p24	61–69	GHQAAMQML	Day, 2003
B*1510 (B71)	Integrase	66–74	THLEGKIIL	Kiepiela *et al.*, 2007
B*1510 (B71)	Vif	79–87	WHLGHGVSI	Honeyborne, 2003
B*1516 (B63)	gp160	375–383	SFNCGGEFF	Wilson *et al.*, 1997; Wilson, 1999
B18	RT	137–146	NETPGIRYQY	Rathod & Bishop, 2006
B18	RT	175–183	NPEIVIYQY	Rathod, 2006
B18	Nef	105–115	RRQDILDLWVY	Yang, 2006
B*1801 (B18)	p24	161–170	FRDYVDRFYK	Ogg *et al.*, 1998
B*1801 (B18)	Vif	102–111	LADQLIHLHY	Altfeld *et al.*, 2001a
B*1801 (B18)	gp160	31–39	AENLWVTVY	Liu *et al.*, 2006
B*1801 (B18)	gp160	61–69	YETEVHNVW	Liu *et al.*, 2006
B*1801 (B18)	Nef	135–143	YPLTFGWCY	Culmann *et al.*, 1991; Culmann-Penciolelli *et al.*, 1994

Table I-A.1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
B27	Vpr	31–39	VRHFPRIWL	Addo & Rathod, 2004
B*2703 (B27)	p24	131–140	RRWIQLGLQK	Rowland-Jones *et al.*, 1998; Rowland-Jones, 1999
B*2705 (B27)	p17	19–27	IRLRPGGKK	McKinney *et al.*, 1999; Lewinsohn, 1999
B*2705 (B27)	p24	131–140	KRWIILGLNK	Nixon *et al.*, 1988; Buseyne *et al.*, 1993; Goulder *et al.*, 1997c
B*2705 (B27)	Integrase	186–194	KRKGGIGGY	Payne & Goulder, 2009
B*2705 (B27)	gp160	786–795	GRRGWEALKY	Lieberman *et al.*, 1992; Lieberman, 1999
B*2705 (B27)	Nef	105–114	RRQDILDLWI	Goulder *et al.*, 1997b
B*3501 (B35)	p17	36–44	WASRELERF	Goulder *et al.*, 1997a
B*3501 (B35)	p17	124–132	NSSKVSQNY	Rowland-Jones *et al.*, 1995
B*3501 (B35)	p24	122–130	PPIPVGDIY	Rowland-Jones *et al.*, 1995
B*3501 (B35)	RT	107–115	TVLDVGDAY	Wilkes & Ruhl, 1999; Wilson *et al.*, 1999
B*3501 (B35)	RT	118–127	VPLDEDFRKY	Sipsas *et al.*, 1997; Shiga *et al.*, 1996
B*3501 (B35)	RT	175–183	HPDIVIYQY	Rowland-Jones *et al.*, 1995; Shiga *et al.*, 1996; Sipsas *et al.*, 1997
B*3501 (B35)	gp160	42–52	VPVWKEATTTL	Wilkes & Ruhl, 1999
B*3501 (B35)	gp160	78–86	DPNPQEVVL	Shiga *et al.*, 1996
B*3501 (B35)	gp160	606–614	TAVPWNASW	Johnson *et al.*, 1994
B*3501 (B35)	Nef	74–81	VPLRPMTY	Culmann *et al.*, 1991; Culmann-Penciolelli *et al.*, 1994
B*3701 (B37)	Nef	120–128	YFPDWQNYT	Culmann *et al.*, 1991; Culmann, 1999
B*3801 (B38)	Vif	79–87	WHLGQGVSI	Sabbaj *et al.*, 2004
B*3801 (B38)	gp160	104–112	MHEDIISLW	Cao, 2002
B*3901 (B39)	p24	61–69	GHQAAMQML	Kurane & West, 1999
B*3910 (B39)	p24	48–56	TPQDLNTML	Honeyborne & Kiepiela, 2005
B*4001 (B60)	p17	92–101	IEIKDTKEAL	Altfeld *et al.*, 2000
B*4001 (B60)	p24	44–52	SEGATPQDL	Altfeld *et al.*, 2000
B*4001 (B60)	p2p7p1p6	118–126	KELYPLTSL	Yu *et al.*, 2002b
B*4001 (B60)	RT	5–12	IETVPVKL	Draenert *et al.*, 2004b
B*4001 (B60)	RT	202–210	IEELRQHLL	Altfeld *et al.*, 2000
B*4001 (B60)	gp160	805–814	QELKNSAVSL	Altfeld *et al.*, 2000
B*4001 (B60)	Nef	37–45	LEKHGAITS	Draenert *et al.*, 2004b
B*4001 (B60)	Nef	92–100	KEKGGLEGL	Altfeld *et al.*, 2000
B*4002 (B61)	p17	11–19	GELDRWEKI	Sabbaj *et al.*, 2003
B*4002 (B61)	p24	70–78	KETINEEAA	Sabbaj *et al.*, 2003
B*4002 (B61)	p24	78–86	AEWDRVHPV	Sabbaj *et al.*, 2003
B*4002 (B61)	p2p7p1p6	64–71	TERQANFL	Sabbaj *et al.*, 2003
B*4002 (B61)	Nef	92–100	KEKGGLEGL	Sabbaj *et al.*, 2003; Altfeld *et al.*, 2000

Table I-A.1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
B42	Integrase	28–36	LPPIVAKEI	Kiepiela *et al.*, 2007
B42	Integrase	260–268	VPRRKAKII	Kiepiela & Goulder, 2002
B*4201 (B42)	p24	48–56	TPQDLNTML	Goulder *et al.*, 2000a
B*4201 (B42)	RT	271–279	YPGIKVRQL	Wilkes & Ruhl, 1999
B*4201 (B42)	Nef	71–79	RPQVPLRPM	Honeyborne, 2006
B*4201 (B42)	Nef	128–137	TPGPGVRYPL	Goulder, 1999
B44	Protease	34–42	EEMNLPGRW	Rodriguez *et al.*, 2004
B44	gp160	31–39	AENLWVTVY	Borrow *et al.*, 1997
B*4402 (B44)	p24	162–172	RDYVDRFYKTL	Ogg *et al.*, 1998
B*4402 (B44)	p24	174–184	AEQASQDVKNW	Lewinsohn, 1999
B*4402 (B44)	gp160	31–40	AENLWVTVYY	Borrow *et al.*, 1997
B*4403 (B44)	p17	78–86	LYNTVATLY	Masemola *et al.*, 2004
B*4415 (B12)	p24	28–36	EEKAFSPEV	Bird *et al.*, 2002
B*4501 (B45)	p2p7p1p6	1–10	AEAMSQVTNS	Sabbaj *et al.*, 2004
B50	Nef	37–45	LEKHGAITS	Draenert *et al.*, 2004b
B51	Vif	57–66	IPLGDAKLII	Bansal *et al.*, 2004
B51	Vpr	29–37	EAVRHFPRI	Cao *et al.*, 2003
B*5101 (B51)	RT	42–50	EKEGKISKI	Haas *et al.*, 1998; Haas, 1999
B*5101 (B51)	RT	128–135	TAFTIPSI	Sipsas *et al.*, 1997
B*5101 (B51)	gp160	416–424	LPCRIKQII	Tomiyama *et al.*, 1999
B*5201 (B52)	p24	143–150	RMYSPTSI	Wilkes & Ruhl, 1999; Wilson *et al.*, 1997
B53	Nef	135–143	YPLTFGWCF	Kiepiela & Goulder, 2002
B*5301 (B53)	p24	48–56	TPYDINQML	Gotch *et al.*, 1993
B*5301 (B53)	p24	176–184	QASQEVKNW	Buseyne *et al.*, 1996, 1997; Buseyne, 1999
B*5301 (B53)	Tat	2–11	EPVDPRLEPW	Addo *et al.*, 2001
B*5301 (B53)	Nef	135–143	YPLTFGWCY	Sabbaj *et al.*, 2003
B*5501 (B55)	gp160	42–51	VPVWKEATTT	Shankar *et al.*, 1996; Lieberman, 1999

Table I-A.1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
B57	p24	32–40	FSPEVIPMF	Frahm *et al.*, 2005
B57	Protease	70–77	KAIGTVLV	Frahm *et al.*, 2005
B57	Integrase	123–132	STTVKAACWW	Rodriguez *et al.*, 2004; Addo & Rathod, 2004
B57	Nef	116–124	HTQGYFPDW	Draenert, 2002
B57	Nef	127–135	YTPGPGIRY	Frahm *et al.*, 2005
B57	Nef	137–145	LTFGWCFKL	Frahm *et al.*, 2005
B*5701 (B57)	p24	15–23	ISPRTLNAW	Johnson *et al.*, 1991; Goulder *et al.*, 1996b
B*5701 (B57)	p24	30–40	KAFSPEVIPMF	Goulder *et al.*, 1996b
B*5701 (B57)	p24	108–117	TSTLQEQIGW	Goulder *et al.*, 1996b
B*5701 (B57)	p24	176–184	QASQEVKNW	Goulder *et al.*, 1996b
B*5701 (B57)	RT	244–252	IVLPEKDSW	van der Burg *et al.*, 1997; Hay, 1999
B*5701 (B57)	Integrase	173–181	KTAVQMAVF	Goulder *et al.*, 1996b; Hay, 1999
B*5701 (B57)	Vpr	30–38	AVRHFPRIW	Altfeld *et al.*, 2001a
B*5701 (B57)	Vif	31–39	ISKKAKGWF	Altfeld *et al.*, 2001a
B*5701 (B57)	Rev	14–23	KAVRLIKFLY	Addo *et al.*, 2001
B*5701 (B57)	Nef	116–125	HTQGYFPDWQ	Culmann *et al.*, 1991
B*5701 (B57)	Nef	120–128	YFPDWQNYT	Culmann *et al.*, 1991
B*5703 (B57)	p24	30–37	KAFSPEVI	Goulder *et al.*, 2000b
B*5703 (B57)	p24	30–40	KAFSPEVIPMF	Goulder *et al.*, 2000b
B*5703 (B57)	Nef	83–91	AAFDLSFFL	Gray *et al.*, 2009
B58	p17	76–86	RSLYNTVATLY	Frahm *et al.*, 2005
B58	Tat	2–11	EPVDPRLEPW	Frahm & Brander, 2005
B58	gp160	59–69	KAYETEVHNVW	Rathod & Bishop, 2006
B*5801 (B58)	p24	108–117	TSTLQEQIGW	Goulder *et al.*, 1996b; Bertoletti *et al.*, 1998
B*5801 (B58)	RT	375–383	IAMESIVIW	Kiepiela & Goulder, 2002
B*5801 (B58)	Rev	14–23	KAVRLIKFLY	Addo *et al.*, 2001
B62	Nef	19–27	RMRRAEPAA	Cao, 2002
B63	p17	76–86	RSLYNTVATLY	Frahm *et al.*, 2005
B63	p24	15–23	ISPRTLNAW	Frahm *et al.*, 2005
B63	p24	30–40	KAFSPEVIPMF	Frahm *et al.*, 2005
B63	Rev	14–23	KAVRLIKFLY	Frahm *et al.*, 2005
B63	Nef	127–135	YTPGPGIRY	Frahm *et al.*, 2005
B63	Nef	137–145	LTFGWCFKL	Frahm *et al.*, 2005
B81	Protease	80–90	TPVNIIGRNML	Honeyborne *et al.*, 2006
B81	RT-Integrase	560-8	LFLDGIDKA	Addo, 2002
B*8101 (B81)	p24	48–56	TPQDLNTML	Goulder *et al.*, 2000a
B*8101 (B81)	Vpr	34–42	FPRIWLHGL	Altfeld *et al.*, 2001a

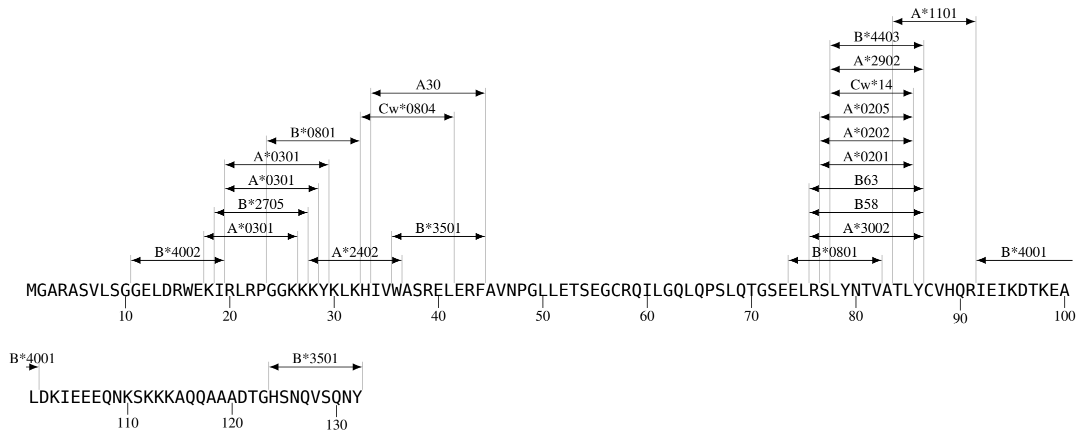
Table I-A.1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
Cw1	gp160	218–226	CAPAGFAIL	Zuñiga, 2008; Streeck *et al.*, 2008
Cw*0102 (Cw1)	p24	36–43	VIPMFSAL	Goulder *et al.*, 1997a
Cw*0102 (Cw1)	Gag-Pol TF	24–31	NSPTRREL	Liu *et al.*, 2006
Cw3	Nef	83–91	AALDLSHFL	Draenert *et al.*, 2004b
Cw*0303 (Cw9)	p24	164–172	YVDRFFKTL	Honeyborne, 2003
Cw*0304 (Cw10)	p24	164–172	YVDRFFKTL	Honeyborne, 2003
Cw*0304 (Cw10)	gp160	557–565	RAIEAQQHL	Currier *et al.*, 2002; Trocha, 2002
Cw*0401 (Cw4)	gp160	375–383	SFNCGGEFF	Wilson *et al.*, 1997; Johnson *et al.*, 1993
Cw5	p24	174–185	AEQASQEVKNWM	Draenert *et al.*, 2004b
Cw*0501	Rev	67-75	SAEPVPLQL	Addo *et al.*, 2001
Cw6	Nef	120–128	YFPDWQNYT	Frahm & Brander, 2005
Cw7	Nef	105–115	KRQEILDLWVY	Kiepiela & Goulder, 2002; Yu *et al.*, 2002a
Cw8	gp160	557–565	RAIEAQQHM	Bishop & Honeyborne, 2006
Cw8	Nef	82–91	KAAVDLSHFL	Harrer *et al.*, 1996b
Cw*0802 (Cw8)	p24	48–56	TPQDLNTML	Goulder *et al.*, 2000a; Honeyborne & Kiepiela, 2005
Cw*0802 (Cw8)	RT	495–503	IVTDSQYAL	Rathod & Honeyborne, 2006
Cw*0802 (Cw8)	Nef	83–91	AAVDLSHFL	Cao *et al.*, 2003; Rathod & Honeyborne, 2006
Cw*0804 (Cw8)	p17	33–41	HLVWASREL	Masemola *et al.*, 2004
Cw12	Tat	30–37	CCFHCQVC	Cao *et al.*, 2003; Nixon *et al.*, 1999
Cw14	p17	78–85	LYNTVATL	Horton & Havenar-Daughton, 2005
Cw15	gp160	557–565	RAIEAQQHL	Trocha, 2002
Cw18	p24	142–150	VRMYSPVSI	Honeyborne, 2006
Cw18	p24	161–169	FRDYVDRFF	Honeyborne & Kiepiela, 2005
Cw18	Integrase	165–172	VRDQAEHL	Rathod & Honeyborne, 2006
Cw18	Vpu	5–13	YRLGVGALI	Honeyborne, 2006

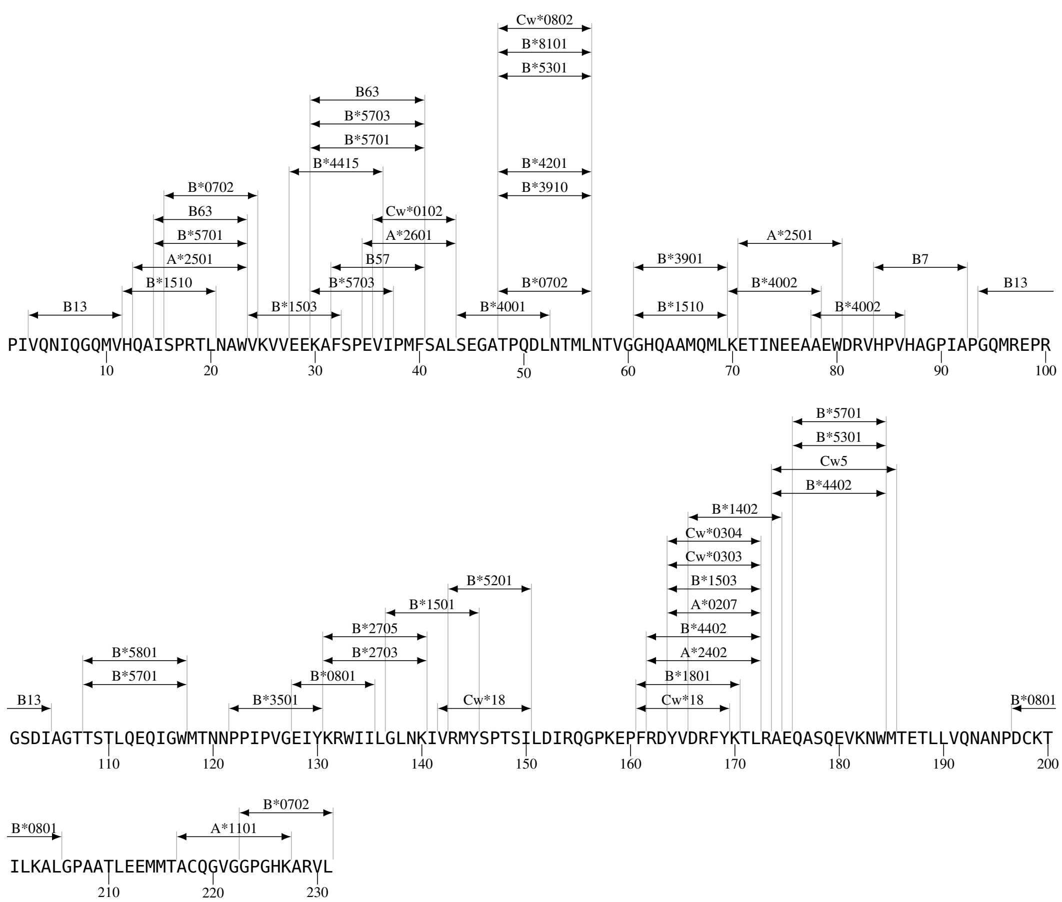
I-A-4 Map of optimal HIV-1 CTL epitopes

The location and HLA restriction elements of CTL epitopes are indicated on protein sequences of HXB2. These maps are meant to provide the relative location of defined epitopes on a given protein, but the HXB2 sequence may not actually carry the epitope of interest, as it may vary relative to the sequence for which the epitope was defined.

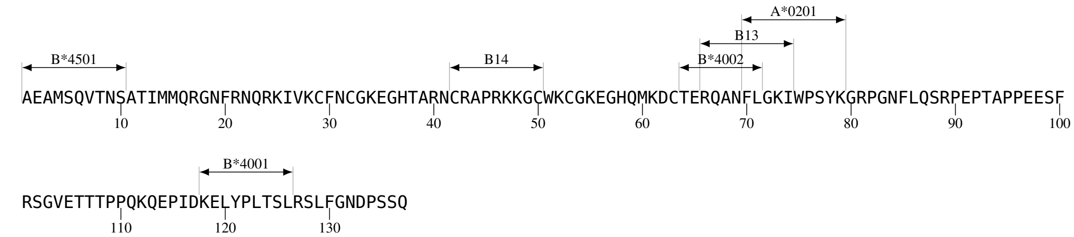
p17 Optimal CTL Epitope Map



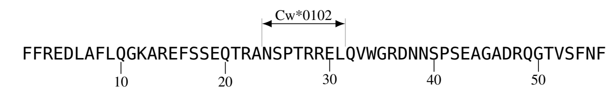
p24 Optimal CTL Epitope Map



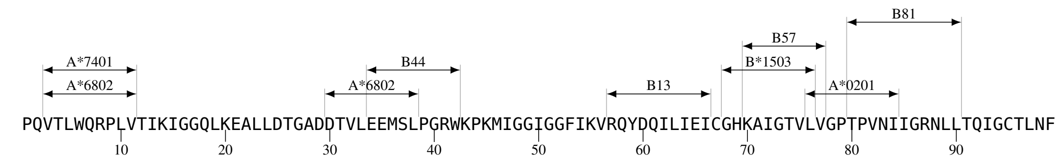
p2p7p1p6 Optimal CTL Epitope Map



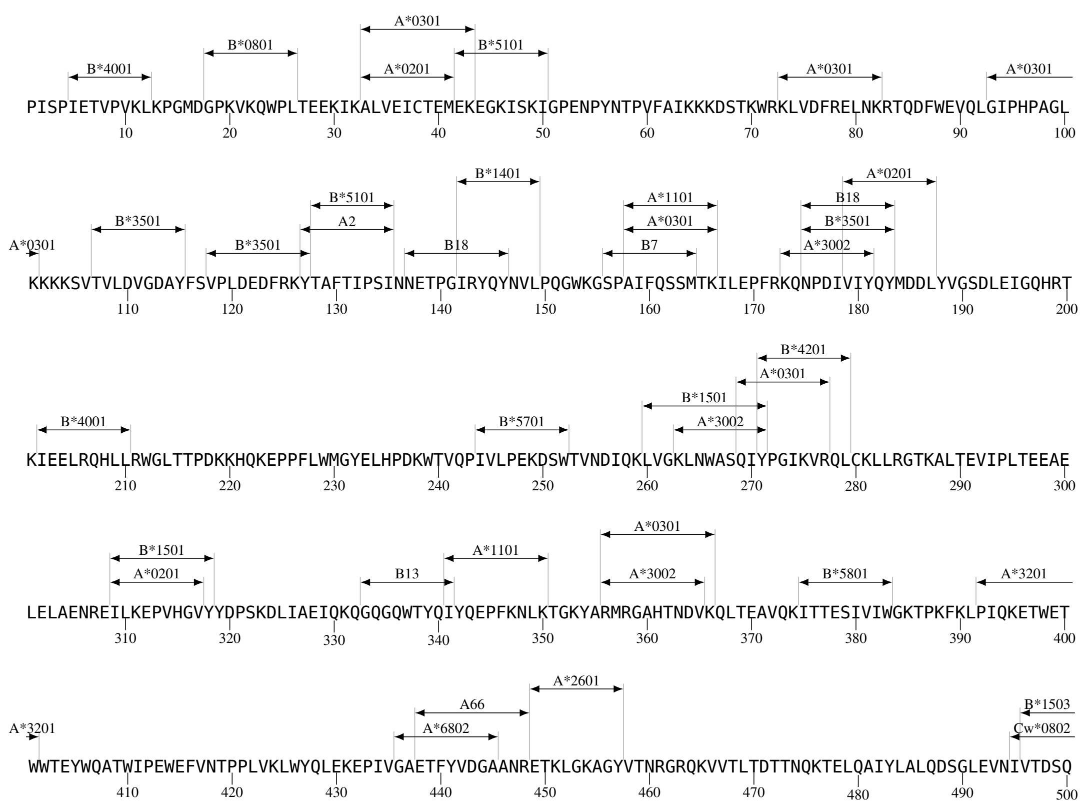
Gag/Pol TF Optimal CTL Epitope Map

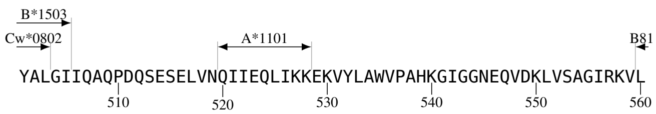


Protease Optimal CTL Epitope Map

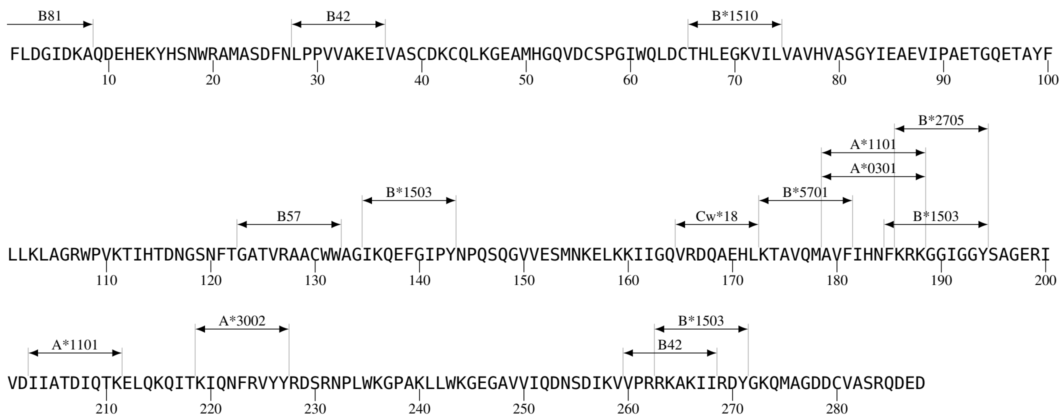


RT Optimal CTL Epitope Map

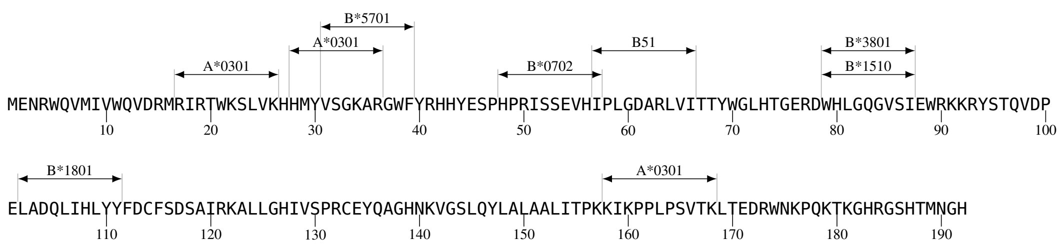




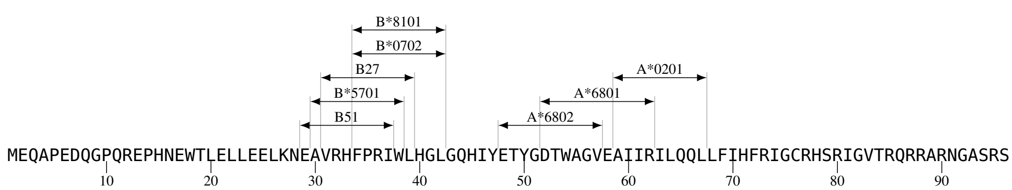
Integrase Optimal CTL Epitope Map



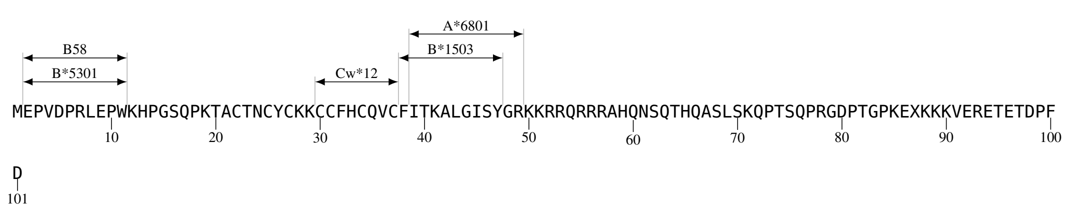
Vif Optimal CTL Epitope Map



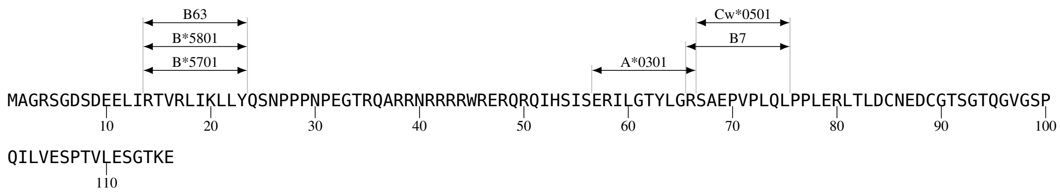
Vpr Optimal CTL Epitope Map



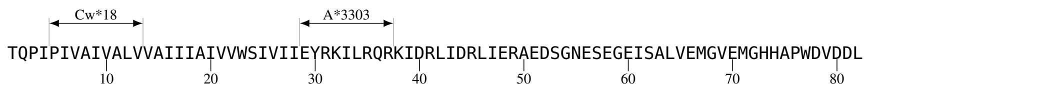
Tat Optimal CTL Epitope Map



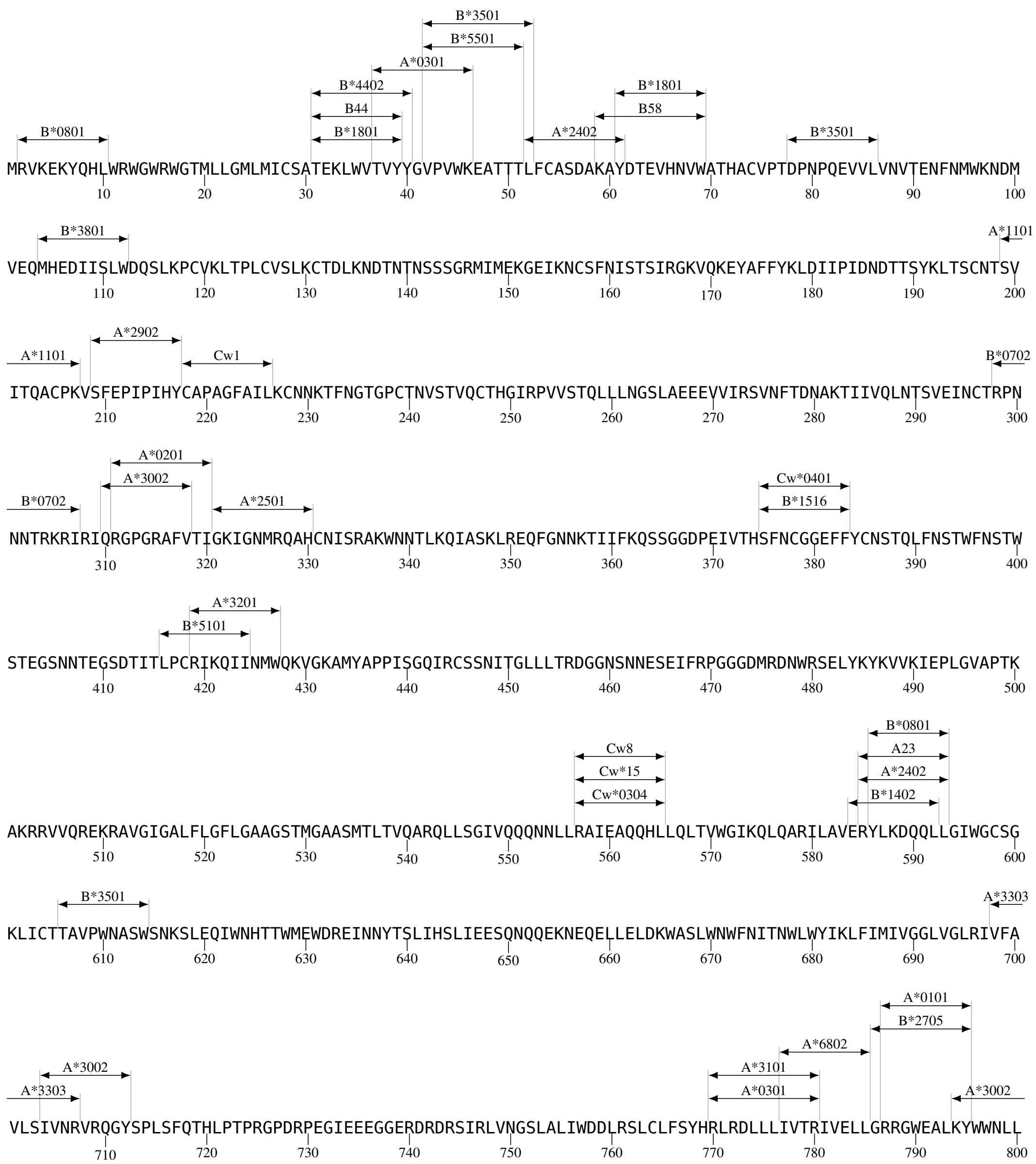
Rev Optimal CTL Epitope Map

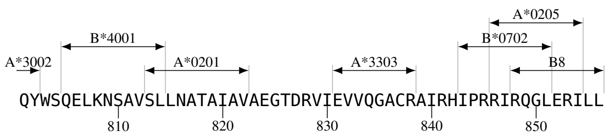


Vpu Optimal CTL Epitope Map

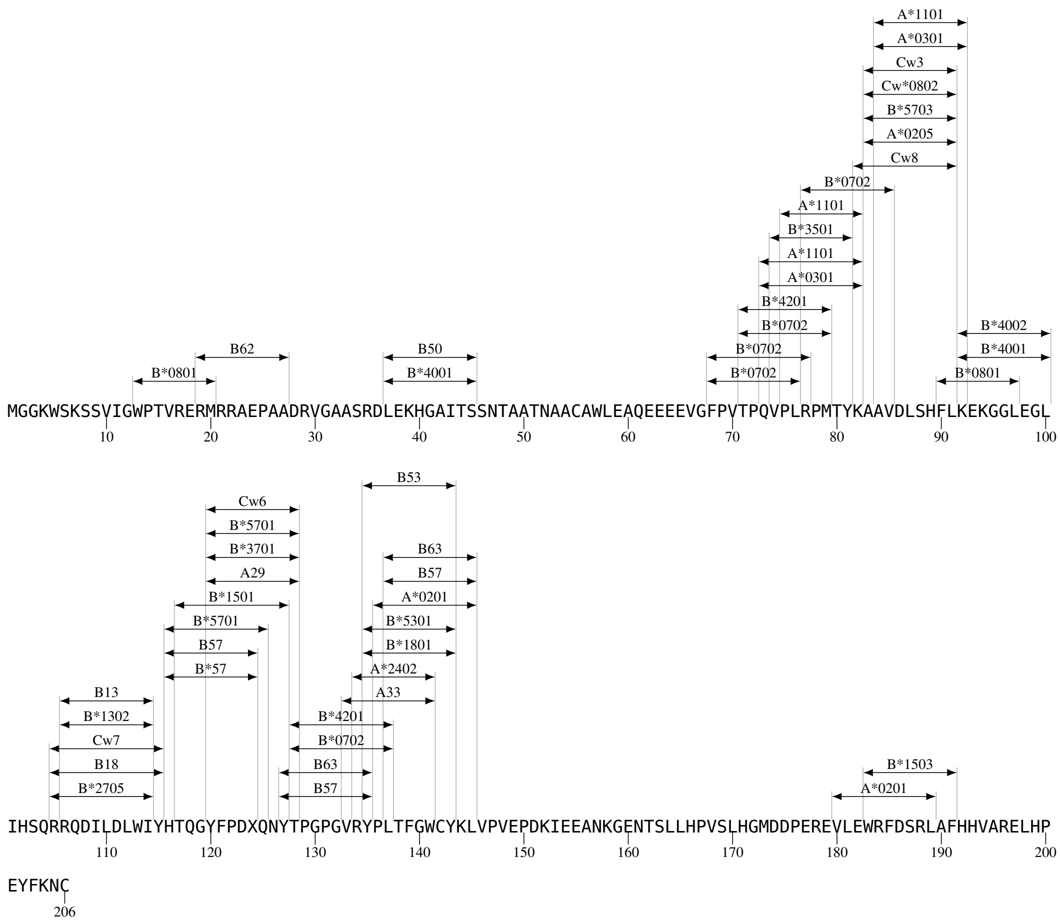


gp160 Optimal CTL Epitope Map





Nef Optimal CTL Epitope Map



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Part II

HIV CTL/CD8+ Epitopes

II-A

Summary

This part includes tables, maps, and associated references of HIV-specific CTL epitopes found in the literature arranged sequentially according to the location of the proteins in the HIV-1 genome. We attempted to make this part as comprehensive as possible, requiring that the epitope be contained within a defined region of a maximum of 30 amino acids, but not that the optimal boundaries be defined. Studies that were based on the analysis of whole proteins are described at the end of each protein section. The same epitope can have multiple entries, as each entry represents a single publication in this part of the database. For more recent updates, epitope sequence alignments, and useful search capabilities, please see our web site: `http://www.hiv.lanl.gov/content/immunology`. For a concise listing of only the best defined CTL epitopes, see the summary by Nicole Frahm, Brett Baker and Christian Brander on page 3 in Part I of this compendium. CTL responses to proteins with no defined epitopes are listed at the end of each protein section.

Recent studies utilize multiple functions attributed to T cells to define responses, and the simple distinctions of cytotoxic T-cell and helper T-cells have become blurred as more is learned about the range of responses triggered in CD4 and CD8 positive T-cells responding to antigenic stimulus. When adding the most recent studies to the database, we have tried to place T cell responses in a reasonable manner into our traditional helper T cell and CTL parts, and to specify the assay used to measure the response in each study.

II-A-1 Epitope tables

Each CTL reference has a multi-part basic entry:

HXB2 location: The viral strain HXB2 (GenBank Accession Number K03455) is used as a reference strain throughout this publication. The position of the defined epitope location relative to the sequence of the HXB2 protein is indicated. The numbering in this table corresponds to the protein maps. Because of HIV-1 variation the epitope may not actually be present in HXB2; rather, the position in HXB2 indicates the position aligned to the epitope. HXB2 was selected as the reference strain because so many studies use HXB2, and because crystal structures for HXB2-related proteins are often available. The precise positions of an epitope on the HXB2 reference strain can be readily obtained using the interactive position locator at our web site: `http://www.hiv.lanl.gov/content/sequence/LOCATE/locate.html`.

Author location: The amino acid positions of the epitope boundaries and the reference sequence are listed as given in the primary publication. Frequently, these positions as published are imprecise, and do not truly correspond to the numbering of the sequence, but they provide a reasonable guide to the peptide's approximate location in the protein. Also, in many cases the reference sequence identification was not provided, and in such cases it is not possible to use these numbers to specify precise locations.

Epitope: The amino acid sequence of the epitope of interest as defined in the reference, based on the reference strain used in the study defining the epitope. On occasions when only the position numbers and not the actual peptide sequence were specified in the original publication, we tried to fill in the peptide sequence based on the position numbers and reference strain. If the sequences were numbered inaccurately by the primary authors, or if we made a mistake in this process, we may have misrepresented the binding site's amino acid sequence. Because of this uncertainty, epitopes that were not explicitly written in the primary publication, that we determined by looking up the reference strain and the numbered location, are followed by a question mark in the table.

Epitope name: If the epitope has a name attributed by the publication, it is recorded here, e.g. "SL9".

Subtype: The subtype under study, if specified in the primary publication; this is generally not specified for B subtype.

Immunogen: The antigenic stimulus of the CTL response. Often this is an HIV-1 infection. If a vaccine was used as the original antigenic stimulation, not a natural infection, this is noted, and additional information about the vaccine antigen is provided as available.

Species (MHC): The species responding and MHC or HLA specificity of the epitope.

Donor MHC: The HLA genotype of the individual that responded to the epitope.

Country: The country where the samples were obtained; this is generally not specified if the study was conducted in the United States.

Assay type: Assays used to characterize the response.

Keywords: Keywords are a searchable field for the web interface that is included in the T-cell sections of the printed version to help identify entries of particular interest.

Reference: The primary reference (sometimes two or more directly related studies are included). Details for some of the earlier references are in Part V.

Following the entry for a given CTL epitope brief comments explain the context in which the epitope was studied and what was learned about the epitope in a given study.

II-A-2 HIV protein epitope maps

All HIV CTL epitopes mapped to within a region of 14 amino acids or less are indicated on the HIV protein epitope maps. The location and HLA restriction elements of CTL epitopes are indicated on protein sequences of HXB2. These maps are meant to provide the relative location of defined epitopes on a given protein, but the HXB2 sequence may not actually carry the epitope of interest, as it may vary relative to the sequence for which the epitope was defined. Epitopes with identical boundaries and HLA fields are included in the maps only once. If one laboratory determines HLA presenting molecules at the serotype level (example: A2) and another at the genotype level (example: A*0201) both will be included in the map. MHC specificities are indicative of the host species; when no MHC presenting molecule is defined, the host species is noted.

II-A-3 Alignments

To conserve space, no epitope alignments are provided in this book, but they can be generated using the CTL epitope search tool at `http://www.hiv.lanl.gov/content/immunology`. The master protein sequence alignment files from which the epitope alignments were created are available at our web site at `http://www.hiv.lanl.gov/content/sequence/NEWALIGN/align.html`.

II-B

HIV CTL/CD8+ Epitope Tables

All HIV CTL epitopes are arranged by protein position. The table entries are sorted in a nested way—first by protein, then by HXB2 start location, and finally by HLA presenting molecule. CTL reactions against proteins with undefined epitopes are listed at the end of the protein that stimulated the response.

II-B-1 Gag p17 CTL/CD8+ epitopes

HXB2 Location p17 (1–10)
Author Location Gag
Epitope MGARASVLSG
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Thailand
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords optimal epitope
References Kantakamalakul *et al.* 2006

- T cell responses in CRF01_AE infected individuals from Thailand were studied.
- A single peptide elicited IFN-gamma responses from three subjects and may be an A*1101 binding peptide. It may contain a novel T cell epitope, MGARASVLSG.

HXB2 Location p17 (5–13)
Author Location Gag (5–13 SUMA)
Epitope ASVLSGGEL
Epitope name Gag AL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*1103, A*2402, B*1402, B*1501, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, acute/early infection, characterizing CD8+ T cells
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T-cell counts through 7 years of followup. In contrast to more rapid progressors WEAU and BORI, SUMA had a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only 4 epitopes acquired escape mutations in SUMA over time, and this was 1 of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

HXB2 Location p17 (5–15)
Author Location Gag (5–15)
Epitope ASILRGGKLDK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p17 (5–19)
Author Location p17 (5–19)
Epitope ASVLSGGELDRWEKI
Epitope name AI14
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, subtype comparisons, acute/early infection
References Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (ANC) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the

CTL CD8+

different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- This peptide, ASVLSGGELDRWEKI contains the CON clade-B putative epitope AI14. No cross-recognition of variants was seen across clades or intra-clade central sequences. Variant ASVLSGGkLDaWEKI was seen in clade A and M-group; variant ASiLrGGkLDkWEKI in clade C; ASVLSGGkLDkWEKI in clade-B ANC; and variant ASVLSGGELDkWEKI in clade-B COT.

HXB2 Location p17 (6–15)
Author Location Gag (Henan isolate)
Epitope SVLSGGQLDR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006
- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p17 (8–18)
Author Location Gag (8–18)
Epitope LSGGELDRWEK
Epitope name Gag 1.2
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade *HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu
Species (MHC) macaque
Assay type T-cell Elispot, Intracellular cytokine staining
Keywords subtype comparisons, variant cross-recognition or cross-neutralization, memory cells
References Amara *et al.* 2005
- A clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02_AG consensus Gag in macaques. The activity was better conserved for CD8 than CD4 T cells.
- All 5 CD8 and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation. The similar reported human epitope in this case is GELDRWEKI. HLA restriction: B*4002, B62
- Conservation across other clades: none. The form that is most common in CRF02, LSGGkLDaWEK, does not cross-react with the B clade elicited response.

HXB2 Location p17 (9–23)
Author Location
Epitope SGGELDRWEKIRLRP
Immunogen HIV-1 infection
Species (MHC) human (B44, B60)
Donor MHC A11, A2, B44, B60; A2, A24, B15, B40; A11, A2, B60, B7
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008
- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 3 (NIH ARRP Cat# 7874), SGGELDRWEKIRLRP, which contains epitopes restricted by HLA-B44 and -B60 in different patients elicited the following CTL responses: (1) > 1000 sfu/million PBMC for 22+ years in a living non-progressor (2) 18+ years in another living non-progressor and (3) 12+ years in a low-viremic non-progressor who succumbed to a non-AIDS death.

HXB2 Location p17 (11–19)
Author Location
Epitope GELDRWEKI
Epitope name Gag-GI9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*4002)
Donor MHC 01RCH46: A*0201, A*0217, B*0801, B*4002, Cw*0303, Cw*0701
Keywords HAART, ART
References Sabbaj *et al.* 2003
- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- This epitope was newly defined in this study.
- Patient 01RCH46 was Hispanic, on HAART, and had a viral load of 21000 and CD4 count of 623 – she also recognized KETINEEAA p24(70-78), HLA B*4002, and TAFTIPSI, RT(128-135), HLA A*0217.
- Among HIV+ individuals who carried HLA B40, 2/5 (40%) recognized this epitope.

HXB2 Location p17 (11–19)

Author Location p17 (11–19)
Epitope GELDRWEKI
Immunogen HIV-1 infection
Species (MHC) human (B*4002)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location p17 (11–19)
Author Location p17 (11–19)
Epitope GELDRWEKI
Epitope name GI9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B40)
Donor MHC A*30, B*18, B*40, Cw*02, Cw*05
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, acute/early infection, viral fitness and reversion
References Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- The escape variant geldrwKki was detected in 10/10 maternal clones from a B40-positive mother, but was absent in all sequences from her B40-negative infant, sampled at months 2, 4, and 11, suggesting either transmission of a minority wild-type variant, or rapid reversion in the absence of continued CTL pressure.
- geldrwKki elicted lower responder cell frequencies than GELDRWEKI.

HXB2 Location p17 (11–19)
Author Location p15
Epitope GELDRWEKI
Epitope name B40-GI9(p15)
Immunogen HIV-1 infection
Species (MHC) human (B40)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p17 (11–19)
Author Location p17
Epitope GQLDRWEKI
Epitope name GI9(p17)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope GQLDRWEKI elicited an immune response as part of peptide SGGQLDRWEKIRLRPGGK. This epitope differs from the previously described epitope, GELDRWEKI, at 1 residue, GqLDRWEKI.
- 1 of the 20 HLA-B40 carriers responded to GqLDRWEKI-containing peptide with a magnitude of CTL response of 50 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p17 (11–22)
Author Location Gag
Epitope GKLDSWEKIRLR
Subtype A, CRF02_AG, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide GKLDSWEKIRLR from subtypes CRF02_AG and A and to peptide GKLDaWEKIRLR from subtype CRF01_AE.

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HXB2 Location p17 (11–22)
Author Location Gag
Epitope GKLDAWEKIRLR
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide GKLDAWEKIRLR from subtype CRF01_AE, and to peptide GKLDsWEKIRLR of subtypes CRF02_AG and A.

HXB2 Location p17 (11–30)
Author Location Gag (11–30)
Epitope GELDRWEKIRLRPGGKKKYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62)
Donor MHC A2, A32, B27, B62
Assay type Chromium-release assay
Keywords genital and mucosal immunity
References Musey *et al.* 2003

- CTL clones from blood, semen, cervix and rectum samples from 12 individuals were compared. CTL clones derived from blood and mucosal samples had similar high lysis efficiency, primarily perforin dependent, and TCRβ VDJ region sequencing revealed cases of expansion of the same clone in different compartments.
- CD8+ T cell clones directed at this epitope were derived from blood and semen.

HXB2 Location p17 (12–21)
Author Location p17
Epitope ELDRWEKIRL
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B63)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This is a putative HLA B63 epitope containing the B58 supertype binding motif embedded in a reactive peptide. There is no evidence for B57/B58 cross-presentation of this epitope.

HXB2 Location p17 (13–27)
Author Location
Epitope LDRWEKIRLRPGGKK
Immunogen HIV-1 infection
Species (MHC) human (A3, B60)
Donor MHC A11, A2, B60, B7; A25, A3, B18, B27; A11, A2, B44, B60
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 4 (NIH ARRP Cat# 7875), LDRWEKIRLRPGGKK, which contains epitopes restricted by HLA-B60 and -A3 in different patients elicited the following CTL responses: (1) <100 sfc/ million PBMC in a living non-progressor for 22+ years; (2) in another living non-progressor from >1000 sfc/million PBMC at 12.5 years to <1000 sfc/million PBMC at 22+ years; and (3) only at year 12 post-infection in a low viremic non-progressor who succumbed to a non-AIDS death.

HXB2 Location p17 (16–30)
Author Location p17 (16–30 HXB2)
Epitope WEKIRLRPGGKKKYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.

- Responses to this peptide were detected in 19% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location p17 (17–31)
Author Location
Epitope EKIRLRPGGKKYKL
Immunogen HIV-1 infection
Species (MHC) human (B27, B7)
Donor MHC A2, A32, B44, B7; A25, A3, B18, B27
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 5 (NIH ARRP Cat# 7876), EKIRLRPGGKKYKL, which contains epitopes restricted by HLA-B7 and -B27 elicited the following CTL responses: (1) in a living non-progressor for 19+ years; (2) in another living non-progressor from >1000 sfc/million PBMC at 12.5 years to <1000 sfc/million PBMC at 22+ years.

HXB2 Location p17 (17–31)
Author Location p17 (17–31)
Epitope EKIRLRPGGKKKYKL
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008

- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.
- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.
- CTL immune response to consensus sequence EKIRLRPG-GKKKYKL was elicited in 2 subjects. Consensus epitopes of subject 0015 and of subject 0016 were the same as Clade B consensus.

HXB2 Location p17 (17–34)
Author Location p17
Epitope EKIRLRPGGKKKYKLKHI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, EKIRLRPGGKKKYKLKHI, had an overall frequency of recognition of 16.7% - 22% AA, 15.4% C, 15.9% H, 4.8% WI.

HXB2 Location p17 (18–26)
Author Location p17
Epitope KIRLRPGGK
Immunogen peptide-HLA interaction
Species (MHC) human (A*03)
Assay type Tetramer binding
Keywords binding affinity
References Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with

CTL CD8+

Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, KIRLRPGGK (MHC Class I restriction, serotype Bw6) complexed with MHC A03 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C.

HXB2 Location p17 (18–26)
Author Location p17 (18–26 IIIB)
Epitope KIRLRPGGK
Immunogen
Species (MHC) human (A*0301)
Keywords optimal epitope
References Llano *et al.* 2009
- C. Brander notes that this is an A*0301 epitope.

HXB2 Location p17 (18–26)
Author Location
Epitope KIRLRPGGK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords acute/early infection
References Wilson *et al.* 2000a
- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B2705; and A*0201, A*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK.
- The subject with A*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705.
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

HXB2 Location p17 (18–26)
Author Location p17 (18–26 SF2)
Epitope KIRLRPGGK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
References Altfeld *et al.* 2001a
- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- The reactive peptide p17 gag WEKIRLRPGGKKKYK contained two A*0301-restricted epitopes, KIRLRPGGK and RLRPGGKKK A*0301.

HXB2 Location p17 (18–26)
Author Location p17 (18–26)
Epitope KIRLRPGGK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords Th1, characterizing CD8+ T cells
References Kleen *et al.* 2004
- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8+ cells are found, each one constituting 30-40% of the CD8+ cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- Two of seven patients responded to this peptide with GzB producing cells, while none of the patients responded with IFN-gamma producing cells.

HXB2 Location p17 (18–26)
Author Location p17
Epitope KIRLRPGGK
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Donor MHC A*0101, A*0301, B*0801; A*0201, A*3101, B*3501, B*3905
Country United Kingdom
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords escape, acute/early infection, variant cross-recognition or cross-neutralization
References Milicic *et al.* 2005
- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. CTL escape variants were often transmitted. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient.
- A*0301 epitopes RLRPGGKKK and KIRLRPGGK, and B*0801 epitope GGKKKYRL, overlap. In 1 donor, the transmitted virus carried the escape form for 2 of these epitopes. The double substitution kirlrpggR results in escape from response in the donor. Similarly, the double substitution ggRkkyKl results in escape for this epitope.
- The escape mutation kirlrpggR in this epitope resulted in 74% reduction in HLA binding affinity. The other variant tested, kirlrQggR, resulted in 90% reduction.

HXB2 Location p17 (18–26)
Author Location Gag (Henan isolate)
Epitope KIRLRPGGK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p17 (18–26)
Author Location p17 (18–26 IIIB)
Epitope KIRLRPGGK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords responses in children, mother-to-infant transmission, escape
References Wilson *et al.* 1996

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.
- KIRLRPGGR and RIRLRPGGR, naturally occurring variants, were found in mother and are escape mutants.

HXB2 Location p17 (18–26)
Author Location p17 (18–26)
Epitope KIRLRPGGK
Immunogen in vitro stimulation or selection
Species (MHC) human (A3)
Keywords dendritic cells
References Zarling *et al.* 1999

- This study compares the ability of macrophages and dendritic cells to stimulate primary responses in CD8+ lymphocytes isolated from HLA-appropriate HIV-uninfected donors using peptide-pulsed APC – the dendritic cells performed better as APC for the stimulation of primary responses.
- Strong CTL responses were elicited by the epitopes DRFYKTLRA and GEIYKRWII when presented by either immature or mature dendritic cells – macrophages were not able to prime a CTL response against DRFYKTLRA.
- A weak response to KLTPLCVSL was stimulated using macrophages as the APC.
- No detectable response was observed for the following previously-defined HIV epitopes: KIRLRPGGK, ILKEPVHGV, IRLRPGGK, GPKVKQWPL.

HXB2 Location p17 (18–26)
Author Location Gag (18–26)
Epitope KIRLRPGGK
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Brodie *et al.* 1999

- The ability of CTL effector cells was studied by expanding autologous HIV-1 Gag-specific CTL *in vitro*, and adoptive transfer.
- The transferred CTLs migrated to the lymph nodes and transiently reduced circulating productively-infected CD4+ T cells, showing that CTL move to appropriate target sites and mediate anti-viral effects.

HXB2 Location p17 (18–26)
Author Location (18–26)
Epitope KIRLRPGGK
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Brodie *et al.* 2000

- Study tracks and quantifies *in vivo* migration of neo-marked CD8+ HIV-specific CTL.
- Adoptively transferred gene-marked HIV-specific CTL homed to specific lymph node sites, colocalizing within the parafollicular regions of the lymph node adjacent to cells expressing HIV tat-fusion transcripts, indicative of viral replication.
- The CTL clones expressed CCR5 and localized among HIV-1 infected cells expressing MIP-1alpha and MIP-1beta, CC-chemokines produced at sites of viral replication, suggesting a possible homing mechanism.
- This study provides a methodology for tracking and studying antigen specific CTL *in vivo*.

HXB2 Location p17 (18–26)
Author Location p17 (18–26 IIIB)
Epitope KIRLRPGGK
Immunogen HIV-1 infection
Species (MHC) transgenic mouse (A3)
Keywords responses in children, mother-to-infant transmission, escape
References Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- KIRLRPGGR and RIRLRPGGR were escape mutants.
- This epitope was recognized and many escape mutants were detected in an HLA A3 transmitting mother, and was recognized but invariant in an HLA A3 non-transmitting mother.

HXB2 Location p17 (18–26)
Author Location p17 (18–26 IIIB)
Epitope KIRLRPGGK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords review, escape
References Goulder *et al.* 1997e; Goulder *et al.* 1997a

- HLA-identical sibling hemophiliac brothers were both infected with the same batch of factor VIII. Goulder *et al.* [1997e] is a review of immune escape that summarizes this study.
- One had a response to this epitope, the other did not. They were tested 6-8 years after infection.

HXB2 Location p17 (18–26)

CTL CD8+

Author Location p17 (subtype B)
Epitope KIRLRPGGK
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A3)
References Kaul *et al.* 2000

- 11 of 16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8+ gamma-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T-cell epitopes: DTVLEDINL (3 individuals), SLYNTVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

HXB2 Location p17 (18–26)
Author Location p17 (SF2)
Epitope KIRLRPGGK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- WEKIRLRPGGKKKYKLK was the target of the dominant response in Caucasoids (38%) more frequently than non-Caucasoids (12%) – 7/10 that had a dominant response to this epitope were A3, and 5/7 targeted RLRPGGKKK while 2/7 targeted KIRLRPGGK.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

HXB2 Location p17 (18–26)
Author Location p17
Epitope KIRLRPGGK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords HAART, ART
References Seth *et al.* 2001

- CTL responses were studied by tetramer staining in 41 patients with combination therapy – activated CD8+ T-cells decline as the viral load drops in response to therapy, but the overall level of antigen-specific cells capable of differentiating into effectors stays constant and new epitopes may be recognized.

HXB2 Location p17 (18–26)
Author Location p17 (18–26 SF2)
Epitope KIRLRPGGK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A3+ individuals that had a CTL response to this epitope broken down by group: 3/7 group 1, 0/4 group 2, and 2/2 group 3.

HXB2 Location p17 (18–26)
Author Location p17 (18–26)
Epitope KIRLRPGGK
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A3)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- KIRLRPGGK is cross-reactive for A, B, and D clades.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location p17 (18–26)
Author Location p17 (JRCSF)
Epitope KIRLRPGGK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Severino *et al.* 2000

- Primary HLA-A3+ CD4+ and HLA-mismatched lymphocytes from uninfected donors were infected with JRCSF after isolation then cocultured with the A3-restricted CTL clone 11504/A7 specific for KIRLRPGGK, and viral inhibition was MHC-restricted.
- Primary monocytes and monocyte-derived DC were generated from the same donors, replication of HIV-1 in these cell types was less efficient than in lymphocytes and could also be inhibited by MHC-restricted CTL.
- DC-lymphocyte cluster cultures allowed vigorous viral replication and MHC-restricted CTL viral inhibition was blunted or lost depending on the ratio of DC to CD4+ lymphocyte in the culture.

HXB2 Location p17 (18–26)
Author Location p17 (18–26)
Epitope KIRLRPGGK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords rate of progression, acute/early infection

References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP).
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant.

HXB2 Location p17 (18–26)
Author Location p17
Epitope KIRLRPGGK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords dendritic cells
References Ostrowski *et al.* 2000

- The role of CD4+ T-cell help in expansion of virus-specific memory CTL was studied through co-culture *ex vivo*.
- Optimal expansion of HIV-1-specific memory CTL depended on CD4+ T cell help in 9 of 10 patients – CD40 ligand trimer (CD40LT) could enhance CTL in the absence of CD4+ T cell help to a variable degree in most of patients.
- Those CTL that didn't respond to CD40LT could expand with IL2 present, and IL15 produced by dendritic cells also contributes.
- The T-helper epitope used for CD4+ T-cell stimulation was the universal tetanus helper epitope TET830-843 (QYIKANSKFIGITE)

HXB2 Location p17 (18–26)
Author Location p17 (18–26)
Epitope KIRLRPGGK
Epitope name A3-KK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), immunodominance, acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 8/14 HLA-A3 positive individuals had detectable A3-restricted responses during acute infection. Only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 7/8 individuals with acute responses had specific responses for this epitope.
- KIRLRPGGK and RLRPGGKKK were the most commonly recognized HLA-A3 epitopes during acute infection, after 1 year of treatment, and after STI. RLRPGGKKK was immunodominant.

HXB2 Location p17 (18–26)
Author Location p17 (18–26)
Epitope KIRLRPGGK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epotopes, but this increased over time.

HXB2 Location p17 (18–26)
Author Location p17 (18–26 B consensus)
Epitope KIRLRPGGK
Epitope name KK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords epitope processing, immunodominance, escape, acute/early infection, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2004

- KK9 and RK9 overlap, are presented by HLA-A3, and are frequently immunodominant and involved in acute-phase primary responses. A mutation in the C-terminal flanking residue of KK9 (K to Q) (kirlrpkkg-Q) inhibits processing of the immunodominant gag KK9 epitope, resulting in rapid decline in the KK9 specific CD8+ T-cell response. At the same time it abrogates the response to RK9 through the embedded mutation rlrpggkQk. Transmission of this mutation to patients expressing HLA-A3 prevents acute-phase response to these epitopes, although the mutation can eventually revert to wild-type allowing a delayed response to the epitope.

HXB2 Location p17 (18–26)
Author Location p17
Epitope KIRLRPGGK
Epitope name KK9
Immunogen HIV-1 infection

CTL CD8+

Species (MHC) human (A3)
Keywords review, epitope processing, escape
References Goulder & Watkins 2004

- This paper is a review of the role of CTL in HIV infection, and it uses KK9 as an example of an epitope that escapes due to a mutation beyond the epitope on the C-terminal side that probably affects proteasomal processing.

HXB2 Location p17 (18–26)
Author Location (B consensus)
Epitope KIRLRPGGK
Epitope name KK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, B14, B60, Cw3, Cw7
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- One of nine individuals recognized this epitope.

HXB2 Location p17 (18–26)
Author Location p17
Epitope KIRLRPGGK
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A3)
Donor MHC A01, A03, B39, B44, Cw4, Cw6
Assay type T-cell Elispot
Keywords HIV exposed persistently seronegative (HEPS)
References Missale *et al.* 2004

- HIV-specific T-cell response was tested in patients exposed to blood from a patient with highly replicating HIV; these patients were nosocomially infected with HBV, but uninfected with HIV. HIV-specific T-cell responses were directed to structural and non-structural HIV proteins in 2 patients, suggesting that the virus replicated in these patients sufficiently to prime a cell-mediated immune response that protected them from HIV infection.
- This patient responded to 3/11 HIV epitopes tested in an IFNgamma EliSpot assay. Responses were detected 16 and 20 weeks after exposure, but were lost by week 80.

HXB2 Location p17 (18–26)
Author Location Gag (18–26)
Epitope KIRLRPGGK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location p17 (18–26)
Author Location p24
Epitope KIRLRPGGK
Epitope name KK9
Immunogen
Species (MHC) (A3)
Keywords review, immunodominance, acute/early infection, kinetics, viral fitness and reversion
References Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

HXB2 Location p17 (18–26)
Author Location p17 (18–26)
Epitope KIRLRPGGK
Epitope name KR9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A*03, A*31, B*08, B*15, Cw*04, Cw*07
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, acute/early infection, viral fitness and reversion
References Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- The escape variant kirlrpggR was present in 10/10 clones from an A3+ mother, was transmitted to her infant,and present in 10/10 clones at months 2 and 4, but decreased to 0/10 clones by 15 months of age in her A3- child.

HXB2 Location p17 (18–26)

Author Location p17
Epitope KIRLRPGGK
Epitope name A3-KK9(p17)
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p17 (18–26)
Author Location p17 (18–28 B1 and B2)
Epitope KIRLRPGGK
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A3, A32, B62, B8, Cw3
Country Netherlands
Assay type Other
Keywords subtype comparisons, computational epitope prediction, superinfection
References Kozaczynska *et al.* 2007

- The influence of superinfection upon changes in HIV-1 strains was studied in a triple infected subject. While continuous expression of all three strains was observed, the LTR promoters of subtype AE had highest activity of all 3 strains, and subtype B2 had the lowest. Env-V3 sequences were present in higher numbers in strains B2 and CRF01_AE. Recombination was seen between viruses B1/B2 in gag and vpr genes.
- This HLA-A03 restricted epitope, KIRLRPGGK, is the dominant gag epitope in Caucasians and varied to KIRLRPGGr or KIRLRPGGs. Mutant KIRLRPGkK was found at 42% in strain B1 after 4 years while mutant KIRLRPGGs was found in 100% of B2 after 3 years. Though the infecting variant in CRF01_AE was KIRLRPGGq, no changes were seen in it with time.

HXB2 Location p17 (18–26)
Author Location p17 (18–26 SF2, HXBc2/Bal R5)
Epitope KIRLRPGGK
Epitope name KK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A2, A3, B15, B7, Cw3, Cw6; A29, A3, B44, B7, Cw3, Cw7; A24, A3, B7, B8, Cw7
Country United States
Assay type Cytokine production, Flow cytometric T-cell cytokine assay, Degranulation, CD107a and b cell surface mobilization
Keywords supervised treatment interruptions (STI), variant cross-recognition or cross-neutralization, characterizing CD8+ T cells, drug resistance
References Daucher *et al.* 2008

- A detailed analysis of 6 chronically infected patients' CTL responses to autologous virus was performed after ART and SIT (structured interruption of therapy). Qualitative responses including degranulation and production of IFN-gamma, MIP-1beta, TNF-alpha, IL-2, but not memory CD27, CD45RO and CD57 T cells correlated with extended low plasma viremia. Frequency and breadth of CTL response as well as immune escape did not influence virological outcome.
- One patient exhibited drug resistance mutations K170R (to NNRTI efavirenz) and D76N, K70R (to NRTIs).
- Autologous epitopes were preferentially recognized over optimal, consensus sequences.
- Patients with favorable virological outcomes demonstrated CTL recognition within multiple, conserved regions of Gag and Nef.
- Patients with poor virological outcomes recognized optimal epitopes with much lower frequencies, though this was not significant.
- HLA-A3-restricted epitope, KIRLRPGGK, elicited a response in 3 patients and is found in Gag immunodominant regions WEKIRLRPGGKKKYKL, WEKIRLRPGGKKKYK or LDRWEKIRLRPGGKKKYKL. The autologous sequence in one patient was KIRLRPGGr.
- In a patient who had one of the lowest viremias, the highest frequency of CTL response was to 2 immunodominant regions in Gag containing epitopes KK9, RK9 (RLRPGGKKK) and p17 RPGGKKKYK.

HXB2 Location p17 (18–26)
Author Location p17
Epitope KIRLRPGGK
Epitope name KK9(p17)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.

CTL CD8+

- Although the tested peptide sequence, SGGQLDRWEKIRL-RPGGK, contains the exact sequence of a previously described HLA-A3 optimal epitope, KIRLRPGGK, none of the 3 HLA-A3 carriers responded to it (author communication and Fig.1).

HXB2 Location p17 (18–26)
Author Location p17 (18–26)
Epitope KIRLRPGGK
Immunogen HIV-1 infection
Species (MHC) human (A*0301, A3, B27)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p17 (18–26)
Author Location p17 (18–26)
Epitope KIRLRPGGK
Epitope name A3-KK9 Gag
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords epitope processing, supervised treatment interruptions (STI), escape, early treatment, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response. This epitope did not vary, although the response declined over time. The authors suggest this might be due to a downstream Arg -> Thr substitution at C+2 that may impair processing.

HXB2 Location p17 (18–26)
Author Location p17 (18–26)
Epitope KIRLRPGGK
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101, A*0301, B*0801; A*0201, A*3101, B*3501, B*3905
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate escape rate for this epitope, KIRLRPGGK, was 0.002 (SE 0.006), and best estimate reversion rate was 0/day with a SE of 0.
- The variant K26R confers escape in A*0301+ individuals. On transmission to an HLA A*0301-negative recipient, the mutation did not revert to wild type over a period of 1 year.

HXB2 Location p17 (18–26)
Author Location Gag
Epitope KIRLRPGGK
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Garrison *et al.* 2007

- The study examined the influence of HIV-1 infection on human endogenous retroviruses (HERVs) activity and explored T cells cross-reactivity in regions of HIV-1/HERV similarity.
- T cell responses to HERV peptides were identified in HIV-1 positive individuals. There was an inverse correlation between anti-HERV T cell responses and HIV-1 viral load.
- HIV-1 epitope KIRLRPGGK has a corresponding HERV peptide KIRLPPGYF. These 2 peptides were used in measuring IFN-γ ELISPOT responses in HIV-1-positive and -negative individuals.

HXB2 Location p17 (18–26)
Author Location p17 (18–26)
Epitope KIRLRPGGK
Epitope name KK9
Subtype A1
Immunogen HIV-1 infection
Species (MHC) human
Country Kenya
References Peters *et al.* 2008a

- Gag sequences from 468 HIV-1 positive sex workers from the Kenyan Pumwani cohort were analyzed to bioinformatically identify positively selected residues that could be related to antigen processing. Mutation effects on disease progression were followed by mean CD4 counts. This method is also one way of identifying potential CTL epitopes and classifying them.
- A Gag positive selection map was generated and sites were classified as beneficial or harmful to HIV. They were correlated to antigen processing (proteasomal cleavage), antigen presentation (TAP transport efficiency) and T-cell receptor binding.
- p17 and p24's structural constraints limited their diversity, while p7-p1-p6 showed a higher average entropy.
- Epitope KK9, KIRLRPGGK, is known to bind HLA-A*0301.

HXB2 Location p17 (18–27)

Author Location (C consensus)
Epitope KIRLRPGGKK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p17 (18–27)
Author Location Gag
Epitope KIRLRPGGKK
Epitope name 1272
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for KIRLRPGGKK: 36%. This epitope has been previously reported to be presented by A3, B27, B62, Bw62 and is an A11 binder, but was not confirmed as a CTL target in this study.

HXB2 Location p17 (18–27)
Author Location Gag (Henan isolate)
Epitope KIRLRPGGKK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p17 (18–27)
Author Location p17 (18–27)
Epitope KIRLRPGGKK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong T-helper cell responses. Only patients starting with moderately high viral load (VL) were able to reduce the VL set point. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up.
- 8/14 patients recognized this epitope.

HXB2 Location p17 (18–27)
Author Location p17 (18–27 LAI)
Epitope KIRLRPGGKK
Subtype B
Immunogen
Species (MHC) human (B27)
References Brander & Walker 1996

- D. Lewinsohn, pers. comm.

HXB2 Location p17 (18–27)
Author Location p17 (18–27)
Epitope KIRLRPGGKK
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Birk *et al.* 1998b

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

HXB2 Location p17 (18–27)
Author Location Gag
Epitope KIRLRPGGKK
Epitope name KK10
Immunogen HIV-1 infection
Species (MHC) human (B27)
Assay type Other
Keywords rate of progression, escape
References Gao *et al.* 2005b

CTL CD8+

- Three distinct HLA alleles known to alter the rate of AIDS progression were studied. B*57-mediated protection occurs early in infection and the protective effect of this allele subsides after CD4 cell count drops. In contrast, B*27 shows no protection against progression to CD4<200, but rather delays progression to an AIDS-defining illness after the CD4 counts have dropped. B*35-mediated rapid progression to AIDS is probably a function of early decline in CD4 counts.
- KK10 escape occurs late and was shown to precede a sharp increase in viral load. The authors hypothesize the B27 benefit may arise due to enduring HLA restriction after escape from many other allotype responses has occurred.

HXB2 Location p17 (18–27)
Author Location Gag
Epitope KIRLRPGGKK
Epitope name KK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- KK10(Gag-p17, 18-27), KIRLRPGGKK, is a known HLA-B27-restricted epitope used as a positive control for eliciting CTL IFN-gamma response.

HXB2 Location p17 (18–31)
Author Location p17 (18–31)
Epitope KIRLRPGGKKKYKL
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Birk *et al.* 1998b

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

HXB2 Location p17 (18–31)
Author Location p17 (18–31)
Epitope KIRLRPGGKKKYKL
Immunogen HIV-1 infection
Species (MHC) human (B62)
References Lubaki *et al.* 1997

- 82 HIV-1-specific CTL clones from 5 long-term non-progressors were isolated and analyzed for breadth of CTL response.
- A sustained Gag, Env and Nef response was observed, and clones were restricted by multiple HLA epitopes, indicating a polyclonal response.
- A subject who was HLA-B62+ had CTL that recognized this peptide, and p24 LGLNKIVRMYS, and one additional unknown epitope.

HXB2 Location p17 (18–32)
Author Location Gag (17–31)
Epitope KIRLRPGGKKKYKLK
Epitope name KK15
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- One subject responded to peptide KK15 which had a K26R mutation, KIRLRPGGKrKYKLK, in a minority of plasma virus clones.

HXB2 Location p17 (18–42)
Author Location p17 (18–42 IIIB)
Epitope KIRLRPGGKKKYKLKHIVWASRELE
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Jassoy *et al.* 1992

- Epitope recognized by CTL clone derived from CSF.

HXB2 Location p17 (18–42)
Author Location p17 (18–42 PV22)
Epitope KIRLRPGGKKKYKLKHIVWASRELE
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Jassoy *et al.* 1993

- HIV-1 specific CTLs release γ-IFN, and α- and β-TNF.

HXB2 Location p17 (18–42)
Author Location p17 (18–42 BH10)
Epitope KIRLRPGGKKKYKLKHIVWASRELE
Immunogen HIV-1 infection
Species (MHC) human (B62)
References Johnson *et al.* 1991

- Gag CTL response was studied in three individuals.

HXB2 Location p17 (19–27)
Author Location p17 (19–27 JRCSF)
Epitope IRLRPGGKK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*2705)
Keywords optimal epitope

References Llano *et al.* 2009

- Noted by Brander to be B*2705.

HXB2 Location p17 (19–27)
Author Location
Epitope IRLRPGGKK
Immunogen HIV-1 infection
Species (MHC) human (B*2705)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope IRLRPGGKK elicited a magnitude of response of 520 SFC with a functional avidity of 0.5nM.

HXB2 Location p17 (19–27)
Author Location p17 (19–27 LAI)
Epitope IRLRPGGKK
Subtype B
Immunogen
Species (MHC) human (B27)
References Brander & Walker 1996

HXB2 Location p17 (19–27)
Author Location p17 (19–27 JRCSF)
Epitope IRLRPGGKK
Subtype B
Immunogen HIV-1 infection
Species (MHC) scid-hu mouse (B27)
Keywords escape
References McKinney *et al.* 1999

- Epitope-specific CTL were infused in infected human PBL-SCID mice, and transient decreases in viral load were observed, however virus was not eradicated and the HIV-specific CTL rapidly disappeared.
- No escape mutants were observed.
- Control CTL were long lived in both infected and uninfected mice, showing the rapid loss of CTL was due to target interaction.

HXB2 Location p17 (19–27)
Author Location p17 (SF2)
Epitope IRLRPGGKK
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- WEKIRLRPGGKKKYKLK was the target of the dominant response in Caucasoids (38%) more frequently than non-Caucasoids (12%) – 2/3 individuals that were B27+ had a dominant response to this epitope.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

HXB2 Location p17 (19–27)
Author Location p17 (19–27)
Epitope IRLRPGGKK
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Day *et al.* 2001

HXB2 Location p17 (19–27)
Author Location p17 (19–27)
Epitope IRLRPGGKK
Epitope name IK9
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords immunodominance, escape
References Goulder *et al.* 2001b

- This B27 epitope is generally recognized only if there is escape in the B27 dominant epitope, p24 KRWIILGLNK.

HXB2 Location p17 (19–27)
Author Location Gag
Epitope IRLRPGGKK
Epitope name IK9
Immunogen HIV-1 infection
Species (MHC) human (B27)
Donor MHC A26, B27
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, rate of progression, immunodominance, escape
References Feeney *et al.* 2004

- Viral load in a perinatally infected child remained low until emergence of an escape variant (kTwiilglnk) in the immunodominant CTL epitope KRWIILGLNK when the child was 7.4 years old. The emergence of this escape mutation was followed by an increase in viremia and an increase in the number of targeted CTL epitopes, measured again when the child was 9.2 years old. A low level response to IK9 was the only other epitope recognized prior to the loss of immune control and broadening of the response, and was detected in the 7.4 year sample.

HXB2 Location p17 (19–27)
Author Location p17 (19–27)
Epitope IRLRPGGKK
Immunogen HIV-1 infection

CTL CD8+

Species (MHC) human (B27)
Donor MHC A1, A3, B35, B8
Country United States
Assay type Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, escape, variant cross-recognition or cross-neutralization
References Casazza *et al.* 2005

- Evidence of continued viral evolution during HAART therapy despite low viral load was found in 1/5 patients studied.
- The dominant viral sequence was irlrpggRk, found in 12/15 clones, while the screening sequence IRLRPGGKK was found in 3/15 clones. The least frequent variant stimulated the strongest response.
- IRLRPGGKK was previously characterized as a B27 optimized epitope, which is a mismatch with patient's HLA.

HXB2 Location p17 (19–27)
Author Location p17
Epitope `IRLRPGGKK`
Epitope name IK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords superinfection
References Streeck *et al.* 2008b

- Loss of viral replication control by an elite controller after superinfection was found to coincide with rapid recombination events in 2, ∼50 residue regions of Gag and Env that include immunodominant epitopes KK10 (KRWIILGLNK) and CL9 (CAPAGFAIL). Viral escape was seen at both epitopes and consequent CTL responses against the epitope-variants.
- CTL responses to previously described HLA-B27-restricted IRLRPGGKK, were seen post-superinfection and -recombination.

HXB2 Location p17 (19–27)
Author Location
Epitope `IRLRPGGKK`
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* Other *HIV component:* gp160
Species (MHC) human
Donor MHC A3, A33; B15 (63), B27
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location p17 (19–28)
Author Location Gag
Epitope `IRLRPGGKKK`
Epitope name 1271
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A11, A3, B62)
Donor MHC A03, A11, B14, B51, Cw08, Cw13
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for IRLRPGGKKK:43% Promiscuous epitope binding to A03, B62, Bw62 and A11.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope `RLRPGGKKK`
Immunogen HIV-1 infection
Species (MHC) human (A*03)
Keywords review, escape
References Goulder *et al.* 1997e; Goulder *et al.* 1997a

- HLA-identical sibling hemophiliac brothers were both infected with the same batch of factor VIII.
- They were tested 6-8 years after infection. One had a response to gag A3 epitope RLRPGGKKK, the other non-responder carried the sequence RLRPGGKKC.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope `RLRPGGKKK`
Epitope name RK9
Subtype A1
Immunogen HIV-1 infection
Species (MHC) human (A*03)
Country Kenya
Keywords epitope processing, escape
References Peters *et al.* 2008a

- Gag sequences from 468 HIV-1 positive sex workers from the Kenyan Pumwani cohort were analyzed to bioinformatically identify positively selected residues that could be related to antigen processing. Mutation effects on disease progression were followed by mean CD4 counts. This method is also one way of identifying potential CTL epitopes and classifying them.
- A Gag positive selection map was generated and sites were classified as beneficial or harmful to HIV. They were correlated to antigen processing (proteasomal cleavage), antigen presentation (TAP transport efficiency) and T-cell receptor binding.
- p17 and p24's structural constraints limited their diversity, while p7-p1-p6 showed a higher average entropy.
- HLA-A*03-restricted epitope, RLRPGGKKK, contained a positive selection at K28Q i.e. RLRPGGKKq (RQ9), a probable proteasome escape variant. 2 possible TAP escape mutants were seen at R20Q to qLRPGGKKK (QK9) and K28Q to RLRPGGKKq (RQ9 - see above), both of which had decreased TAP binding affinity. Mutant RQ9 is also suspected to reduce recognition of peptide to HLA-A*0301.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope RLRPGGKKK
Epitope name RK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*03)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-A*03-associated substitution within optimally defined epitope RLRPGGKKK is at position K9, RLRPGGKKk.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope RLRPGGKKK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an A*0301.

HXB2 Location p17 (20–28)
Author Location p17
Epitope RLRPGGKKK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords acute/early infection
References Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B2705; and A*0201, A*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK.
- The subject with A*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705.
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

HXB2 Location p17 (20–28)
Author Location p17 (20–28 SF2)
Epitope RLRPGGKKK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
References Altfeld *et al.* 2001a

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- The reactive peptide p17 gag WEKIRLRPGGKKKYK contained two A*0301-restricted epitopes, KIRLRPGGK and RLRPGGKKK A*0301.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope RLRPGGKKK
Epitope name RK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Donor MHC A11, A3, B35, B51
Keywords mother-to-infant transmission
References Sabbaj *et al.* 2002

- IFNgamma T-cell responses in breast milk of 5 HIV-1 infected women from the US and 6 from Zambia were tested using Elispot. 11/11 women responded to Gag, 8/11 responded to Pol, 7/11 women to Nef, and 2/5 women to Env peptide pools. These responses were shown to be primarily due to CD8+ T-cells in one woman, and another woman had cytolytic responses measured by Cr-release.

CTL CD8+

- Tetramer analysis of breast milk and peripheral blood samples of one volunteer showed responses to RLRPGGKKK in both compartments, 0.65% of CD3+/CD8+ cells in breast milk, and 0.22% of CD3+/CD8+ cells in peripheral blood cells.
- The frequencies of responses in the two compartments differed, and 2/4 women who responded to epitopes in Nef 101-205 and Pol 601-710 showed responses in breast milk but no detectable responses in peripheral blood cells.

HXB2 Location p17 (20–28)
Author Location Gag (20–28)
Epitope RLRPGGKKK
Epitope name RK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Donor MHC A*0201, A*0301, B*3501, B*51, Cw*04, Cw*06
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords escape, acute/early infection, characterizing CD8+ T cells
References Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- rlrpggkkQ escape mutant showed drastically reduced avidity. The response to this peptide was not apparent until month 20, by month 32 the escape variant was present.

HXB2 Location p17 (20–28)
Author Location p17
Epitope RLRPGGKKK
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Donor MHC A*0101, A*0301, B*0801; A*0201, A*3101, B*3501, B*3905
Country United Kingdom
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords escape, acute/early infection, variant cross-recognition or cross-neutralization
References Milicic *et al.* 2005

- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. CTL escape variants were often transmitted. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient.
- Certain escape mutations in RLRPGGKKK, rlrpggkkQ, rlrpggkkR and rlrpggkkT, resulted in nearly complete reduction in binding affinity for A*0301. The form that was transmitted in one of the donor pairs was rlrpggRkk, and it binds to A*0301 with comparable affinity to RLRPGGKKK. However, an escape variant was on the rise in the donor near the time of transmission, rlrpggRkT, which eventually came to fixation in the donor, illustrating the importance of the timing of transmission regarding which variant is transmitted.
- A*0301 epitopes RLRPGGKKK and KIRLRPGGK, and B*0801 epitope GGKKKYRL, overlap. In 1 donor, the transmitted virus carried the escape form for 2 of these epitopes. The double substitution kirlrpggR results in escape from response in the donor. Similarly, the double substitution ggRkkyKl results in escape for this epitope.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope RLRPGGKKK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Donor MHC A*0101, A*0301, B*0801
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, RLRPGGKKK, was found to be 0.032/day, with SE of 0.008.
- The K28T substitution conferred escape from CTL responses of both the RLRPGGKKK and GGKKKYRL epitopes.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope RLRPGGKKK
Epitope name RLR
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells
References Turnbull *et al.* 2006

- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.
- This epitope, A3-RLR (that has no assoication with accelerated or delayed progression to AIDS) and its natural variants are not cross-recognized. Its alanine-substituted variants were extremely inconsistent between individuals showing very efficient or poor cross-reactivity.

HXB2 Location p17 (20–28)
Author Location p17
Epitope RLRPGGKKK
Immunogen
Species (MHC) human (A*0301)
References Zimbwa *et al.* 2007

- E169D is a processing mutation for HLA-B*0702 restricted SPAIFQSSM (SM9) as well as an epitope variation for HLA-A*0301 restricted MTKILEPFR (MR9).
- CTL recognition of p17 Gag RLRPGGKKK was detected post-infection with either wild type (169E) or mutant 169D HIV-1.

HXB2 Location p17 (20–28)
Author Location Gag (Henan isolate)
Epitope RLRPGGKKK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope RLRPGGKKK
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Goulder *et al.* 2000c

- Two clonal CTL responses were generated in donor 021-BMC (HLA A3/3001, B42/-, Cw17/-) against different optimal versions of this epitope, one nine amino acids long, one ten.
- A previously described optimal A3 epitope overlapping this region, KIRLRPGGK, was not recognized by CTL from 021-BMC.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope RLRPGGKKK
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Goulder *et al.* 1997f

- A control CTL line that reacts with this peptide was included in the study.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope RLRPGGKKK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords subtype comparisons
References Cao *et al.* 1997a

- The consensus peptide of A, B, and D clade viruses is RLRPGGKKK.
- The consensus peptide of C clade viruses is RLRPGGKKH and is equally reactive.

HXB2 Location p17 (20–28)
Author Location p17 (SF2)
Epitope RLRPGGKKK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- WEKIRLRPGGKKKYKLK was the target of the dominant response in Caucasoids (38%) more frequently than non-Caucasoids (12%) – 7/10 that had a dominant response to this epitope were A3, and 5/7 targeted RLRPGGKKK while 2/7 targeted KIRLRPGGK.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

HXB2 Location p17 (20–28)
Author Location p17 (20–28 SF2)
Epitope RLRPGGKKK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.

CTL CD8+

- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with preseroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A3+ individuals that had a CTL response to this epitope broken down by group: 5/7 group 1, 2/4 group 2, and 2/2 group 3.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope RLRPGGKKK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope RLRPGGKKK
Epitope name RK9
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords acute/early infection
References Goulder *et al.* 2001b

- Responses to this dominant A3-restricted Gag epitope are present during the time of decreasing viral load in acute infection.
- Mutations in this epitope were observed in autologous clones of subjects who were A3-positive with a higher frequency than those who were A3-negative (P = 0.0002)
- These mutations are being sexually transmitted in adult infections.

HXB2 Location p17 (20–28)
Author Location
Epitope RLRPGGKKK
Epitope name Gag-RK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A03, 7/20 (35%) recognized this epitope.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope RLRPGGKKK
Epitope name A3-RK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), immunodominance, acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06 was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 8/14 HLA-A3 positive individuals had detectable A3-restricted responses during acute infection. Only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 7/8 individuals with acute responses had specific responses for this epitope.
- KIRLRPGGK and RLRPGGKKK were the most commonly recognized HLA-A3 epitopes during acute infection, after 1 year of treatment, and after STI. RLRPGGKKK was immunodominant during acute infection and throughout the study period in the 5/6 individuals who targeted it.

HXB2 Location p17 (20–28)
Author Location Gag (LAI)
Epitope RLRPGGKKK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords class I down-regulation by Nef
References Lewinsohn *et al.* 2002

- CTL kill targets through releasing perforin, that forms pores in the plasma membrane, and granzymes, that induce apoptosis.
- Vpr is capable of arresting infected cells in the G2 phase, and it was hypothesized that Vpr may inhibit CTL-mediated apoptosis because it interacts with the granzyme B molecular complex.
- Vpr expression in the target cell did not inhibit epitope specific lysis – neither perforin or granzyme mediated events were inhibited, as measured by a Chromium release assay and a TUNEL assay.
- In contrast, deletion of Nef, which is thought to protect primary HIV infected cells by down-regulating cell-surface expression of MHC class I complexes, increased the susceptibility of HIV-1 infected cells to CTL mediated killing 2-fold using the TUNEL assay.

HXB2 Location p17 (20–28)
Author Location p17
Epitope RLRPGGKKK
Subtype B

Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A11, A3, B35, B51
Keywords mother-to-infant transmission
References Sabbaj *et al.* 2002

- IFNgamma T-cell responses in breast milk of 5 HIV-1 infected women from the US and 6 from Zambia were tested with using Elispot. 11/11 women responded to Gag, 8/11 responded to Pol, 7/11 women to Nef, and 2/5 women to Env peptide pools. These responses were shown to be primarily due to CD8+ T-cells in one woman, and another woman had cytolytic responses measured by Cr-release.
- T-cells in breast milk from a volunteer who was HLA A3, A11, B35, B51 induced IFNgamma after stimulation with a peptide that carries known A3 epitope RLRPGGKKK.
- The frequencies of responses in the two compartments differed, and 2/4 women that responded to epitopes in Nef 101-205 and Pol 601-710 showed responses in breast milk but no detectable responses in peripheral blood cells.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope RLRPGGKKK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A*0201, A3, B44, B57, Cw5, Cw6; A1, A3, B14, B7, Cw*0702, Cw*0802; A1, A3, B35, B8; A1, A3, B62, B8, Cw3, Cw7
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- This epitope was recognized in four individuals during early infection, each time presented by A3.
- All HIV-1 proteins except Vpu were recognized, and responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope RLRPGGKKK
Epitope name A3-RK9 Ga9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), escape, early treatment, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The second infecting strain had the variant rlrpggkkT. The CTL response declined over time, and the response to the second variant was lower than to the first one throughout.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope RLRPGGKKK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 5 epitopes from this individual that varied over time where the internal mutations became fixed; 4/5 epitopes (all except p17 RLRPGGKKK, this eptiope) showed a dramatic decrease in CTL activity against the wild type epitope as the mutation arose. The rlrpggkkR variant was found at 47 and 120 months post-seroconversion.

HXB2 Location p17 (20–28)
Author Location Gag
Epitope RLRPGGKKK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords HIV exposed persistently seronegative (HEPS)
References Koning *et al.* 2004

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A*11, A*31 and Cw*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.

CTL CD8+

- 0/5 HLA A3+ infection-resistant men, and 0/3 pre-seroconversion men who went on to become infected, reacted to this epitope.

HXB2 Location p17 (20–28)
Author Location Gag (20–28)
Epitope RPRPGGKKK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type Cytokine production, proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, memory cells, characterizing CD8+ T cells
References Daniel *et al.* 2004

- CD4+ and CD8+ responses in chronically HIV-1 infected patients on HAART were weak with decreased polyclonality. Only 33% of patients had CD4+ T-cells that could proliferate, and only 22% had HIV-specific CD8+ T-cell responses, and those rare responses showed low perforin levels and persistent expression of CD27, indicating incomplete differentiation and loss of lytic function.

HXB2 Location p17 (20–28)
Author Location p17 (20–28 B consensus)
Epitope RLRPGGKKK
Epitope name RK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords immunodominance, escape, acute/early infection, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2004

- KK9 and RK9 overlap, are presented by HLA-A3, and are frequently immunodominant and involved in acute-phase primary responses. A mutation in the C-terminal flanking residue of KK9 (K to Q) (kirlrpkkg-Q) inhibits processing of the immunodominant gag KK9 epitope, resulting in rapid decline in the KK9 specific CD8+ T-cell response. At the same time it abrogates the response to RK9 through the embedded mutation rlrpggkQk. Transmission of this mutation to patients expressing HLA-A3 prevents acute-phase response to these epitopes, although the mutation can eventually revert to wild-type allowing a delayed response to the epitope.

HXB2 Location p17 (20–28)
Author Location (B consensus)
Epitope RLRPGGKKK
Epitope name RK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A02, A03, B08, B62, Cw10, Cw7; A01, A03, B08, B14, Cw7, Cw8
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 2/9 individuals recognized this epitope, presented by HLA-A3.

HXB2 Location p17 (20–28)
Author Location Gag
Epitope RLRPGGKKK
Epitope name RK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 9, rrlpggkkR, was found in the most polymorphic residue in the epitope.This was shared between clades B and C.

HXB2 Location p17 (20–28)
Author Location Gag (20–28 BRU)
Epitope RLRPGGKKK
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 0/9 CRF02_AG-infected Ivorians, and 2/9 B-infected French subjects.

HXB2 Location p17 (20–28)
Author Location p24
Epitope RLRPGGKKK
Epitope name RK9

Immunogen
Species (MHC) (A3)
Keywords review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion
References Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

HXB2 Location p17 (20–28)
Author Location p17
Epitope RLRPGGKKK
Epitope name A3-RK9(p17)
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope RLRPGGKKK
Epitope name RK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, subtype comparisons, acute/early infection
References Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (ANC) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- Epitope sequences for this eptiope, RK9 are invariant between CON B, COT B, ANC B and M-group. Cross-recognition is seen with both C- and A-clades. Anchor residues are at positions 2 and 9; while the C-clade variant contains a change at position 9 to RLRPGGKKh. Typically, magnitude and avidity of binding for T-cell responses were much lower to the C-clade variant. HLA-A03 restriction was inferred based on 5 subjects possessing appropriate HLA class I allele and prior publication.

HXB2 Location p17 (20–28)
Author Location
Epitope RLRPGGKKK
Epitope name RK9
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location p17 (20–28)
Author Location p15
Epitope RLRQGGKKK
Epitope name RK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.

- 3 untreated patients with HIV epitope RLRPGGKKK variations to RLRPGGKKr, RLRPGGKKt and RLRPGGKKq after 350, 405 and 68 days. In addition, a 4th patient carried variant RLRqGGrKK which did not alter in time.
- Surprisingly, after first testing, the epitope RLRPGGKKK went from monofunctional to dual- and triple-functional in the response it was able to elicit. Previously published HLA-restriction for RK9 is HLA-A3.

HXB2 Location p17 (20–28)
Author Location Gag
Epitope RLRPGGKKK
Epitope name 1332
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A*0301, A3, B42, B62)
Donor MHC A03, A23, B49, B57; A03, A24, B27, B57, Cw13, Cw18; A03, A26, B08, B52
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction, immunodominance, cross-presentation by different HLA
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for RLRPGGKKK: 34% Promiscuous epitope binding to A03, A0301, B62,Bw62, B42. Immunodominant epitope.

HXB2 Location p17 (20–28)
Author Location Gag (20–28)
Epitope RLRPGGKKK
Immunogen peptide-HLA interaction
Species (MHC) (A3, A30, A31, A68)
Assay type HLA binding
Keywords binding affinity, immunodominance
References Racape *et al.* 2006

- Interaction between purified HLA-A3 molecules and several dominant CD8 epitopes was characterized. Amplitude, stability, and kinetic parameters of the interaction between HLA-A3, peptides, and anti-HLA mAbs were tested.
- Epitopes tested bound strongly to HLA-A3 and formed very stable complexes.
- Gag epitope RLRPGGKKK and Nef epitope RLAFHHVAR complexes with HLA-A3 were not recognized by the A11.1 mAb specific to HLA-A3 alleles. The proposed explanation was that Arg at position P1 of the peptide may push the α2 helix residue and affect mAb recognition.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope RLRPGGKKK
Immunogen HIV-1 infection
Species (MHC) human (A3, A30, B42, B62)
Donor MHC A2, A31, B51, B58w4
Country United States
Assay type Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, escape, variant cross-recognition or cross-neutralization
References Casazza *et al.* 2005

- Evidence of continued viral evolution during HAART therapy despite low viral load was found in 1/5 patients studied.
- The majority of viral sequences prior to therapy were rlrpggkkQ. At week 14 of therapy a major change in the viral quasispecies occurred: the variants present were found to be rlrpggkkK (14/16 clones) and rlrpggkkR (2/16 clones), both well recognized by HIV-specific CD8 T cells. At week 19, the quasispecies reverted back to the less well-recognized rlrpggkkQ variant.

HXB2 Location p17 (20–28)
Author Location p17 (20–28 SF2, HXBc2/Bal R5)
Epitope RLRPGGKKK
Epitope name RK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3, B7)
Donor MHC A2, A3, B15, B7, Cw3, Cw6; A29, A3, B44, B7, Cw3, Cw7; A24, A3, B7, B8, Cw7
Country United States
Assay type Cytokine production, Flow cytometric T-cell cytokine assay, Degranulation, CD107a and b cell surface mobilization
Keywords supervised treatment interruptions (STI), immunodominance, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells, drug resistance
References Daucher *et al.* 2008

- A detailed analysis of 6 chronically infected patients' CTL responses to autologous virus was performed after ART and SIT (structured interruption of therapy). Qualitative responses including degranulation and production of IFN-gamma, MIP-1beta, TNF-alpha, IL-2, but not memory CD27, CD45RO and CD57 T cells correlated with extended low plasma viremia. Frequency and breadth of CTL response as well as immune escape did not influence virological outcome.
- One patient exhibited drug resistance mutations K170R (to NNRTI efavirenz) and D76N, K70R (to NRTIs).
- Autologous epitopes were preferentially recognized over optimal, consensus sequences.
- Patients with favorable virological outcomes demonstrated CTL recognition within multiple, conserved regions of Gag and Nef.
- Patients with poor virological outcomes recognized optimal epitopes with much lower frequencies, though this was not significant.
- HLA-A3 and -B7-restricted epitope, RLRPGGKKK, elicited a response in 3 patients and is found in Gag immunodominant regions WEKIRLRPGGKKKYKL, WEKIRLRPGGKKKYK or LDRWEKIRLRPGGKKKYKL. The autologous sequence in one patient was RLRPGGrKr.

- In a patient who had one of the lowest viremias, the highest frequency of CTL response was to 2 immunodominant regions in Gag containing epitopes KK9 (KIRLRPGGK), RK9 (RLRPGGKKK) and p17 RPGGKKKYK.

HXB2 Location p17 (20–28)
Author Location p17 (20–28)
Epitope RLRPGGKKK
Immunogen HIV-1 infection
Species (MHC) human
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- Three of the four individuals that responded to SLYNTVATL recognized HIV epitopes, and one individual who was A*0201, A31 and B51 and B58w4 recognized this epitope (previously described as HLA A3.1), as well as one other.

HXB2 Location p17 (20–28)
Author Location
Epitope RLRPGGKKK
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A3, A32; B38, B64
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- AAVDLSHFL was recognized by a placebo patient after infection.

HXB2 Location p17 (20–28)
Author Location
Epitope RLRPGGKKK
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A*0201, A*0301; B*4501, B*5301
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location p17 (20–29)
Author Location p17 (20–29)
Epitope RLRPGGKKKY
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
References Brander & Walker 1995

- Unpublished, C. Jassoy and Beatrice Culman, pers. comm.

HXB2 Location p17 (20–29)
Author Location p17 (20–29 LAI)
Epitope RLRPGGKKKY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
References Wilkens & Ruhl 1999

- Pers. comm., B. Wilkens and D. Ruhl.

HXB2 Location p17 (20–29)
Author Location p17 (20–29 LAI)
Epitope RLRPGGKKKY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*0301 epitope.

HXB2 Location p17 (20–29)
Author Location (C consensus)
Epitope RLRPGGKKHY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- RLRPGGKKHY is an optimal epitope.

HXB2 Location p17 (20–29)
Author Location p17 (20–29)

CTL CD8+

Epitope RLRPGGKKKY
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Goulder *et al.* 2000c

- Two clonal CTL responses were generated in donor 021-BMC (HLA A3/3001, B42/-, Cw17/-) against different optimal versions of this epitope, one nine amino acids long, one ten.
- A previously described optimal A3 epitope overlapping this region, KIRLRPGGK, was not recognized by CTL from 021-BMC.

HXB2 Location p17 (20–29)
Author Location p17
Epitope RLRPGGKKKY
Epitope name A3-RY11(p17)
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p17 (20–29)
Author Location Gag
Epitope RLRPGGKKKK
Subtype B, F
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country Argentina
Keywords dynamics, escape, HLA associated polymorphism
References Dilernia *et al.* 2008

- Dynamics of CTL escape mutations was studied theoretically by analyzing plasma samples from 302 subjects (collected over 20 years). HLA associated polymorphisms accumulated in a subtype-specific manner.
- Epitope RLRPGGKKKK with anchor residues at R(L)RPGGKKK(K) contains polymorphisms RLRPGGKKKq and RLRPGGKKKr, that are strongly supported as escape by phylogenetic correction.

HXB2 Location p17 (20–29)
Author Location p17
Epitope RLRPGGKKKK
Epitope name RK9(p17)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A3-restricted epitope RLRPGGKKKK elicited an immune response in Chinese HIV-1 positive subjects as part of peptide EKIRLRPGGKKKKYRLKHL.
- 2 of the 3 HLA-A3 carriers responded to the RLRPGGKKKK-containing peptide with average magnitude of CTL response of 285 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p17 (20–29)
Author Location p17
Epitope RLRPGGKKKKY
Epitope name RK10(p17)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A3-restricted epitope RLRPGGKKKKY elicited an immune response in Chinese HIV-1 positive subjects as part of peptide EKIRLRPGGKKKKYRLKHL.
- 2 of the 3 HLA-A3 carriers responded to RLRPGGKKKKY-containing peptide with average magnitude of CTL response of 285 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p17 (20–29)
Author Location p17 (20–29)
Epitope RLRPGGKKKY
Immunogen HIV-1 infection
Species (MHC) human (A3, A30, B42, B62)
Donor MHC A2, A3, B44, B7
Country United States
Assay type Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

Keywords HAART, ART, escape, variant cross-recognition or cross-neutralization
References Casazza *et al.* 2005

- Evidence of continued viral evolution during HAART therapy despite low viral load was found in 1/5 patients studied.
- The epitope RLRPGGKKKY was invariant (18/18 sequences) prior to therapy in the patient that recognized it.

HXB2 Location p17 (20–29)
Author Location p17 (20–29)
Epitope RLRPGGKKKY
Epitope name RY10
Immunogen HIV-1 infection
Species (MHC) human (A30)
Donor MHC A*24, A*30, B*39, B*47, Cw*12, Cw*17; A*30, B*18, B*40, Cw*02, Cw*05
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, acute/early infection, viral fitness and reversion
References Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- RLRPGGKKKY was recognized in 2 mothers, and is an A*30 epitope. The variant RLRPGGKKqY was found in 9/10 of 1 mother's sequences. This form was transmitted to her child, and 10/10 clones were this variant at months 2 and 6 in the infant; by month 12, 9/10 were RLRPGGKKqY. RLRPGGKKrY was the form found in the other mother. The variant gradually diminished in frequency in her child, 10/10 sequences at 2 months, 9/10 at 4 months, and 6/10 at 12 months.

HXB2 Location p17 (20–29)
Author Location p17 (20–29)
Epitope RLRPGGKKKY
Immunogen HIV-1 infection
Species (MHC) human (A*0301, A30)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the A2+ individuals was A30, and one was A3, and both responded to RLRPGGKKKY.
- The A2+ A3 individual also reacted with two other A3.1 epitopes.

HXB2 Location p17 (20–29)
Author Location p17 (20–29 IIIB)
Epitope RLRPGGKKKY
Immunogen HIV-1 infection
Species (MHC) human (B42)
Keywords responses in children, mother-to-infant transmission
References Wilson *et al.* 1996

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.
- RLRPGGKKRY, a naturally occurring variant, was found in non-transmitting mother and is recognized.
- Binds HLA-A3 and Bw62 as well.

HXB2 Location p17 (20–29)
Author Location p17 (20–29)
Epitope RLRPGGKKKY
Immunogen HIV-1 infection
Species (MHC) human (B42, B62)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p17 (20–29)
Author Location p17 (20–29 LAI)
Epitope RLRPGGKKKY
Subtype B
Immunogen
Species (MHC) human (B62)
Keywords review
References McMichael & Walker 1994

- Review of HIV CTL epitopes.
- Also P. Johnson, pers. comm.

HXB2 Location p17 (20–29)
Author Location p17 (20–29)
Epitope RLRPGGKKKY
Immunogen HIV-1 infection
Species (MHC) human (B62)
References Brodie *et al.* 2000

- Study tracks and quantifies *in vivo* migration of neo-marked CD8+ HIV-specific CTL.
- Adoptively transferred gene-marked HIV-specific CTL homed to specific lymph node sites, colocalizing within the parafollicular regions of the lymph node adjacent to cells expressing HIV tat-fusion transcripts, indicative of viral replication.
- The CTL clones expressed CCR5 and localized among HIV-1 infected cells expressing MIP-1α and MIP-1β, CC-chemokines produced at sites of viral replication, suggesting a possible homing mechanism.
- This study provides a methodology for tracking and studying antigen specific CTL *in vivo*.

HXB2 Location p17 (20–29)
Author Location Gag (20–29)
Epitope RLRPGGKKKY
Epitope name RY10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62)
Donor MHC A*01, A*11, B*08, B*15, Cw*04, Cw*07
Country United States

CTL CD8+

Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords escape, variant cross-recognition or cross-neutralization
References Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- The RY10 variant RLRPGGrKKY was the only form of the epitope detected over a 5 year time period in this person. Elispot reactions were stronger to the autologous form than to RLRPGGKKKY, the B clade consensus form.

HXB2 Location p17 (20–30)
Author Location p17 (SF2)
Epitope RLRPGGKKKYK
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- WEKIRLRPGGKKKYKLK was the target of the dominant response in Caucasoids (38%) more frequently than non-Caucasoids (12%) – the dominant response in a Haitian immigrant living in Boston who was HLA A24/29 B7/B44 Cw6/7 was to this epitope, although the restricting element was not determined.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

HXB2 Location p17 (20–30)
Author Location Gag (25–35)
Epitope RLRPGGKKHYM
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 3/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p17 (20–31)
Author Location Gag
Epitope RLRPGGKKRYRL
Subtype A, CRF02_AG, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide RLRPGGKKRYRL from subtype CRF02_AG, and to peptide RLRPGGKKkYRL from subtypes A and CRF01_AE.

HXB2 Location p17 (20–35)
Author Location p17 (90–105 SF2)
Epitope CLRPGGKKKYKLKHIV
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA A-2, A-24, B-13, B-35.

HXB2 Location p17 (21–35)
Author Location
Epitope LRPGGKKKYKLKHIV
Immunogen HIV-1 infection
Species (MHC) human (A11, B7)
Donor MHC A2, A32, B44, B7; A11, A2, B60, B7
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.

CTL CD8+

- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 6 (NIH ARRP Cat# 7877), LRPGGKKKYKLKHIV, which contains epitopes restricted by HLA-A11 and -B7 in different patients elicited the following CTL responses:(1) in a living non-progressor for 22+ years; (2) in another living non-progressor for 19+ years.

HXB2 Location p17 (21–35)
Author Location Gag
Epitope LRPGGKKKYKLKHIV
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords TCR usage
References Weekes *et al.* 1999b

- Peptide 703.3: Almost all CD8+ T cells are CD28+ at birth, and the proportion of CD28-CD8+ cells increases with age – this study examines the contribution of CD8+CD28- cells to CTL memory pools for CTL clones specific for two persistent human viruses, CMV and HIV – clones were found to be similarly distributed in the CD28 depleted cell population.
- HIV CTL responses to 3 Env and 2 Gag peptides were studied.
- The clonal composition of the TCR Vβ responses was studied and was found to be highly focused, with one TCR beta-chain sequence tending to dominate the peptide-specific response – clones to this epitope were Vβ13.1 and Vβ5.2.

HXB2 Location p17 (21–35)
Author Location p17 (21–35)
Epitope LRPGGKKKYKLKHIV
Epitope name Peptide 703.3
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A2, A3, B44, B7
Country United Kingdom
Assay type Flow cytometric T-cell cytokine assay, Other
Keywords HAART, ART, immunodominance, TCR usage, memory cells
References Weekes *et al.* 2006

- The effect of HAART on the population size, phenotype and function of HIV- and HCMV-specific CTL clones was analyzed. It was determined that the clonal composition of gag and env HIV-specific CD8 T-cells did not change after HAART. Following HAART, the size of immunodominant HIV-specific CD8 T-cell clones was found to diminish even with the relative preservation of functional memory responses. Maintainance of such strong functional responses implied the preferential loss of HIV-specific cells that have reduced cloning efficiency in vitro. HCMV-specific CTL clones had different kinetics and phenotypes than HIV-specific CTL clones in the same subject.

HXB2 Location p17 (21–35)
Author Location p17 (21–35)
Epitope LRPGGKKKYKLKHIV
Immunogen
Species (MHC) human (B8)
References Nixon & McMichael 1991

- Two CTL epitopes defined (see also p24(191-205))

HXB2 Location p17 (21–35)
Author Location p17 (21–35)
Epitope LRPGGKKKYKLKHIV
Immunogen HIV-1 infection
Species (MHC) human (B8)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, LRPGGKKKYKLKHIV, was found to be -0.001/day (upper bound on rate of escape = 0.085), with SE of 0.003.
- In the subject studied, K26R grew out steadily to 95% frequency, but then there was a progressive re-emergence of the wild type. If data from all time points were fitted, then the mutant actually had a negative growth rate because it was eventually out-competed by the wild type.

HXB2 Location p17 (21–35)
Author Location p17 (21–35)
Epitope LRPGGKKKYKLKHIV
Immunogen HIV-1 infection
Species (MHC) human (not B8)
References van Baalen *et al.* 1996

- Unknown HLA specificity, but not B8.

HXB2 Location p17 (21–35)
Author Location Gag
Epitope LRPGGKKKYKLKHIV
Immunogen HIV-1 infection
Species (MHC) human
References Weekes *et al.* 1999a

- Peptide 703.3: Memory CTL specific for HIV-1 may contribute to oligoclonal expansions within the CD57+ CD28- CD8+ CTL populations.

HXB2 Location p17 (21–35)
Author Location p17 (91–105 SF2)

CTL CD8+

Epitope LRPGGKKKYKLKHIV
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A1, A2, B50, B57.

HXB2 Location p17 (21–35)
Author Location p17 (24–31)
Epitope LRPGGKKKYRLKHLV
Subtype A, D
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*6601, A*6801, B*5301, B*5802; A*3002, A*6801, B*5703, B*5802
Country Uganda
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References Barugahare *et al.* 2005

- T-cell immune responses were examined in HIV-1 infected Ugandans. Similar levels of cross-clade responses for Gag, Env and Nef were observed. Higher frequencies of responses in conserved regions were found for Gag within a single clade, while areas with higher viral sequence variation had fewer detectable responses. Differential interclade sequence homologies between the Gag regions did not affect the respective level of cross-clade recognition.
- The sequence contains a known B8 epitope, but the subjects recognizing it were B8-negative. The autologous viral sequence was lrpggkkkyKlkhlv, and the peptide was recognized.

HXB2 Location p17 (21–40)
Author Location p17 (21–40 subtype A)
Epitope LRPGGKKKYRLKHLVWASRE
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (Cw4)
Keywords subtype comparisons
References Dorrell *et al.* 1999

- CTL responses in three individuals with non-clade B infections were studied, 2 with subtype A infections, 1 with subtype C – their infections all originated in East Africa.
- This epitope was defined in an A subtype infection – the B clade variant (LRPGGKKKYKLKHIVWASRE) has two mutations relative to the A subtype form, and the CTLs from this patient were not A-B cross-reactive.

HXB2 Location p17 (22–29)
Author Location Gag (22–29)
Epitope RPGGKKHY
Subtype A, C, D
Immunogen HIV-1 infection
Species (MHC) human (B07, B42)
Country Tanzania
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, immunodominance
References Geldmacher *et al.* 2007a

- 56 ART-naive subjects were studied to assess whether T-cell responses to Gag and Nef are biased towards infecting subtype recognition, in a setting of epidemic consisting of subtypes A,C and D and their recombinant forms. The infecting subtype was determined by multi-region hybridization assay. Overlapping 15-mer isolate-based Gag and Nef peptide sets representative of local subtypes were used. The best recognized epitope variant in terms of magnitude and breadth corresponded to infecting subtype, in this case usually type-C. Hot spots of CTL recognition in Gag were in p24, p17 and p15; hotspots against Nef were in its central, conserved region.
- Epitope variants RPGGKKhY, RPGGKKkY and RPGGKKqY were studied as peptide sequences EKIRL-RPGGKKhY-ML (subtype C), EKIRL-RPGGKKkY-RL (subtypes A and D) and EKIRL-RPGGKKqY-RM with 12.5% responders. Subtype A was best recognized. Associated HLAs frequently expressed within the studied cohort are listed in the study as B07, B42.

HXB2 Location p17 (22–30)
Author Location p17 (22–30 SF2, HXBc2/Bal R5)
Epitope RPGGKKKYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A2, A3, B15, B7, Cw3, Cw6; A29, A3, B44, B7, Cw3, Cw7; A24, A3, B7, B8, Cw7
Country United States
Assay type Cytokine production, Flow cytometric T-cell cytokine assay, Degranulation, CD107a and b cell surface mobilization
Keywords supervised treatment interruptions (STI), immunodominance, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells, drug resistance
References Daucher *et al.* 2008

- A detailed analysis of 6 chronically infected patients' CTL responses to autologous virus was performed after ART and SIT (structured interruption of therapy). Qualitative responses including degranulation and production of IFN-gamma, MIP-1beta, TNF-alpha, IL-2, but not memory CD27, CD45RO and CD57 T cells correlated with extended low plasma viremia. Frequency and breadth of CTL response as well as immune escape did not influence virological outcome.
- One patient exhibited drug resistance mutations K170R (to NNRTI efavirenz) and D76N, K70R (to NRTIs).
- Autologous epitopes were preferentially recognized over optimal, consensus sequences.
- Patients with favorable virological outcomes demonstrated CTL recognition within multiple, conserved regions of Gag and Nef.
- Patients with poor virological outcomes recognized optimal epitopes with much lower frequencies, though this was not significant.
- HLA-B7-restricted epitope, RPGGKKKYK, elicited a response in 3 patients and is found in Gag immunodominant regions WEKIRLRPGGKKKYKL, WEKIRLRPGGKKKYK or LDRWEKIRLRPGGKKKYKL. The autologous sequence

in one patient was RPGGKKKrYK and in the other 2 was RPGGKKKKYr.
- In a patient who had one of the lowest viremias, the highest frequency of CTL response was to 2 immunodominant regions in Gag containing epitopes KK9 (KIRLRPGGK), RK9 (RLRPGGKKK) and this epitope p17 RPGGKKKYK.

HXB2 Location p17 (22–30)
Author Location p17 (22–30)
Epitope RPGGKKRYM
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- RPGGKKRYM is a novel epitope that may be subtype C-specific and was putatively restricted by HLA-B*35 and -Cw*0602 in two different subjects.

HXB2 Location p17 (22–31)
Author Location Gag (22–31)
Epitope RPGGKKKYML
Subtype A, C, D
Immunogen HIV-1 infection
Species (MHC) human (B*0702, B*4201)
Country Tanzania
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords rate of progression, immunodominance
References Geldmacher *et al.* 2007b
- The objectives of this study were to find antiviral epitopic determinants of Gag HIV-specific CTL response and to find 'host HLA-CTL response' correlations. By studying 56 ART-naive subjects including low viral load (LVL) responders, the authors show that subjects expressing the "protective" HLA-B*0702, -B*5801, and -B*8101 have broader Gag epitope recognition which may be abrogated if co-expressed with HLA-B alleles associated with rapid AIDS progression. Also, a negative linear relation was seen between Gag epitope numbers and plasma viral load while a positive relationship was seen with CD4 T-cell count. Finally, LVL subjects recognized specific Gag regions at the N- and C-termini of the protein more often than peptides in the middle of the protein.
- Epitope RPGGKKKYML, presented by HLA-B*0702 and B*4201 is strongly associated with LVL. However, the last position RPGGKKKYMl is highly variable.

HXB2 Location p17 (22–31)
Author Location Gag (22–31)
Epitope RPGGKKRYKL
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Jin *et al.* 2000b
- This B7 epitope is one of three subdominant CTL responses detected in a long-term non-progressor.
- A dominant B7 epitope was defined using conventional methods, and three additional sub-dominant HLA B7 epitopes were defined by first using a non-anchor based strategy, EpiMatrix, to identify 2078 possible epitopes in the autologous HIV-1, followed by B7 anchor residue prediction to narrow the set to 55 peptides for experimental testing.

HXB2 Location p17 (22–31)
Author Location p17
Epitope RPGGKKKYKL
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human (Cw4)
Donor MHC A23, A34, B44, B53, Cw4, Cw6
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References Geels *et al.* 2005
- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence had an K5N change, RPGGnKKYKL.

HXB2 Location p17 (23–34)
Author Location Gag
Epitope PGGKKRYRLKHL
Subtype A, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

CTL CD8+

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma EliSpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. Fifteen test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide PGGKKRYRLKHL from subtype CRF02_AG and to peptide PGGKKkYRLKHL from subtype A.

HXB2 Location p17 (24–31)
Author Location p17 (24–31)
Epitope GGKKKYKL
Epitope name GL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*08)
Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords rate of progression, immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-B*08-restricted autologous epitope GGKKKYKL elicited CTL responses at the earliest time point, with a reduction in response frequency just before disease progression at the second time point. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location p17 (24–31)
Author Location p17
Epitope GGKKKYKL
Epitope name GL8
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Donor MHC A*0101, A*0301, B*0801; A*0201, A*3101, B*3501, B*3905
Country United Kingdom
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords escape, acute/early infection, variant cross-recognition or cross-neutralization
References Milicic *et al.* 2005

- Escape mutation ggRkkyKl in this epitope, GGKKKYRL, resulted in failure of recognition by CTLs, and the ggkkQyRl mutations resulted in 82% reduction in HLA binding affinity.
- A*0301 epitopes RLRPGGKKK and KIRLRPGGK, and B*0801 epitope GGKKKYRL, overlap. In 1 donor, the transmitted virus carried the escape form for 2 of these epitopes. The double substitution kirlrpggR results in escape from response in the donor. Similarly, the double substitution ggRkkyKl results in escape for this epitope.

HXB2 Location p17 (24–31)
Author Location p17 (24–31)
Epitope GGKKKYRL
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Donor MHC A*0101, A*0301, B*0801
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, GGKKKYRL, was found to be 0.032/day, with SE of 0.008.
- The K28T substitution conferred escape from CTL responses of both the RLRPGGKKK and GGKKKYRL epitopes.

HXB2 Location p17 (24–31)
Author Location p17 (24–31)
Epitope GGKKKYKL
Immunogen
Species (MHC) human (B8)
References Goulder *et al.* 1997g

- The crystal structure of this peptide bound to HLA-B8 was used to predict new epitopes and the consequences of epitope variation.
- The predictions were experimentally confirmed.
- The anchors for HLA-B8 epitopes, as defined by peptide elution data, are P3 (K), P5 (K/R), and P8 (L).
- Structural data suggests that a positive charge at P5 is essential, but that the constraints on P3 may be less severe.
- Small hydrophobic residues at P2 may be favorable for binding.

- A spacious F-pocket favors mid-sized hydrophobic residues in the C-term anchor.

HXB2 Location p17 (24–31)
Author Location p17 (24–31 SF2)
Epitope GGKKKYKL
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords subtype comparisons
References McAdam *et al.* 1998

- CTL from a patient infected with clade B virus did not recognize Ugandan variants of this epitope.

HXB2 Location p17 (24–31)
Author Location p17 (24–31 LAI)
Epitope GGKKKYKL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords TCR usage
References Reid *et al.* 1996

- The variants 7R: GGKKKYRL, 7Q: GGKKKYQL, 5R: GGKKRYKL, and 3R: GGRKKYKL, were studied.
- Crystal structures were obtained to study these peptides in the context of HLA-B8, and CTL binding and activity were determined.
- 3R has been detected in 3 patients, and it abolishes recognition causing extensive conformational changes upon binding including MHC main chain movement.
- 7Q and 7R alter the TCR exposed surface, and retain some recognition.
- Reactivity of 5R depends on the T cell clone, this amino acid is embedded in the C pocket of B8 when the peptide is bound.
- Optimal peptide is 8-mer, not 9-mer, and positions 3, 5, and 8 are the anchor residues.

HXB2 Location p17 (24–31)
Author Location p17 (24–31 LAI)
Epitope GGKKKYKL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Price *et al.* 1997

- A weak CTL response to the index peptide was observed in an HLA-B8+ infected individual.
- Sequences from the earliest available time point showed that a variant at position 5, an anchor residue, GGKKQYKL, was present.

HXB2 Location p17 (24–31)
Author Location p17
Epitope GGKKKYKL
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART
References Seth *et al.* 2001

- CTL responses were studied by tetramer staining in 41 patients with combination therapy – activated CD8+ T-cells decline as the viral load drops in response to therapy, but the overall level of antigen-specific cells capable of differentiating into effectors stays constant and new epitopes may be recognized.
- In Figure 4 legend, epitope GGKKKkYKL is printed as having been used. We chose to record the epitope as GGKKKYKL seen elsewhere in this paper, as it is more commonly annotated as such in the literature.

HXB2 Location p17 (24–31)
Author Location p17 (24–31 SF2)
Epitope GGKKKYKL
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with preseroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B8+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 1/3 group 2, and 2/2 group 3.

HXB2 Location p17 (24–31)
Author Location p17 (24–31)
Epitope GGKKKYRL
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B8)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location p17 (24–31)
Author Location p17 (24–31)
Epitope GGKKKYKL
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Day *et al.* 2001

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual.

HXB2 Location p17 (24–31)
Author Location p17
Epitope GGKKKYKL

CTL CD8+

Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords binding affinity, review, subtype comparisons, epitope processing, escape
References McMichael & Hanke 2002

- CTL response-eliciting vaccines are reviewed. The natural epitope interactions with the HLA class I presenting molecules and T-cell receptors are described, using the structure of this epitope, taken from Reid *et al.* [1996], as an example.

HXB2 Location p17 (24–31)
Author Location (B consensus)
Epitope GGKKKYKL
Epitope name GL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A01, A03, B08, B14, Cw7, Cw8
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location p17 (24–31)
Author Location p17
Epitope GGKKKYKL
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A1A1, B55, B8, Cw3, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence had an L8M change, GGKKKYKm.

HXB2 Location p17 (24–31)
Author Location Gag (24–31 BRU)
Epitope GGKKKYKL
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 1/9 CRF02_AG-infected Ivorians, and 0/9 B-infected French subjects.

HXB2 Location p17 (24–31)
Author Location p17 (24–31)
Epitope GGKKKYKL
Epitope name GL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A*03, A*31, B*08, B*15, Cw*04, Cw*07
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, characterizing CD8+ T cells, viral fitness and reversion
References Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- Variant sequence ggRkkykl was present in 10/10 clones from a B8-positive mother, but decreased to 0/10 clones by 15 months of age in her B8-negative child.
- The variant ggRkkykl was present in 10/10 clones from a B8+ mother, was transmitted to her infant, and present in 10/10 clones at months 2 and 4, but decreased to 0/10 clones by 15 months of age in her B8- child.

HXB2 Location p17 (24–31)
Author Location p17 (24–31 HXB2)
Epitope GGKKKYKL
Epitope name GL8
Subtype B

CTL CD8+

Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A*0101, A*0201, B*0801, B*50, Cw*0602, Cw*0701
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, viral fitness and reversion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- Gag epitope GGKKKYKf (p17-31F) presumed escape variant was transmitted from a B8 positive donor to a B8 negative recipient. Reversions to GGKKKYKl were found in the recipient.

HXB2 Location p17 (24–31)
Author Location
Epitope GGKKKYKL
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade MN *HIV component:* gp160
Species (MHC) human
Donor MHC A1, A33; B44, B8
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location p17 (24–32)
Author Location p17 (24–32)
Epitope GGKKKYKLK
Epitope name GK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*08)
Country Australia, Canada, Germany, United States
Keywords escape, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*08-associated substitution within optimally defined epitope GGKKKYKLK is at positions K3, GGkKKYKLK. GK9 has a very low recognition frequency and rate of escape.

HXB2 Location p17 (24–32)
Author Location p17 (24–32 LAI)
Epitope GGKKKYKLK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes epitope to be presented by B*0801.

HXB2 Location p17 (24–32)
Author Location p17 (24–32)
Epitope GGKKKYKLK
Epitope name GGK
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells
References Turnbull *et al.* 2006

- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.
- This epitope, B8-GGK and its alanine-substituted variants are very weakly cross-recognized and reactive.

HXB2 Location p17 (24–32)
Author Location p17 (24–32 LAI)
Epitope GGKKKYKLK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Sutton *et al.* 1993

- Exploration of HLA-B8 binding motif through peptide elution.

CTL CD8+

HXB2 Location p17 (24–32)
Author Location p17 (24–32 LAI)
Epitope GGKKKYKLK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords epitope processing
References Rowland-Jones *et al.* 1993

- Study of an individual with partially defective antigen processing.

HXB2 Location p17 (24–32)
Author Location p17 (24–32)
Epitope GGKKKYKLK
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Klenerman *et al.* 1994

- Naturally occurring variants GGKKKYQLK and GGKKRYRLK may act as antagonists.

HXB2 Location p17 (24–32)
Author Location p17 (24–32)
Epitope GGKKKYKLK
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Klenerman *et al.* 1995

- Naturally occurring antagonist GGKKKYQLK found in viral PBMC DNA and RNA.

HXB2 Location p17 (24–32)
Author Location p17 (24–32)
Epitope GGKKKYKLK
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords escape
References Nowak *et al.* 1995

- Longitudinal study of CTL response and immune escape – the variant GGRKKYKLK binds to HLA-B8 but is not reactive.

HXB2 Location p17 (24–32)
Author Location p17 (24–32)
Epitope GGKKKYKLK
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Dyer *et al.* 1999

- CTL specific responses were measured over a 1.3 to 1.5 year period in members of the Sydney Blood Bank Cohort (SBBC) who had been infected with a natural attenuated strain of HIV-1 that was Nef-defective.
- Some of these patients had prolonged high levels of CTL effector and memory cells despite low viral load.

HXB2 Location p17 (24–32)
Author Location p17
Epitope GGKKKYKLK
Immunogen
Species (MHC) human (B8)
References Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective.
- HIV-2 sequence: GGKKKYKMK – no cross-reactivity Phillips *et al.* [1991].

HXB2 Location p17 (24–32)
Author Location p17 (24–32)
Epitope GGKKKYKLK
Epitope name GGK
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART, supervised treatment interruptions (STI), immunodominance, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- This epitope was recognized by 1/7 study subjects that were HLA-B8+.
- Patient SC12(HLA A1, B8/39, Cw0701/0702, DR2/3, DR51/52, DQ2/6) had sustained therapy started during acute infection and maintained an immunodominant response to FLKEKGGL throughout and minor responses to GEIYKRWII, DCKTILKAL, GGKKKYKLK – GEIYKRWII and GGKKKYKLK responses were stimulated by a brief period off therapy.

HXB2 Location p17 (24–32)
Author Location p17
Epitope GGKKKYKLK
Epitope name GGK
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART, supervised treatment interruptions (STI)
References Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFNgamma elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

HXB2 Location p17 (24–32)
Author Location p17
Epitope GGKKKYKLK
Epitope name B8-GK9(p17)
Immunogen HIV-1 infection
Species (MHC) human (B8)

Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p17 (24–32)
Author Location
Epitope GGKKKYKLK
Immunogen
Species (MHC) (B8)
Keywords review, immunodominance, escape, vaccine antigen design
References Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection (recognized by about 20% of subjects).

HXB2 Location p17 (24–32)
Author Location Gag
Epitope GGKKKYKLK
Epitope name GK9-B08
Subtype B, F
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country Argentina
Keywords HLA associated polymorphism
References Dilernia *et al.* 2008

- Dynamics of CTL escape mutations was studied theoretically by analyzing plasma samples from 302 subjects (collected over 20 years). HLA associated polymorphisms accumulated in a subtype-specific manner.
- Known epitope GGKKKYKLK with anchor residues at GG(K)K(K)YKLK contains polymorphism GGKKKYkLK. The consensus sequence is GGKKKYRLK.

HXB2 Location p17 (24–35)
Author Location p17 (25–35 SF2)
Epitope GGKKKYKLKHIV
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords review, immunodominance, escape
References Goulder *et al.* 1997a; Phillips *et al.* 1991

- Longitudinal study of CTL escape mutants in people with the appropriate HLA types – little variation was observed in the immunodominant B27 epitope, relative to B8 epitopes, which varied over time.
- Goulder *et al.* [1997a] is a review of immune escape that points out that there may be a protective effect associated with B27, and that HLA-B8 individuals tend to progress more rapidly than HLA-B27 patients.

HXB2 Location p17 (24–35)
Author Location p17 (25–35)
Epitope GGKKKYKLKHIV
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Birk *et al.* 1998b

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

HXB2 Location p17 (25–39)
Author Location
Epitope GKKKYKLKHIVWASR
Immunogen HIV-1 infection
Species (MHC) human (A24, B7)
Donor MHC A11, A2, B60, B7; A2, A32, B44, B7; A2, A24, B15, B40
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 7 (NIH ARRP Cat# 7878), GGKKYKLKHIVWASR, which contains epitopes restricted by HLA-B7 and -A24 in different patients elicited the following CTL responses: (1) >100 sfc/ million PBMC in a living non-progressor for 19+ years; (2) in another living non-progressor upto 22+ years; and (3) in a third living non-progressor at 12.1 years, decreasing to <50 sfc/million PBMC after 21 years.

HXB2 Location p17 (25–39)
Author Location p17 (25–39)
Epitope GKKKYKLKHIVWASR
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate
Species (MHC) human

CTL CD8+

Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008

- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.
- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.
- CTL immune response to consensus sequence GKKKYKLKHIVWASR was elicited in subject 00015. Consensus epitope of subject 0015 was the same as Clade B consensus and of subject 0016 was GKKqYKLKHIVWASR.

HXB2 Location p17 (27–35)
Author Location p17 (27–35)
Epitope `KRYMIKHLV`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope KRYMIKHLV was conserved only across clade C and was predicted to be restricted by HLA-Cw*0602.

HXB2 Location p17 (28–36)
Author Location (C consensus)
Epitope `HYMLKHIVW`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the M in the third residue HYMLKHIVW are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location p17 (28–36)
Author Location Gag (28–36)
Epitope `HYMLKHIVW`
Subtype A, C
Immunogen HIV-1 infection
Species (MHC) human (A*2301)
Country Tanzania
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, immunodominance
References Geldmacher *et al.* 2007a

- 56 ART-naive subjects were studied to assess whether T-cell responses to Gag and Nef are biased towards infecting subtype recognition, in a setting of epidemic consisting of subtypes A,C and D and their recombinant forms. The infecting subtype was determined by multi-region hybridization assay. Overlapping 15-mer isolate-based Gag and Nef peptide sets representative of local subtypes were used. The best recognized epitope variant in terms of magnitude and breadth corresponded to infecting subtype, in this case usually type-C. Hot spots of CTL recognition in Gag were in p24, p17 and p15; hotspots against Nef were in its central, conserved region.
- Epitope variants hYmLKHiVW, kYrLKHlVW and qYrLKHlVW were studied as peptide sequences GKK-hYmLKHiVW-ASR (subtype C), GKK-kYrLKHlVW-ASR (subtype A) and GKK-qYrLKHlVW-ASR with 21% responders. Subtype C sequences were recognized best. Associated HLA frequently expressed within the studied cohort is listed in the study as A*2301.

HXB2 Location p17 (28–36)
Author Location Gag
Epitope `HYMLKHLVW`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Chopera *et al.* 2008

- Transmission of HIV-1-escape variants from individuals with protective HLA-B*57/-B*5801 alleles to those without these alleles was studied to determine if infection with such replication-deficient mutants offered any advantage to the new host. Dependency between slower rate of disease progression in the newly infected subject and protective genotype of the infecting individual was suggested.

- HLA-A*2301-restricted epitope HYMLKHLVW, within peptide GKKHYMLKHLVWASREL was able to elicit CTL response in 2 wild type virus-carrying subjects.

HXB2 Location p17 (28–36)
Author Location (C consensus)
Epitope HYMLKHLVW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2301, A*2402)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords cross-presentation by different HLA, characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p17 (28–36)
Author Location
Epitope HYMLKHLVW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2301, A*2402)
Donor MHC A*2301, B*0801, B*1510, Cw*0701, Cw*1601
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- Known epitope HYMLKHLVW is HLA-A*2301 and -A*2402-restricted. Response to a peptide containing this epitope was detected in a rapid progressor 12 weeks post-infection.

HXB2 Location p17 (28–36)
Author Location Gag
Epitope KYKLKHIVW
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (A*24)
Country Canada, South Africa
Keywords escape
References Carlson *et al.* 2008

- A statistical model, the phylogenetic dependency network (PDN), was developed to differentiate the confounding effects of codon variation, linkage disequilibrium of HLA alleles and HIV phylogeny from HLA-associated evolution including HIV selection by HLA-pressure and codon evolution.
- This approach was applied to 2 cohorts of 1144 Gag sequences from HIV-infected individuals, generating associations between HIV codons themselves and codons with HLA alleles. Results generated predicted escapes that confirmed that escape kinetics and compensating mutations are consistent across clades. General patterns of covariation and CTL adaptation were determined. Some clade-based differences were identified.
- HLA-A*24-restricted optimal epitope KYKLKHIVW has a mutant, resistant form, KYrLKHIVW in clade B consensus sequences. The clade C susceptible consensus sequence is KYMLKHIVW.

HXB2 Location p17 (28–36)
Author Location Gag
Epitope KYMLKHIVW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*24)
Country Canada, South Africa
References Carlson *et al.* 2008

- A statistical model, the phylogenetic dependency network (PDN), was developed to differentiate the confounding effects of codon variation, linkage disequilibrium of HLA alleles and HIV phylogeny from HLA-associated evolution including HIV selection by HLA-pressure and codon evolution.
- This approach was applied to 2 cohorts of 1144 Gag sequences from HIV-infected individuals, generating associations between HIV codons themselves and codons with HLA alleles. Results generated predicted escapes that confirmed that escape kinetics and compensating mutations are consistent across clades. General patterns of covariation and CTL adaptation were determined. Some clade-based differences were identified.
- HLA-A*24-restricted epitope KYMLKHIVW is a clade C optimal epitope. Its clade B equivalent epitope is KYKLKHIVW.

HXB2 Location p17 (28–36)
Author Location p17 (28–36)
Epitope KYKLKHIVW
Epitope name KW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*24)
Country Australia, Canada, Germany, United States
Keywords escape, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag

CTL CD8+

B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-A*24-associated substitutions within optimally defined epitope KYKLKHIVW are at positions K1 and K3, kYkLKHIVW. KW9 epitope escape frequency (2nd most rapidly escaping) exceeded its recognition frequency, and could be due to an overestimation of escape.

HXB2 Location p17 (28–36)
Author Location p17 (28–36 LAI)
Epitope KYKLKHIVW
Subtype B
Immunogen
Species (MHC) human (A*2402)
Keywords optimal epitope
References Llano *et al.* 2009
- C. Brander notes that this is an A*2402 epitope.

HXB2 Location p17 (28–36)
Author Location p17 (28–36 SF2)
Epitope KYKLKHIVW
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
References Ikeda-Moore *et al.* 1998
- Strong CTL activity to this peptide was detected in 2/3 HIV-infected individuals who were HLA A24+.
- HLA A24 is very common in Japanese (70% carry it) and is common globally.
- This epitope was detected by looking for peptides with appropriate A24 anchor residues (Y at position 2, carb-term ILF or W) – 16/17 such peptides bound to A24 – KYKLKHIVW was found to be a naturally processed epitope that elicits a strong CTL response.

HXB2 Location p17 (28–36)
Author Location (28–36)
Epitope HYMLKHLVW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Assay type Other
Keywords HLA associated polymorphism
References Boutwell & Essex 2007
- Publicly available HIV-1 subtype C sequences from South Africa and Botswana were analyzed, and 94 HLA-associated amino acid polymorphisms were found. Many polymorphisms were associated with multiple HLA allele classes. 12% associations were negative: association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles accounted for 50% of associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes.
- HYMLKHLVW was a previously defined A*2402 presented epitope that encompassed an A*24 associated polymorphism, HYmLKHLVW, in the third position.

HXB2 Location p17 (28–36)
Author Location p17
Epitope KYKLKHIVW
Immunogen peptide-HLA interaction
Species (MHC) human (A*2402)
Assay type Tetramer binding
Keywords binding affinity
References Gillespie *et al.* 2007
- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, KYKLKHIVW (MHC Class I restriction, serotype Bw4) complexed with MHC A*2402 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C. However, the A*2402-KYKLKHIVW complex does bind inhibitory KIR3DL1 subtype KIR3DL1*005.

HXB2 Location p17 (28–36)
Author Location p17 (28–36 LAI)
Epitope KYKLKHIVW
Subtype B
Immunogen
Species (MHC) human (A23)
References Goulder & Walker 1999
- P. Goulder, pers. comm.

HXB2 Location p17 (28–36)
Author Location p17 (28–36 LAI)
Epitope KYKLKHIVW
Subtype B
Immunogen
Species (MHC) human (A24)
References Brander & Walker 1996
- D. Lewinsohn, pers. comm.

HXB2 Location p17 (28–36)
Author Location p17 (28–36 SF2)
Epitope KYKLKHIVW
Immunogen HIV-1 infection
Species (MHC) human (A24)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b
- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.

- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A24+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 2/3 group 2, and 0/0 group 3.

HXB2 Location p17 (28–36)
Author Location p17 (28–36 93TH253 subtype CRF01)
Epitope KYKLKHIVW
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A24)
Keywords subtype comparisons
References Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- The only HLA-A24 FSWs tested did not recognize the E clade version of this epitope KYKMKHLVW, which differs from the previously defined B clade version by two amino acids, KYKLKHIVW.

HXB2 Location p17 (28–36)
Author Location p17
Epitope KYKLKHIVW
Epitope name KW9
Immunogen HIV-1 infection
Species (MHC) human (A24)
Donor MHC A2, A24, B38, B60, Cw12, Cw2
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), acute/early infection
References Montefiori *et al.* 2003

- HIV-1 + patient AC10 underwent early HAART treatment, which was discontinued 1.5 years later. At this timepoint potent NAb responses against autologous virus were detected. Treatment interruption initially induced weak CD8+ responses directed against 5 epitopes. By days 873d and 923d the CTL response had broadened to target 22 epitopes; of these six were fully characterized. Eventually the virus escaped the NAb response, but escape was not accompanied by a rise in viral load, and the authors suggest the virus was contained by the CTL response.

HXB2 Location p17 (28–36)
Author Location p17 (28–36)
Epitope KYKLKHIVW
Immunogen HIV-1 infection
Species (MHC) human (A24)
Donor MHC A*0201, A*2402, B*52, B75, Cw*03; A*0207, A*2402, B*46, B*52, Cw*01; A*2402, A*26, B*07, B*5101, Cw*07
Country Japan
Assay type Chromium-release assay
Keywords epitope processing, escape
References Yokomaku *et al.* 2004

- Epitope variants escaped from being killed by CTLs in an endogenous expression system although they were recognized when corresponding synthetic peptides were exogenously loaded onto the cells. Escape is thus probably due to changes that occur during the processing and the presentation of epitopes in infected cells.
- Epitope variants recognized when added exogenously but not when processed endogenously were: kyRlkhLvw, RyRlkhLvw and QyRlkhivw.

HXB2 Location p17 (28–36)
Author Location p17 (28–36)
Epitope KYKLKHIVW
Epitope name QW9
Immunogen HIV-1 infection
Species (MHC) human (A24)
Donor MHC A*24, A*30, B*39, B*47, Cw*12, Cw*17; A*23, A*24, B*07, B*39, Cw*12, Cw*17
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, acute/early infection, viral fitness and reversion
References Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- qYKLKHIVW is an escape variant of the A*24 epitope KYKLKHIVW, found in 9/10 clones from the mother. It was transmitted to her infant, and persisted for 15 months. Both the mother and child are A*24+.
- qYKLKHIVW elicted lower responder cell frequencies than KYKLKHIVW.

HXB2 Location p17 (28–36)
Author Location p17
Epitope KYKLKHIVW
Epitope name A24-KW9(p17)
Immunogen HIV-1 infection
Species (MHC) human (A24)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.

CTL CD8+

- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p17 (28–36)
Author Location
Epitope KYKLKHIVW
Immunogen HIV-1 infection
Species (MHC) human (A24)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (A24), an additional HLA (A23) was statistically predicted to be associated with this epitope.

HXB2 Location p17 (28–36)
Author Location Gag
Epitope KYKLKHIVW
Epitope name KW9-A24
Subtype B, F
Immunogen HIV-1 infection
Species (MHC) human (A24)
Country Argentina
Keywords dynamics, escape, HLA associated polymorphism
References Dilernia *et al.* 2008

- Dynamics of CTL escape mutations was studied theoretically by analyzing plasma samples from 302 subjects (collected over 20 years). HLA associated polymorphisms accumulated in a subtype-specific manner.
- Known epitope KYKLKHIVW with anchor residues at K(Y)KLKHIV(W) contains polymorphism KYkLKHIVW which is moderately supported as escape by phylogenetic correction. Mutations in this position increased in time and KYrLKHIVW became a consensus.

HXB2 Location p17 (28–36)
Author Location p17 (728–736 subtype A)
Epitope KYRLKHLVW
Subtype A
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (Cw4)
Keywords HIV exposed persistently seronegative (HEPS), immunodominance
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-Cw4 women, 2/2 HEPS and 7/11 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in both of the 2/2 HEPS cases and in 3 of the 7/11 HIV-1 infected women.

HXB2 Location p17 (28–36)
Author Location p17 (28–36)
Epitope KYRLKHLVW
Immunogen HIV-1 infection
Species (MHC) human (Cw4)
References Appay *et al.* 2000

- This epitope is newly defined in this study.
- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α.

HXB2 Location p17 (28–36)
Author Location
Epitope KYRLKHLVW
Immunogen HIV-1 infection
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 1/22 HEPS sex worker controls (ML1573).

HXB2 Location p17 (28–36)
Author Location Gag (28–36)
Epitope HYMLNHIVW

Subtype A, C, D
Immunogen HIV-1 infection
Species (MHC) human
Country Tanzania
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords rate of progression, immunodominance
References Geldmacher *et al.* 2007b

- The objectives of this study were to find antiviral epitopic determinants of Gag HIV-specific CTL response and to find 'host HLA-CTL response' correlations. By studying 56 ART-naive subjects including low viral load (LVL) responders, the authors show that subjects expressing the "protective" HLA-B*0702, -B*5801, and -B*8101 have broader Gag epitope recognition which may be abrogated if co-expressed with HLA-B alleles associated with rapid AIDS progression. Also, a negative linear relation was seen between Gag epitope numbers and plasma viral load while a positive relationship was seen with CD4 T-cell count. Finally, LVL subjects recognized specific Gag regions at the N- and C-termini of the protein more often than peptides in the middle of the protein.
- Epitope HYMLNHIVW is overrepresented for recognition within the LVL group. However, this immunodominant epitope is most variable of all.

HXB2 Location p17 (28–36)
Author Location Gag
Epitope `HYMLKHLVW`
Subtype B, C, A1
Immunogen HIV-1 infection
Species (MHC) human
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, variant cross-recognition or cross-neutralization
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
- Response magnitude was high—Gag and Nef, Env, Tat (in descending order). While Gag, Pol, Env and Nef were highly immunogenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- Broadly immunogenic epitope HYMLKHLVW, had subtype variants that were recognized by less than half its patient responders. HLA supertype restriction was predicted to be supertype A24.

HXB2 Location p17 (28–36)
Author Location p17
Epitope `KYRLKHLVW`
Epitope name KW9(p17)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope KYRLKHLVW elicited an immune response in Chinese HIV-1 positive subjects as part of peptide GKKKYRLKHLVWASREL. This epitope differs from the previously described HLA-A24-restricted epitope , KYKLKHIVW, at 2 residues, KYrLKHlVW.
- 6 of the 30 HLA-A24 carriers responded to KYrLKHlVW-containing peptide with average magnitude of CTL response of 179 SFC/million PBMC (author communication and Fig. 1).

HXB2 Location p17 (28–38)
Author Location Gag (33–43)
Epitope `HYMLKHLVWAS`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p17 (32–46)
Author Location p17
Epitope `KHIVWASRELERFAV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

CTL CD8+

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, KHIVWASRELERFAV, had an overall frequency of recognition of 16.7% - 23.7% AA, 19.2% C, 9.1% H, 4.8% WI.

HXB2 Location p17 (33–41)
Author Location p17 (33–41)
Epitope HLVWASREL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0602)
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- HLVWASREL is a novel predicted epitope with >80% conservation to subtype A, that is shown to be restricted by HLA-Cw*0602.

HXB2 Location p17 (33–41)
Author Location p17
Epitope HLVWASREL
Epitope name HL-9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0804)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords subtype comparisons, epitope processing, immunodominance, cross-presentation by different HLA
References Masemola *et al.* 2004b

- Highly targeted regions in Gag for CD8+ T-cells were defined for individuals with C clade infections in South Africa. 9 specific epitopes within the most reactive regions were characterized. This is 1 of 5 novel epitopes that were found among subtype C HIV-1 from African patients who hadn't previously been identified in B clade infections. Some epitopes were shown to be promiscuous, presented by multiple class I restricting alleles.
- HLVWASREL was presented by Cw*08 and newly identified in this study; Cw*08 is slightly more common in Zulus than Caucasians (0.066 versus 0.038).

HXB2 Location p17 (33–41)
Author Location
Epitope HLVWASREL
Immunogen
Species (MHC) human (Cw*0804)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an Cw*0804 epitope.

HXB2 Location p17 (34–43)
Author Location Gag (Henan isolate)
Epitope IVWASRELER
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p17 (34–44)
Author Location p17
Epitope LVWASRELERF
Epitope name LF-11
Subtype C
Immunogen HIV-1 infection

Species (MHC) human (A*3002, B*570301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords subtype comparisons, epitope processing, immunodominance, cross-presentation by different HLA
References Masemola *et al.* 2004b

- Highly targeted regions in Gag for CD8+ T-cells were defined for individuals with C clade infections in South Africa. 9 specific epitopes within the most reactive regions were characterized. This is 1 of 5 novel epitopes that were found among subtype C HIV-1 from African patients who hadn't previously been identified in B clade infections. Some epitopes were shown to be promiscuous, presented by multiple class I restricting alleles.
- LVWASRELERF was clearly presented by both A*3002 and B*570301, it might also be cross-presented by A*3001, but not as effectively. A*30 is 10-fold more common among Zulus than Caucasians (allele frequency 0.195 versus 0.019), while B*57 is similar (0.051 versus 0.043).

HXB2 Location p17 (34–44)
Author Location p17 (34–44)
Epitope LVWASRELERF
Immunogen
Species (MHC) human (A30)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an A30 epitope.

HXB2 Location p17 (34–44)
Author Location p17
Epitope LVWASRELERF
Epitope name LF11(p17)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A30)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A30-restricted epitope LVWASRELERF elicited an immune response in Chinese HIV-1 positive subjects as part of peptide KHLVWASRELERFAV.
- 1 of the 15 HLA-A30 carriers responded to LVWASRELERF-containing peptide with a magnitude of CTL response of 260 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p17 (34–44)
Author Location (C consensus)
Epitope LVWASRELERF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5703)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- LVWASRELERF is an optimal epitope.

HXB2 Location p17 (34–44)
Author Location (C consensus)
Epitope LVWASRELERF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p17 (36–44)
Author Location p17 (35–43 LAI)
Epitope WASRELERF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
References Goulder *et al.* 1997d

- Optimal epitope defined from within p17(30-44), LKHIVWASRELERFA.
- Dominant CTL response in an HIV+ asymptomatic donor was to this epitope.
- The Phe in the C-term anchor is distinct from the previously-defined Tyr for B*3501 C-term anchors.

HXB2 Location p17 (36–44)
Author Location p17 (36–44 LAI)
Epitope WASRELERF
Subtype B
Immunogen
Species (MHC) human (B*3501)
Keywords optimal epitope
References Goulder *et al.* 1997b; Llano *et al.* 2009

CTL CD8+

- C. Brander notes this is a B*3501 epitope.

HXB2 Location p17 (36–44)
Author Location p17 (36–44)
Epitope WASRELERF
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Birk *et al.* 1998b

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

HXB2 Location p17 (36–44)
Author Location p17 (36–44)
Epitope WASRELERF
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p17 (36–44)
Author Location p17 (36–44 SF2)
Epitope WASRELERF
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 0/2 group 1, 0/2 group 2, and 1/1 group 3.

HXB2 Location p17 (36–44)
Author Location
Epitope WASRELERF
Epitope name Gag-WF9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B35, 1/21 (5%) recognized this epitope.

HXB2 Location p17 (36–44)
Author Location Gag
Epitope WASRELERF
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords HIV exposed persistently seronegative (HEPS)
References Koning *et al.* 2004

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A*11, A*31 and Cw*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
- No one, 0/3 HLA B35+ infection-resistant men, and 0/5 pre-seroconversion men who went on to become infected, reacted to this epitope.

HXB2 Location p17 (36–44)
Author Location
Epitope WASRELERF
Immunogen HIV-1 infection
Species (MHC) human (B35)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope WASRELERF elicited a magnitude of response of 220 SFC with a functional avidity of 0.01nM and binding affinity of 17432nM.

HXB2 Location p17 (36–44)
Author Location
Epitope WASRELERF
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental

methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B35), an additional HLA (B53) was statistically predicted to be associated with this epitope.

HXB2 Location p17 (36–44)
Author Location p17
Epitope WASRELERF
Epitope name WF9(p17)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008
- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B35-restricted epitope WASRELERF elicited an immune response in Chinese HIV-1 positive subjects as part of peptide KHLVWASRELERFAV.
- 1 of the 12 HLA-B35 carriers responded to WASRELERF-containing peptide with a magnitude of CTL response of 460 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p17 (36–44)
Author Location p17 (SF2)
Epitope WASRELERF
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a
- The dominant response in an African American who was HLA A3/33 B35/B53 Cw4/7 was to this epitope, although the restricting element was not determined – this epitope fell outside the most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

HXB2 Location p17 (36–44)
Author Location p17 (36–44)
Epitope WASRELERF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope WASRELERF showed >80% conservation with subtypes B and D and was predicted to be HLA-Cw*0602-restricted.

HXB2 Location p17 (37–51)
Author Location p17
Epitope ASRELERFAVNPGLL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004
- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol.

76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This overlapping peptide, ASRELERFAVNPGLL, was differentially targeted across ethnic groups and had an overall frequency of recognition of 13.3% - 6.8% AA, 26.9% C, 20.5% H, 0% WI (P value = 0.0068). HLA-A11 was the most commonly present HLA allele among individuals with responses to this peptide.

HXB2 Location p17 (37–51)
Author Location Gag (37–51)
Epitope `ASRELERFAVNPGLL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the ES.

HXB2 Location p17 (42–50)
Author Location Gag
Epitope `ERFAVNPGL`
Epitope name EL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- EL9, ERFAVNPGL, is a novel HLA-B27-restricted epitope that elicits a CTL IFN-gamma response in the same range as Los Alamos database peptides.

HXB2 Location p17 (43–51)
Author Location p17
Epitope `RFAVNPGLL`
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B63)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, cross-presentation by different HLA
References Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This is a putative HLA-B63 epitope is contained within a reactive peptide containing the B58 supertype binding motif. There is no evidence for B57/B58 cross-presentation of this epitope.

HXB2 Location p17 (49–57)
Author Location Gag (Henan isolate)
Epitope `GLLESSEGC`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p17 (59–67)
Author Location Gag (Henan isolate)
Epitope `QILEQLQPA`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p17 (59–68)
Author Location Gag (Henan isolate)
Epitope `QILEQLQPAL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p17 (63–72)
Author Location p17 (63–72)
Epitope `QLQPSLQTGS`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, QLQPSLQTGS, was detected within overlapping peptides QLQPSLQTGSEELRSLY and EGCRQILGQLQPSLQTGS.

HXB2 Location p17 (69–93)
Author Location p17 (69–93 BH10)
Epitope `QTGSEELRSLYNTVATLYCVHQRIE`
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Johnson *et al.* 1991

- Gag CTL response studied in three individuals.

HXB2 Location p17 (70–86)
Author Location p24
Epitope `TGSEELRSLYNTVATLY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, TGSEELRSLYNTVATLY, had an overall frequency of recognition of 22% - 23.7% AA, 23.1% C, 22.7% H, 4.8% WI. This peptide is included in a 34 aa Gag-p17 highly reactive region to be used for vaccine design.

HXB2 Location p17 (71–79)
Author Location Gag (71–79)
Epitope `GSEELRSLY`
Epitope name GY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*01)
Donor MHC A*02, B*08
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

CTL CD8+

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- In one patient, this epitope GSEELRSLY varied at Y79F to GSEELRSLf, at an anchor position, conferring potent viral escape. One other variant seen was GSEELRSLc.

HXB2 Location p17 (71–79)
Author Location p17
Epitope `GTEELRSLY`
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (A*0101)
Donor MHC A*0101, A*0301, B*0801; A*0201, A*3101, B*3501, B*3905
Country United Kingdom
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords escape, acute/early infection, characterizing CD8+ T cells
References Milicic *et al.* 2005

- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient. In an early acute infection of the donor, the precise timing of transmission determines the viral variants transmitted.
- Escape mutation gteelrslF in this epitope resulted in 98% reduction in HLA binding affinity, and was the transmitted variant.

HXB2 Location p17 (71–79)
Author Location p17
Epitope `GSEELRSLY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0101)
Donor MHC A*0101, A*0301, B*0801, B*5101; A*0101, B*0801
Country United Kingdom
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords escape, acute/early infection, characterizing CD8+ T cells
References Milicic *et al.* 2005

- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. CTL escape variants were often transmitted. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient.
- The second donor in the study shares A*0101 and B*0801 with his partner. Escape mutations gseeIKsly in GSEELRSLY resulted in 44% reduction in HLA binding affinity and no response in an Elispot assay, and gseeIKsly was the transmitted form.

HXB2 Location p17 (71–79)
Author Location p17 (71–79 LAI)
Epitope `GSEELRSLY`
Subtype B
Immunogen
Species (MHC) human (A1)
References Brander & Walker 1996

- P. Goulder, pers. comm.

HXB2 Location p17 (71–79)
Author Location p17 (71–79)
Epitope `GSEELRSLY`
Immunogen HIV-1 infection
Species (MHC) human (A1)
References Birk *et al.* 1998b

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

HXB2 Location p17 (71–79)
Author Location p17 (71–79 HXB2)
Epitope `GSEELRSLY`
Epitope name GSE
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A1)
Keywords HAART, ART, supervised treatment interruptions (STI), immunodominance, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- This epitope was not recognized by the 6/8 study subjects that were HLA-A1.

HXB2 Location p17 (71–79)
Author Location p17 (71–79)
Epitope `GSEELRSLY`

Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A1)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-A1 women, 1/1 HEPS and 3/3 HIV-1 infected women recognized this epitope, and the response was the dominant HLA-A1 response in all cases.

HXB2 Location p17 (71–79)
Author Location p17
Epitope `GSEELRSLY`
Epitope name GSE
Immunogen HIV-1 infection
Species (MHC) human (A1)
Keywords HAART, ART, supervised treatment interruptions (STI)
References Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFNgamma Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with supervised treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

HXB2 Location p17 (71–79)
Author Location p17 (71–79)
Epitope `GSEELRSLY`
Immunogen HIV-1 infection
Species (MHC) human (A1)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 3/13 patients recognized this epitope.

HXB2 Location p17 (71–79)
Author Location (71–79 B consensus)
Epitope `GSEELRSLY`
Epitope name GY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A1)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Allen *et al.* 2004

- This study characterizes an escape mutation in a C-terminal flanking residue of the HLA-A3 gag p17 KK9 epitope that inhibits processing, and is embedded in the overlapping HLA-A3 RK9 epitope.
- The immune response was tracked in subject AC-38. The acute immunodominant response was to the B57 TW10 epitope; this response declined following viral escape (tsNlqeqigw) by day 64. The p17 KK9 and RK9 became immunodominant, but then declined as the escape mutation arose. Three other strong responses that persisted were detected, along with 1 sub-dominant response to GY9.

HXB2 Location p17 (71–79)
Author Location Gag
Epitope `GSEELRSLY`
Epitope name GL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A1)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 9, gseelrslF, was found in the most polymorphic residue in the epitope. These were shared between clades B and C.

HXB2 Location p17 (71–79)
Author Location p17
Epitope `GSEELRSLY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A1)
Donor MHC A1A1, B55, B8, Cw3, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence had dramatic changes, the epitope GSEELRSLY peptide was GtegikSLh, and so likely not the actual reactive epitope in the larger peptide.

HXB2 Location p17 (71–79)
Author Location p24 (71–79)
Epitope GSEELRSLY
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country Kenya
References Peters *et al.* 2008a

- Gag sequences from 468 HIV-1 positive sex workers from the Kenyan Pumwani cohort were analyzed to bioinformatically identify positively selected residues that could be related to antigen processing. Mutation effects on disease progression were followed by mean CD4 counts. This method is also one way of identifying potential CTL epitopes and classifying them.
- A Gag positive selection map was generated and sites were classified as beneficial or harmful to HIV. They were correlated to antigen processing (proteasomal cleavage), antigen presentation (TAP transport efficiency) and T-cell receptor binding.
- p17 and p24's structural constraints limited their diversity, while p7-p1-p6 showed a higher average entropy.
- GSEELRSLY is a previously identified HLA-A*0101 restricted epitope.

HXB2 Location p17 (71–85)
Author Location p17 (71–85 SF2)
Epitope GSEELRSLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A1, A11, B8, B27.

HXB2 Location p17 (71–85)
Author Location p17 (71–85 HXB2)
Epitope GSEELRSLYNTVATL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 were chronically infected and treated; 22 started treatment during acute infection; 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- Responses to this peptide were detected in 16% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location p17 (71–90)
Author Location Gag (HXB2)
Epitope GSEELRSLYNTVATLYCVHQ
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A2
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, HAART, ART
References Chitnis *et al.* 2003

- 17 perinatally HIV-1 infected children (0.08-16 years) were evaluated for HLA-A2-restricted IFN-gamma CD8+ CTL responses against 4 immunodominant peptides that carry HLA-A2 epitopes. Two peptides were from gp120 (one at position 112, one from the V3 loop), and one each was from gp41 and Gag. 15/17 patients responded to the Gag peptide, 13/17 to the gp41 and the non-V3 gp120 peptides, and 11/17 responded to the V3 loop. 4 children recognized all 4 peptides.
- In 10/14 children, addition of exogenous IL-15 induced increased frequencies of SFCs to the Gag peptide. IL-2 and IL-7 did not increase SFCs, however IL-2, IL-7 and IL 15 could all increase the intensity of the spots in some patients. In 4 children, IL-15 addition brought the SFC response up to the level of detection.

HXB2 Location p17 (73–82)
Author Location p17 (73–82)
Epitope EELRSLYNTV
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4006)
Country India

Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope EELRSLYNTV is conserved across all clades and shown to be HLA-B*4006-restricted.

HXB2 Location p17 (73–87)
Author Location
Epitope EELRSLYNTVATLYC
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A11, A2, B60, B7; A2, A32, B44, B7; A2, A24, B15, B40; A11, A2, B44, B60; A2, A31, B27, B44
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 19 (NIH ARRP Cat# 7890), EELRSLYNTVATLYC, which contains an epitope restricted by HLA-A2 in different patients elicited the following CTL responses: (1) <1000 sfc/million PBMC in a living non-progressor for 22+ years; (2) in a living non-progressor at <50 sfc/million PBMC from 19 to 22+ years; (3) upto 22+ years at <1000 sfc/million PBMC for yet another living non-progressor; (4) <100 sfc/million PBMC upto 12 years in a low-viremic former non-progressor who succumbed to non-AIDS death; and (5) >100 sfc/million PBMC upto 22+ years in a deceased former non-progressor who lost viremic control.

HXB2 Location p17 (74–82)
Author Location Gag (74–82)
Epitope ELRSLYNTV
Epitope name EV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*08)
Donor MHC A*01, A*02
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- No CTL responses were detected against the EV9 epitope, ELRSLYNTV. A V82I variant, ELRSLYNTi was found.

HXB2 Location p17 (74–82)
Author Location p17 (74–82)
Epitope ELRSLYNTV
Epitope name EV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*08)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*08-associated substitution within optimally defined epitope ELRSLYNTV is at positions T8, ELRSLYNtV. EV9 has very low recognition frequencies and no escape.

CTL CD8+

HXB2 Location p17 (74–82)
Author Location p17
Epitope ELRSLYNTV
Immunogen
Species (MHC) human (B*0801)
Keywords optimal epitope
References Llano *et al.* 2009
- Noted by Brander to be a B*0801 epitope.

HXB2 Location p17 (74–82)
Author Location p17
Epitope ELRSLYNTV
Immunogen
Species (MHC) human (B8)
References Goulder *et al.* 1997g
- Defined in a study of the B8 binding motif.

HXB2 Location p17 (74–82)
Author Location p17 (74–82)
Epitope ELRSLYNTV
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Birk *et al.* 1998b
- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

HXB2 Location p17 (74–82)
Author Location p17 (74–82)
Epitope ELRSLYNTV
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Ferrari *et al.* 2000
- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p17 (74–82)
Author Location p17 (74–82)
Epitope ELRSLYNTV
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Day *et al.* 2001
- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual.

HXB2 Location p17 (74–82)
Author Location (B consensus)
Epitope ELRSLYNTV
Epitope name EV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A11, A29, B08, B44, Cw4, Cw7
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c
- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location p17 (74–82)
Author Location p17
Epitope ELRSLYNTV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A1A1, B55, B8, Cw3, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Geels *et al.* 2005
- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence ELRSLYNTV had dramatic changes, the epitope peptide was gikSLhNTV, and so likely not the actual reactive epitope in the larger peptide.

HXB2 Location p17 (74–82)
Author Location
Epitope ELRSLYNTV
Immunogen
Species (MHC) (B8)
Keywords review, immunodominance, escape, vaccine antigen design
References Altfeld & Allen 2006
- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection.

HXB2 Location p17 (74–82)
Author Location p17 (74–82 B1 and B2)
Epitope ELRSLYNTV
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (B8)

Donor MHC A3, A32, B62, B8, Cw3
Country Netherlands
Assay type Other
Keywords subtype comparisons, computational epitope prediction, superinfection
References Kozaczynska *et al.* 2007

- The influence of superinfection upon changes in HIV-1 strains was studied in a triple infected subject. While continuous expression of all three strains was observed, the LTR promoters of subtype AE had highest activity of all 3 strains, and subtype B2 had the lowest. Env-V3 sequences were present in higher numbers in strains B2 and CRF01_AE. Recombination was seen between viruses B1/B2 in gag and vpr genes.
- This HLA-B08 restricted epitope, ELkSLYNTV, varied to ELRSLYNTV in 50% of viruses in B1 within 4 years, ELkSLfNTV in 67% of viruses in strain B2 within 3 years, and ELkSLYNTV in AE at the earliest time point taken, with no changes over time. A reversion was seen in B2 to ELkSLYNTV i.e. f to Y, suggesting a lack of CTL pressure on this sequence.

HXB2 Location p17 (74–82)
Author Location p17 (74–82)
Epitope ELKSLFNTI
Epitope name EI9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords rate of progression, immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-B8-restricted autologous epitope ELKSLFNTI elicited increasing CTL responses at the last 2 time points. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location p17 (74–82)
Author Location Gag
Epitope ELRSLYNTV
Epitope name EV9-B08
Subtype B, F
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country Argentina
Keywords dynamics, HLA associated polymorphism
References Dilernia *et al.* 2008

- Dynamics of CTL escape mutations was studied theoretically by analyzing plasma samples from 302 subjects (collected over 20 years). HLA associated polymorphisms accumulated in a subtype-specific manner.
- Epitope ELRSLYNTV with anchor residues at EL(R)SLYNTV contains a polymorphism ELrSLYNTV. The variant ELkSLYNTV increases in time.

HXB2 Location p17 (74–83)
Author Location Gag
Epitope ELRSLYNTVA
Epitope name 1241
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for ELRSLYNTVA: 71%. This epitope was previously identified in the literature, but was not confirmed in this study.

HXB2 Location p17 (76–86)
Author Location p17 (74–86 LAI)
Epitope RSLYNTVATLY
Subtype B
Immunogen
Species (MHC) human (A*3002)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*3002 epitope.

HXB2 Location p17 (76–86)
Author Location p17 (SF2)
Epitope RSLYNTVATLY
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a single HIV+ individual from Boston – this epitope fell outside the most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.

CTL CD8+

- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

HXB2 Location p17 (76–86)
Author Location Gag (96ZM651.8)
Epitope RLSYNTVATLY
Immunogen
Species (MHC) human (A*3002)
References Novitsky *et al.* 2001

- This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort.
- Only 3/13 (23.1%) A*3002-positive subjects demonstrated moderate CTL responses to the peptide GTEELRSLYNTVATLYCVHE (residues 71 to 90), which contains the previously described A*3002 epitope RLSYNTVATLY.

HXB2 Location p17 (76–86)
Author Location p17 (76–86)
Epitope RSLYNTVATLY
Epitope name RY11 (p17)
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
References Goulder *et al.* 2001a

- HLA-A*3002 is very common in African populations, 50% of Zimbabweans express HLA-A30, 44% in African Zulu, so five new HIV epitopes were characterized that are presented by this HLA molecule.
- A rapid method was developed combining ELISPOT with intracellular IFN-γ staining of PBMCs to map optimal epitopes, then HLA presenting molecules were defined – this method was completed within 48 to 72 hours of receipt of blood.
- Two individuals were studied: Subject 199 (HLA A*0201/*3002 B*4402/51 Cw2/5), a Caucasian, and Subject 6007 (HLA A*3002/ B53/*5801 Cw4/7) an African-Caribbean.
- In both HLA-A*3002 individuals the response to RSLYNTVATLY was dominant.
- Three quantitative assays, ELISPOT, precursor frequency and chromium release, confirmed a hierarchy of response: RY11 (p17) > KY9 (gp41) > KY9 (RT-53) > IY9 (gp41).
- HLA-A*3001-positive targets do not present RSLYNTVATLY.

HXB2 Location p17 (76–86)
Author Location
Epitope RSLYNTVATLY
Epitope name Gag-RY11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Donor MHC A*3002, A*3201, B*4501, B*5301, Cw*0401, Cw*1202
Keywords HAART, ART
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Subject 00RCH33 was on HAART had a viral load of 2900 and CD4 count of 727 and also recognized the epitopes YPLTFGWCY, Nef(135-143), HLA B*5301; AETFYVDGA, RT(437-445), HLA B*4501; and HIGPGRAFY, gp160(310-318), HLA A*3002.
- Among HIV+ individuals who carried HLA B30, 3/16 (19%) recognized this epitope.

HXB2 Location p17 (76–86)
Author Location (C consensus)
Epitope RSLYNTVATLY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p17 (76–86)
Author Location (C consensus)
Epitope RSLYNTVATLY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- RSLYNTVATLY is an optimal epitope.

HXB2 Location p17 (76–86)
Author Location Gag
Epitope RSLYNTVATLY
Subtype C

Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
References Chopera *et al.* 2008

- Transmission of HIV-1-escape variants from individuals with protective HLA-B*57/-B*5801 alleles to those without these alleles was studied to determine if infection with such replication-deficient mutants offered any advantage to the new host. Dependency between slower rate of disease progression in the newly infected subject and protective genotype of the infecting individual was suggested.
- HLA-A*3002-restricted epitope RSLYNTVATLY, within peptide TGTEELRSLYNTVATL was able to elicit CTL response in a T242N/A146X viral-mutation-carrying subject. T242N/A146X are common HLA-B*57/-B*5801 associated escape mutations.

HXB2 Location p17 (76–86)
Author Location p17 (76–86)
Epitope `RSLYNTVATLY`
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Country Kenya
References Peters *et al.* 2008a

- Gag sequences from 468 HIV-1 positive sex workers from the Kenyan Pumwani cohort were analyzed to bioinformatically identify positively selected residues that could be related to antigen processing. Mutation effects on disease progression were followed by mean CD4 counts. This method is also one way of identifying potential CTL epitopes and classifying them.
- A Gag positive selection map was generated and sites were classified as beneficial or harmful to HIV. They were correlated to antigen processing (proteasomal cleavage), antigen presentation (TAP transport efficiency) and T-cell receptor binding.
- p17 and p24's structural constraints limited their diversity, while p7-p1-p6 showed a higher average entropy.
- RSLYNTVATLY is a previously identified HLA-A*3002 restricted epitope.

HXB2 Location p17 (76–86)
Author Location p17 (74–86 SF2)
Epitope `RSLYNTVATLY`
Immunogen HIV-1 infection
Species (MHC) human (A30)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A30+ individuals that had a CTL response to this epitope broken down by group: 0/1 group 1, 0/0 group 2, and 1/1 group 3.

HXB2 Location p17 (76–86)
Author Location p17
Epitope `RSLYNTVATLY`
Epitope name A30-RY11(p17)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A30)
Donor MHC A30, A32, B18, B27
Keywords HAART, ART, supervised treatment interruptions (STI)
References Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (`http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html`) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8+ T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient D displayed the greatest response to B27-KK10 (p24), and also responded to A30-RY11(p17), A32-PW10(RT), A30-KY11(RT), A32-RW10(gp120), and B18-YY9(Nef).

HXB2 Location p17 (76–86)
Author Location p17
Epitope `RSLYNTVATLY`
Epitope name RY-11
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A30)
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords subtype comparisons, epitope processing, immunodominance, cross-presentation by different HLA
References Masemola *et al.* 2004b

CTL CD8+

- Highly targeted regions in Gag for CD8+ T-cells were defined for individuals with C clade infections in South Africa. 9 specific epitopes within the most reactive regions were characterized.
- RSLYNTVATLY was presented by A*30, which is more common in Zulus than Caucasians (0.195 versus 0.019). This epitope had previously identified in B clade infections.

HXB2 Location p17 (76–86)
Author Location p17
Epitope RSLYNTATLY
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A30)
Donor MHC A*02, A*30, B*15, B*4402
Assay type T-cell Elispot
Keywords HIV exposed persistently seronegative (HEPS)
References Missale *et al.* 2004

- HIV-specific T-cell response was tested in patients exposed to blood from a patient with highly replicating HIV; these patients were nosocomially infected with HBV, but uninfected with HIV. HIV-specific T-cell responses were directed to structural and non-structural HIV proteins in 2 patients, suggesting that the virus replicated in these patients sufficiently to prime a cell-mediated immune response that protected them from HIV infection.
- This patient responded to 4/8 HIV epitopes tested in an IFNgamma Elispot assay or tetramer assay. Responses were detected 8 and 28 weeks after exposure, this particular epitope was only tested with Elispot.

HXB2 Location p17 (76–86)
Author Location p17 (76–86)
Epitope RSLYNTVATLY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A30)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, subtype comparisons, acute/early infection
References Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (ANC) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- This epitope, RSLYNTVATLY, is invariant across CON A, B, C and M-Group sequences, as well as clade B COT and ANC sequences. HLA-A30 restriction was inferred based on subject possessing appropriate HLA class I allele and prior publication.

HXB2 Location p17 (76–86)
Author Location
Epitope RSLYNTVATLY
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (A30)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location p17 (76–86)
Author Location Gag
Epitope RSLYNTVATLY
Epitope name RY11-A30
Subtype B, F
Immunogen HIV-1 infection
Species (MHC) human (A30)
Country Argentina
Keywords HLA associated polymorphism
References Dilernia *et al.* 2008

- Dynamics of CTL escape mutations was studied theoretically by analyzing plasma samples from 302 subjects (collected over 20 years). HLA associated polymorphisms accumulated in a subtype-specific manner.
- Epitope RSLYNTVATLY with anchor residues at RSLYNTVATL(Y) contains a polymorphism RSLYNTVvTLY.

HXB2 Location p17 (76–86)
Author Location Gag
Epitope RSLYNTVAVLY
Epitope name RY11-A30
Subtype B, F
Immunogen HIV-1 infection
Species (MHC) human (A30)
Country Argentina
Keywords dynamics, escape
References Dilernia *et al.* 2008

- Dynamics of CTL escape mutations was studied theoretically by analyzing plasma samples from 302 subjects (collected over 20 years). HLA associated polymorphisms accumulated in a subtype-specific manner.
- Epitope RSLYNTVAVLY with anchor residues at RSLYNTVAVL(Y) and a polymorphism rSLYNTVAVLY mutates to variant kSLYNTVAVLY which increases in time.

HXB2 Location p17 (76–86)
Author Location

Epitope RSLYNTVATLY
Immunogen
Species (MHC) human (B58)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B58 epitope.

HXB2 Location p17 (76–86)
Author Location
Epitope RSLYNTVATLY
Immunogen
Species (MHC) human (B63)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B63 epitope.

HXB2 Location p17 (76–86)
Author Location p17
Epitope RSLYNTVATLY
Epitope name RY11
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B57, B58, B63)
Donor MHC A*02, A*24, B*1517, B*58, Cw*03, Cw*07
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, cross-presentation by different HLA, optimal epitope
References Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This is a putative HLA-B63/57/58 epitope containing the B58 supertype binding motif. Peptide reactivity was enriched for those that carry B63, with a trend for those that carry B57/B58. Optimal epitope was defined in an individual that was B*1517(B63)/B58 positive.

HXB2 Location p17 (76–86)
Author Location p17
Epitope RSLFNTVATLY
Epitope name RY11(p17)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope RSLFNTVATLY elicited an immune response as part of peptide TGSEELRSLFNTVATLY. This epitope differs from the previously described HLA-A30 and B58-restricted epitope , RSLYNTVATLY, at 1 residue, RSLfNTVATLY.
- 0 of the 15 HLA-A30 carriers responded to an RSLfNTVATLY-containing peptide and 1 of the 14 HLA-B58 carriers responded to that peptide with average magnitude of CTL response of 170 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p17 (76–88)
Author Location Gag (76–84 SIV)
Epitope KSLYNTVCV
Epitope name KV9
Immunogen vaccine
Vector/Type: DNA, DNA prime with virus-like particle (VLP) boost *Strain:* SIV *HIV component:* Gag
Species (MHC) mouse (H-2D^{b})
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining
Keywords vaccine-induced epitopes, immunodominance, vaccine antigen design, SIV
References Liu *et al.* 2006a

- An SIV Gag DNA vaccine was studied in mice in order to enhance subdominant immune responses to the KV9 epitope, without compromising its immunodominant response to the Gag AL11 epitope. Both epitopes share a common MHC restricting allele. Novel vaccine strategies including anatomic separation and heterologous prime-boost were investigated to expand vaccine-elicited CTL responses. This was the first study of its kind using DNA gene-based vaccines.
- This epitope, KSLYNTVCV (KV9), was the subdominant epitope studied, but it was capable of eliciting a response of comparable magnitude to the immunodominant epitope, AL11, in the absence of AL11 during vaccine priming.
- This subdominant epitope KV9 had an augmented response even in the presence of immunodominant AL11, making their responses codominant, when vaccine administration used anatomic separation or heterologous boost strategies.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Keywords HAART, ART
References Huang *et al.* 2000

- The single cell ELISPOT assay was optimized and highly specific, and found to work well even after the primary cells had been frozen and thawed.
- Increases in gamma IFN producing cells were observed in response to anti-retroviral therapy using single cell IFN-gamma-production ELISPOT.

- 4/8 A*02 subjects had a positive response to this epitope indicating that it is a major epitope for CD8+ gamma IFN production.
- In 3/3 HLA A*02, B*27 individuals, the dominant response in gag measured by both gamma IFN production and T-cell lysis was a B27 epitope, p24(263-272), not the A2 SLYNTVATL epitope.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Keywords HAART, ART
References Rinaldo *et al.* 2000

- Administration of triple-drug antiretroviral therapy (IDV, 3TC and ZDV) sometimes showed a transient increase and other times failed to increase CTL responses in patients with advanced HIV disease, but there is a stable population of tetramer stained HIV-specific CD8+ CD45RO+ cells that can persist after therapy and long periods of virus being below the level of detection.

HXB2 Location p17 (77–85)
Author Location p17
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Keywords HAART, ART, immunodominance
References Scott-Algara *et al.* 2001

- This study examined with CTL response in HLA A*02+ children by tetramer staining for HLA-A2 immunodominant epitopes SLYNTVATL and ILKEPVHGV.
- 71% of the 28 HIV-1 infected HLA-A*02 positive children recognized both epitopes, with cells from 26 children stained positive by the gag tetramer (SLYNTVATL) and 21 children by the pol tetramer (ILKEPVHGV)
- There were no differences observed in children that had therapy versus those that did not.
- Tetramer-binding cells were memory activated CD28-, CD45RO+, CD45RA- HLADR+, CD69-, CD8+ T-cells.

HXB2 Location p17 (77–85)
Author Location p17
Epitope SLYNTVATL
Epitope name GAG
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country France
Assay type Cytokine production, Tetramer binding, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords responses in children, characterizing CD8+ T cells
References Scott-Algara *et al.* 2005

- Only a fraction of HIV-1-specific CD8 T-cells detected in the PBMC of 17 infected children (ages 2-18) were able to produce cytokines (IFN-gamma, TNF-alpha) or chemokines (CCL4, CCL5) after stimulation with the cognate peptide. A negative correlation was found between the plasma viral load and the precentage of CD8+ Gag-specific T-cells secreting IFN-gamma. Tetramers used in this study were SLYNTVATL-HLA-A*02 and ILKEPVHGV-HLA-A*02.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- The major p17 Gag SL9 epitope, SLYNTVATL, varied to SLYNTiATL with change V82I at position 6 and SLfNTiATL with an additional change Y79F at position 3. The 79F mutant elicited lower magnitude and functional avidity responses than 82I and 79F82I mutants. Even so, in time most variants were Y79F which showed positive selection. This Y79F mutant was seen combined with upstream changes E62G/V/A. In combination with 62E and 62G however, the Y79F mutant did not propagate successfully. Later, in combination with 62A the 79F mutant coincided with increasing viral load.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Assay type CTL suppression of replication
Keywords class I down-regulation by Nef
References Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Late protein Gag epitope SLYNTVATL-recognizing CTLs were affected by Nef.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human (A*02)
Assay type Other
Keywords kinetics
References Wick *et al.* 2005

- Experimental and mathematical models were used to estimate the number of HIV-infected cells that can be killed by CD8+ T-cells. On average, CTLs can kill from 0.7 to 3.0 cells/day.
- CTL clone 18030D23 recognizes epitope SLYNTVATL and was used to study the inhibition of HIV-1 replication in acutely infected cells in vitro.

HXB2 Location p17 (77–85)
Author Location
Epitope SLYNTVATL
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Keywords review, epitope processing, rate of progression, escape, immune evasion, viral fitness and reversion, optimal epitope, HLA associated polymorphism, compensatory mutation
References Blankson *et al.* 2006

- Based on two papers, Iversen 2006 and Frahm 2006, the authors point out that in choosing epitopes for use in AIDS vaccines not only immunogenicity but fitness cost of escape mutations must be considered. Thus immunization may be made to both wild-type and common escape variants.
- Frahm et al. showed subdominant epitopes of an HLA-B*1503 restricted response to HIV were able to reduce viremia. Thus, while epitopes that lack sequence variation may form good targets, so would subdominant epitopes.
- Iversen et al. found 2 pathways of conservative residue change that affect CTL epitope contacts with HLA-A*02: one acquiring escape mutations (SLfNTiAvL) and the other retaining or reverting to index residues in Gag protein's SLYNTVATL (SL9) epitope.
- Since viral loads in patients with escape mutations in SL9 are typically lower, it is suggested that CTL responses to subdominant epitopes in such patients may be involved in replication control.

HXB2 Location p17 (77–85)
Author Location
Epitope SLYNTVATL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Addo *et al.* 2007

- Maturation phenotypes of CTLs were compared between HIV-1 Controller and Progressor subjects. Controllers were found to recognize a median of 18 epitopes compared to 15 by Progressors. While Controllers certainly had higher frequencies of terminally differentiated effector CTLs (CD45RA+/CCR7-), Progressors had higher mean frequencies of CD45RA-/CCR7- effector memory, CD45RA-/CCR7+ central memory (statistically significant) and CD45RA+/CCR7+ naive CTLs. No correlation was seen between CTL effector phenotype and either HLA-type or epitope.
- A*02-restricted epitope SLYNTVATL does not correlate with any particular CTL maturation phenotype.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLYNTVATL
Epitope name SL9
Subtype A, B, C, D, F, G, K
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Chromium-release assay, Other
Keywords subtype comparisons
References Bennett *et al.* 2008

- Cross-clade CTL epitope recognition was tested for functional responses by CTL suppression using endogenously derived cell-surface epitopes rather than supraphysiologic exogenously added peptide epitopes. Functional avidity was actually diminished in non-autologous clade epitopes, calling into question current methods for assessing cross-clade or standard CTL activity and therefore vaccine design.
- SL9 epitope variants used were SLYNTVATL for clades B/A1/C/D, SLYNTVAVL for clades A2/F1, and SLFNTVATL for clades G/K. Clade B-elicited CTLs recognized epitopes from all other clades when tested by Cr-release. Suppression of HIV replication however, as well as functional avidity were reduced for different clade consensus epitope sequences.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen in vitro stimulation or selection
Species (MHC) human (A*02)
Assay type Intracellular cytokine staining, Flow cytometric T-cell cytokine assay, CTL suppression of replication
Keywords escape, TCR usage
References Varela-Rohena *et al.* 2008

CTL CD8+

- An SL9-specific CTL line was used to isolate a supraphysiologically binding TCR, but its dwell time of interaction was <1 min. All escape mutants were able to bind this CTL line and activate CTLs, giving stronger polyfunctional responses that controlled the replication of multiple HIV isolates. This is in contrast to WT TCR-expressing CTL lines.
- Escape variants include SLfNTVATL (Y3F), SLfNTVAvL (Y3F T8V), SYfNTiAvL (Y3F V6I T8V) and SLhNTVATL.
- A modified 'suppression of HIV' assay was used in this study.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-A*02-associated substitution within optimally defined epitope SLYNTVATL is at position A7, SLYNTVaTL. Frequency of escape at this position, however, was 0. Escapes reported at positions 3, 6, 8 are actually associated with other overlapping epitopes of HLA-A*29 and -Cw*14.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLFNTVATL
Epitope name SFL9
Immunogen computer prediction
Species (MHC) human (A*02)
Keywords TCR usage
References Frankild *et al.* 2008

- TCR can recognize multiple and distinct ligands. A model of TCR peptide recognition using amino acid similarity matrices is developed here, to predict cross-reactivity within diverse CTL epitopes. The ability of TCRs to recognize unrelated peptides with high specificity is termed "poly-specificity" here.
- Non-immunogenic HIV peptides were found to be similar to human self-antigens, suggesting that sequence similarity to self-antigens is what discriminates between immunodominant and cryptic epitope-elicited CTL responses.
- TCR specificity is position dependent in SLFNTVATL, similar aa substitutions usually do not affect TCR recognition of epitopes. In this epitope, position 1 is consistently of less importance and can tolerate mutation. Position 5, however, can only tolerate one possible mutation, T5S, to SLFNsVATL. Postions 2-6, and 8-9 are most important for peptide recognition and positions 2 and 9 determine peptide binding.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLYNTVATL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country Canada
Keywords HLA associated polymorphism
References Brumme *et al.* 2008b

- A large chronically infected, treatment naïve cohort was studied to identify and organize HLA I-associated polymorphisms in Gag into an immune escape map. Insertion polymorphisms at p17 C-terminus were associated with HLA-B*44, -A*32, -C*05. Inverse correlations were found between number to HLA-associated sites and pVL as well as escaped Gag residues and pVL. pVL positively correlates with CD4 T-cell count. No enrichment for HLA-associated polymorphisms are seen at anchor residues, showing that CTL escape is primarily not through abrogation of peptide-HLA binding.
- No HLA-A*02 associated substitutions were seen in p17 SLYNTVATL.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLFNTVATL
Epitope name SL9
Subtype A1
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country Kenya
Keywords epitope processing, escape
References Peters *et al.* 2008a

- Gag sequences from 468 HIV-1 positive sex workers from the Kenyan Pumwani cohort were analyzed to bioinformatically identify positively selected residues that could be related to antigen processing. Mutation effects on disease progression were followed by mean CD4 counts. This method is also one way of identifying potential CTL epitopes and classifying them.
- A Gag positive selection map was generated and sites were classified as beneficial or harmful to HIV. They were correlated to antigen processing (proteasomal cleavage), antigen presentation (TAP transport efficiency) and T-cell receptor binding.
- p17 and p24's structural constraints limited their diversity, while p7-p1-p6 showed a higher average entropy.
- HLA-A*0201-restricted SL9, SLFNTVATL, has positively selected F79Y i.e. SLyNTVATL and T81A i.e. SLFNaVATL. SLyNTVATL has significant positive correlations with HLA-A*0202 and negative correlations with HLAs-A*0101, A*3002 and A*3601. The negative correlations suggest that Phe(F) is an escape mutation within SL9 that became fixed in the population. Mutation T81A is negatively correlated with HLA-A*0201. Other positive selections are mutations flanking SL9, viz. L75I and I92M correlating to HLA-A*02 and

are possible peptide processing and recognition mutants. Another HLA-A*0201-restricted SL9 mutation, V82I, SLFNTiATL, correlates with a decrease in CD4 counts.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country Canada, South Africa
Keywords escape
References Carlson *et al.* 2008

- A statistical model, the phylogenetic dependency network (PDN), was developed to differentiate the confounding effects of codon variation, linkage disequilibrium of HLA alleles and HIV phylogeny from HLA-associated evolution including HIV selection by HLA-pressure and codon evolution.
- This approach was applied to 2 cohorts of 1144 Gag sequences from HIV-infected individuals, generating associations between HIV codons themselves and codons with HLA alleles. Results generated predicted escapes that confirmed that escape kinetics and compensating mutations are consistent across clades. General patterns of covariation and CTL adaptation were determined. Some clade-based differences were identified.
- HLA-A*02-restricted, clade B consensus SL9, SLYNTVATL, has previously reported escapes that PDN did not find.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLFNTVATL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country Canada, South Africa
Keywords escape
References Carlson *et al.* 2008

- A statistical model, the phylogenetic dependency network (PDN), was developed to differentiate the confounding effects of codon variation, linkage disequilibrium of HLA alleles and HIV phylogeny from HLA-associated evolution including HIV selection by HLA-pressure and codon evolution.
- This approach was applied to 2 cohorts of 1144 Gag sequences from HIV-infected individuals, generating associations between HIV codons themselves and codons with HLA alleles. Results generated predicted escapes that confirmed that escape kinetics and compensating mutations are consistent across clades. General patterns of covariation and CTL adaptation were determined. Some clade-based differences were identified.
- HLA-A*02-restricted, clade C consensus SL9, SLFNTVATL, has previously reported escapes that PDN did not find.

HXB2 Location p17 (77–85)
Author Location (LAI)
Epitope SLYNTVATL
Epitope name S9L
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other
Species (MHC) human, transgenic mouse (A*02.01)
Country France
Assay type proliferation, CD4 T-cell Elispot - IFNγ, Chromium-release assay, Other
Keywords computational epitope prediction, Th1
References Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQNANPDCKTILKALGPA, KTILKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTILKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQNANPDCKTILKALGPA, NKIVRMYSPTSILDIRQGPK.
- Epitope S9L was one of 2 CTL reporter epitopes in recombinant mouse invariant chain constructs used for readout in a penatmer staining assay.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 HXB2)
Epitope SLYNTVATL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords epitope processing, immunodominance, escape
References Brander *et al.* 1999

- Multiple natural variations in the SL9 flanking regions of the immunodominant epitope SLYNTVATL were tested and found not to adversely affect CTL recognition or prevent epitope processing, suggesting that viral escape from the HLA-A*0201-restricted CTL response against SLYNTVATL is probably not linked to variations in the flanking regions of this epitope.
- The substitution Y79F was an escape mutation in that it interfered with CTL recognition by one CTL clone from an A*0201 infected individual, clone 13010.B17, but it was still recognized by another CTL clone, 115.D4.

HXB2 Location p17 (77–85)
Author Location p17
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords acute/early infection
References Wilson *et al.* 2000a

CTL CD8+

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T-cells and viral load was also found.
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B2705; and A*0201, A*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK.
- The subject with A*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705.
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Tan *et al.* 1999

- Adoptive transfer of two autologous *in vitro*-expanded CTL clones against the A*0201 restricted epitopes SLYNTVATL and VIYQYMDDL were infused into a patient – they were well tolerated, but the SLYNTVATL clone was shown by tetramer staining to be rapidly eliminated through apoptosis, and the treatment had no impact upon viral load and CD4 and CD8 cell counts.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- Individuals who did not respond to SLYNTVATL recognized other HIV epitopes, and 2/4 SLYNTVATL responders had stronger responses to epitopes restricted by other class I alleles.
- SLYNTVATL was the only response detected in a one individual that was HLA A*0201, B44, B70.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords HAART, ART
References Ogg *et al.* 1999

- CTL effector levels were measured after potent ARV therapy using HLA-tetramer complexes for the A*0201 epitopes SLYNTVATL and ILKEPVHGV in seven patients, and the B*3501 epitope DPNPQEVVL in one additional patient.
- Levels of CTL effectors typically decline for 5-7 days and then rebound, fluctuating during the first two weeks of therapy.
- After the early fluctuation, there was a steady exponential decay with a median half-life of 45 days.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Altman *et al.* 1996

- This paper introduces the tetramer methodology that permits quantification of specific CTL based on expression of specific TCRs – HLA-A2 tetramers were prepared that can stain CTL lines specific for ILKEPVHGV and SLYNTVATL, and quantitate HIV-specific CD8+ cell lines in freshly isolated PBMCs.
- Three patients only stained the Gag epitope SLYNTVATL, one patient had the highest frequency of tetramer staining to the Pol epitope (0.77%), less to the Gag epitope (0.28%).

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords HAART, ART
References Gray *et al.* 1999

- Administration of highly active antiretroviral therapy (HAART) reduced CD8+ cell frequency, and the CD8+ cells detected by tetramer staining were likely to be memory cells, indicating that persistently replicating viral populations are needed to maintain high frequencies of HIV-1 specific CTL.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 SF2)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords subtype comparisons
References McAdam *et al.* 1998

- CTL from a patient infected with clade B virus did not recognize the clade A analog of this epitope.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)

Keywords TCR usage
References Wilson *et al.* 1998a

- HIV+ individuals were followed longitudinally using MHC tetramers in combination with 14 anti-BV chain MAbs, and clonal expansion of HIV-specific T cells was followed *in vivo*.
- Seven HIV+ people were studied, and all showed expansions of particular TCR BV clones, often several, relative to uninfected controls.
- Three patients were followed in detail, TCR VB expansions persisted for 2 to 3 years, with occasional transient increases.
- An A2-Gag specific line from one patient was found to be BV8, and at its highest level represented 17.5% of the patient's CD8+ T cells.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Ogg *et al.* 1998b

- HLA-tetrameric complexes were used in a cross-sectional study of 14 untreated HLA A*0201 positive individuals, revealing an inverse relationship between HIV Gag and Pol specific CTL effector cells (CTLe) and viral load.
- Inclusion of both the p17 SLYNTVATL and RT ILKEPVHGV epitopes gives a good representation of HLA A*0201-restricted activity.
- No correlation was observed between the CTLe and CD4 count or clearance rate of productively infected cells.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Keywords epitope processing
References Walter *et al.* 1997

- HLA-A2 heavy chain and β2-microglobulin expressed in E. coli were refolded in the presence of this peptide.
- The HLA-A2-peptide complex elicited HLA-A2 peptide-specific CTL response in cells lacking HLA-A2.
- Suggests that preformed HLA-peptide complexes could provide an alternate to intracellular processing for immunogens.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Lalvani *et al.* 1997

- A peptide-based protocol was optimized for restimulation of CTLp using optimized peptide and IL-7 concentrations – importantly this protocol does not stimulate a primary response, only secondary – peptide-specific CTLp counts could be obtained via staining with peptide-Class I tetramers.
- This peptide was one of the test peptides for optimizing the protocol.

HXB2 Location p17 (77–85)
Author Location p17 (76–84)
Epitope SLYNTVATL
Epitope name SL9
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
References van der Burg *et al.* 1996

- Slow dissociation rate is associated with immunogenicity.
- CTL generated by *in vitro* stimulation of PBMC derived from uninfected individual.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords review, escape
References Goulder *et al.* 1997e; Goulder *et al.* 1997a

- HLA-identical siblings, hemophiliac brothers, were both infected with the same batch of factor VIII.
- One had a response to gag A2 epitope SLYNTVATL, the other to pol A2 epitope ILKEPVHGV. They were tested 6-8 years after infection.
- Viral sequencing from the twin that had no response to SLYNTVATL indicated his virus had the substituted form SLHNAVAVL.
- 71% of an additional set of 22 HIV-1 infected HLA-A*0201 positive donors preferentially responded to gag SLYNTVATL.
- Those individuals with a pol ILKEPVHGV response tended to have mutations in or around SLYNTVATL.
- An additional subject went from SLYNTVATL responder to non-responder coincident with a switch to the variant SLFNTVATL.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords review
References Goulder *et al.* 1997a

- This paper is a review of CTL and immune evasion, but it presents a study of a shift from an HLA-A*0201 response to SLYNTVATL, to a B62 response to GLNKIVRMY.
- As long as a strong CTL response to SLYNTVATL was evident, the epitope variants SLFNTVATL or SLYNTIATL dominated the viral population – eventually the CTL response to the index peptide became undetectable, the CTL response shifted to a focus on GLNKIVRMY, and the index peptide SLYNTVATL once again established itself as the dominant form.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection

CTL CD8+

Species (MHC) human (A*0201)
Keywords HAART, ART
References Gray *et al.* 1999

- Peptide-tetramer complexes of A*0201 and SLYNTVATL or ILKEPVHGV were used to study individuals receiving HAART to determine the frequency of Class I HLA-restricted anti-HIV CD8+ T cells.
- 17/18 asymptomatic patients had a CTL response to one or both epitopes – 72% had a CTL response to SLYNTVATL.
- After HAART, the majority of the epitope-specific CTL were apparently memory cells.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 subtype A)
Epitope SLFNTVATL
Epitope name SL9
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords subtype comparisons
References Dorrell *et al.* 1999

- CTL responses in three individuals with non-clade B infections were studied, two with subtype A infections, one with subtype C – their infections all originated in East Africa.
- This epitope is most commonly SLYNTVATL in B subtype, and CTL from the C subtype infection did not recognize B clade gag or the 3Y form of the epitope, but did recognize the predominant A and C clade form, SLFNTVATL.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords immunodominance
References Brander *et al.* 1998a

- Of 17 infected HLA A*0201 subjects, 13 had CTL responses against the p17 SLYNTVATL epitope, six recognized ILKEPVHGV and five recognized VIYQYMDDL, and there was no correlation between viral load and recognition of a specific epitope.
- Only one subject had CTL against all three epitopes.
- There was significant heterogeneity in the CTL response to this immunodominant epitope.
- The overall variation in this epitope among the 17 who had a CTL response and 11 non-HLA A*0201 HIV-1 + individuals was similar, suggesting a lack of immune pressure.
- Subjects were part of the San Francisco City Clinic Cohort, the ARIEL project and from the Boston area.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 HXB2)
Epitope SLYNTVATL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords rate of progression, immunodominance
References Hay *et al.* 1999

- CTL response to IPRRIRQGL was the immunodominant response in a rapid progressor – there was a subdominant response to SPAIFQSSM in Pol, and interestingly, no response to commonly immunodominant HLA A*0201 epitope SLYNTVATL, although this individual was HLA A*0201.
- The individual showed a strong initial CTL response at the time of the initial drop in viremia, but it was quickly lost, although memory cells persisted.
- Despite the initial narrow response to two epitopes, no other CTL responses developed.
- No HIV-specific lymphoproliferative responses were detected in this patient, and neutralizing antibody response was weak.
- A variant of this epitope was observed *in vivo* (–F—-V-), but this mutation is recognized by SLYNTVATL-specific CTL, and in this case the patient's cells could present the peptide to SLYNTVATL-specific CTL.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords HAART, ART
References Kalams *et al.* 1999b

- Two patients were followed before and after HAART – reduced plasma HIV-1 RNA levels resulted in a decline in HIV-specific in-vivo activated CTL such that by day 260 CTL activities were undetectable.
- ERYLKDQQL was the dominant response in one of the individuals, SLYNTVATL subdominant.
- Sporadic breakthrough in viremia resulted in transient increases in CTLp.
- Memory CTL frequency directed against Vac-Gag, Vac-RT, Vac-Env, and Vac-Nef initially increased with HAART and then decreased with the decline of the viral load.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Spiegel *et al.* 2000

- High levels of CD8+ HIV-1 specific and cytomegalovirus specific CTL were detected by HLA-A*0201-peptide tetramers in 3 infected subjects with very low CD4 counts, but CD8 T cell mediated effector activity was not seen.
- Thus HIV-1 specific CD8+ cells may be present but may lack direct effector activity in late disease, suggesting that overcoming antigen unresponsiveness may be a useful therapeutic strategy.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Larsson *et al.* 1999

- ELISPOT was used to assay the CD8+ T-cell response to the HIV-1 proteins Gag, Pol, Nef or Env expressed in vaccinia vectors in 19 HIV+ people.

- The highest CTL frequency was directed at epitopes Pol.
- In A*0201 individuals, higher numbers of spot-forming T cells were directed against HIV-1 proteins expressed in vaccinia than to peptides SLYNTVATL and ILKEPVHGV presented by A2.

HXB2 Location p17 (77–85)
Author Location p17 (SF2)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in 11/25 HLA A2 (A*0201 or A*0202) HIV+ individuals from Boston and in 1/8 HLA A2 HIV+ individuals from Durban.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 LAI)
Epitope SLYNTVATL
Subtype B
Immunogen
Species (MHC) human (A*0201)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*0201 epitope.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 SF2)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords escape, acute/early infection
References Goulder *et al.* 2001a

- This epitope is targeted by 75% of HLA-A*0201, HIV+ adults, and the magnitude of the response is inversely correlated with viral load.
- CTL responses to SL9 and autologous SL9 variants were not detected in 11 HLA-A*0201 positive subjects during acute infection.
- Longitudinal studies of two individuals (AC13 and PI004) showed that the initial control of viremia was independent of the SL9 CTL response.
- Low Gag expression levels did not correlate with the delayed CTL response to this epitope.
- Autologous SL9 variants SLYNTIAVL, SLYNTVAVL, SLFNTVATL, SLFNTVATL, and SLFNTVATL are each capable of inducing a range of CTL responses, sometimes strong, sometimes diminished, and sometimes complete escape relative to the wild type variant SLYNTVATL in patients with chronic HIV-1 infection – the ability to cross-react with a particular variant was patient dependent.

HXB2 Location p17 (77–85)
Author Location p17
Epitope SLYNTVATL
Epitope name p17 SL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords subtype comparisons, supertype, computational epitope prediction
References Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, including p17 SL9, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2).
- p17 SL9 was recognized in 12/22 patients with chronic HIV-1 infection.
- Only 1/13 patients with acute HIV-1 infection recognized p17 SL9.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLYNTVATL
Epitope name (SL9)
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Goepfert *et al.* 2000

- This paper describes a comparison of results of different CTL assays, a SL9 tetramer assay and IFN-gamma ELISPOT, using 7 HIV-positive patients.
- The IFN-gamma ELISPOT assay was compared using the single SL9, a pool of overlapping 20 mers, and recombinant vaccinia encoding Gag as antigen – pooled peptides gave the highest number of spot forming cells, vaccinia gave high background.
- A correlation with results of the tetramer assay was found only for ELISPOT using the Gag epitope as antigen, but the tetramer assay detected a 10-fold higher number of cells than could produce IFN-gamma in the ELISPOT assay – the authors suggest not all tetramer-positive cells may produce IFN-gamma, some may be undergoing apoptosis, some may be producing other cytokines.
- The tetramer assay could detect a reaction to SLYNTVATL in most of the HLA-A*0201 chronically HIV-1 infected study subjects.

HXB2 Location p17 (77–85)

Author Location Gag (77–85)
Epitope SLYNTVATL
Immunogen
Species (MHC) human (A*0201)
Keywords binding affinity
References Sandberg *et al.* 2000

- This epitope served as a positive control in a study comparing peptide binding affinity to HLA-A201 to CTL responses upon vaccination with a nef DNA vaccine.

HXB2 Location p17 (77–85)
Author Location Gag (LAI)
Epitope SLYNTVATL
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Keywords dendritic cells
References Engelmayer *et al.* 2001

- Recombinant canarypox virus vector containing HIV-1 sequences, upon infection of mature dendritic cells, can trigger specific lysis through *in vitro* by T-cells from HIV-1 infected individuals at levels comparable to the response seen to HIV carried in vaccinia vectors.
- Recombinant canarypox virus vector containing HIV-1 sequences can also stimulate HIV-specific CD4+ helper T-cell responses.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 LAI)
Epitope SLYNTVATL
Epitope name G3
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords HAART, ART
References Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using tetramer staining or CD8+ cell IFNgamma production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Gea-Banacloche *et al.* 2000

- In a study including many long-term non-progressors, no correlation between plasma virus levels and number of HIV-specific CD8+ T-cells was found.
- High frequencies of circulating CD8+ T-cells were HIV-1 specific, and the majority of these responses were to gag-pol gene products.
- 4/21 subjects were HLA-(A*0201), and of these only 2 subjects (patient 3 and 19) tested positive to this epitope.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 SF2)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- Tetramer staining with A2, beta2microglobulin, and either SLYNTVATL, KLVGKLNWA, or LTFGWCFKL revealed that tetramers detected more HIV-specific sells in LTNP than in progressors, activated effector cells were the minority population, and ELISPOT correlated better with the effector cell subpopulation than the total tetramer stained population.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords HAART, ART, rate of progression
References Jin *et al.* 2000a

- The CTL effector levels (CTLe) were compared in long term non-progressors (LTNP) with low viral load and in patients whose virus was well-suppressed by therapy, using a tetramer assay.
- LTNPs have high memory CTLe numbers and low viral load, while HAART patients had low CTLe numbers and low viral load.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Appay *et al.* 2000

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.

- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Goulder *et al.* 2000b

- Tetramer assays were compared with three functional assays in 42 people with chronic HIV infection: ELISPOT, intracellular cytokine staining, and precursor frequency (limiting dilution assay [LDA]).
- HIV-specific tetramer staining CTLs appeared to be active, and inert CTL were not found to play a significant role in chronic pediatric or adult HIV infection.

HXB2 Location p17 (77–85)
Author Location p17
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords dendritic cells
References Ostrowski *et al.* 2000

- The role of CD4+ T-cell help in expansion of virus-specific memory CTL was studied through co-culture *ex vivo*.
- Optimal expansion of HIV-1-specific memory CTL depended on CD4+ T cell help in 9/10 patients – CD40 ligand trimer (CD40LT) could enhance CTL in the absence of CD4+ T cell help to a variable degree in most of patients.
- Those CTL that didn't respond to CD40LT could expand with IL2 present, and IL15 produced by dendritic cells also contributes.
- The T-helper epitope used for CD4+ T cell stimulation was the universal tetanus helper epitope TET830-843 (QYIKANSKFIGITE).

HXB2 Location p17 (77–85)
Author Location
Epitope SLYNTVATL
Subtype B
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost, canarypox prime with gp160 boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* Gag, gp120, gp41, Nef, Pol
Species (MHC) human (A*0201)
Keywords vaccine-specific epitope characteristics
References Ferrari *et al.* 2001

- Different HIV strains were used for different regions: gp41 LAI, Gag LAI, gp120 MN, gp120 SF2.
- Two vaccinees with Gag responses were HLA-A*0201+, but neither made SLYNTVATL responses to the Gag vaccine, in contrast to its frequent recognition in natural infections. No HLA-A*0201 responses were observed to an Env vaccine.

HXB2 Location p17 (77–85)
Author Location
Epitope SLYNTVATL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords rate of progression, immunodominance
References Migueles & Connors 2001

- CTL activity was monitored in 27 individuals, including 10 LTNP with an over-expression of HLA B*5701 – these individuals have viral loads below the threshold of infection without therapy, and their immune response tends to be focused on peptides that contain B*5701 epitopes ISPRTLNAW, KAFSPEVIPMF, TSTLQEQIGW, and QASQEVKNW.
- CTL responses are broader in B*5701+ individuals with progressive viremia than those that control viremia.
- The HLA-A*0201 SLYNTVATL epitope response was not as strong in individuals that carried both A2 and B57.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords epitope processing, immunodominance
References Sewell *et al.* 2002

- Epitope processing of three different HLA-A*0201 HIV epitopes was shown to use different pathways, which might influence patterns of immunodominance. 174 cells were used that lack TAP1 and TAP2 genes, as well as the LMP2 and LMP7 genes that encode the beta-subunits of the immunoproteasome. These genes could be added back through transfection to study processing.
- ILKEPVHGV was efficiently presented in TAP-1 and -2 transfected cells while VIYQYMDDL and SLYNTVATL were not. VIYQYMDDL was destroyed by the MB1 subunit of the protease, and could be expressed in the presence of the proteasome inhibitor lactacystin, but SLYNTVATL expression was not restored. SLYNTVATL expression was unaltered by lactacystin in a wild type cell line.

HXB2 Location p17 (77–85)
Author Location Gag (ADA)
Epitope SLYNTVATL
Epitope name SL-9
Subtype B
Immunogen HIV-1 infected monocyte-derived
Species (MHC) mouse (A*0201)
References Poluektova *et al.* 2002

- Nonobese diabetic NOD-C.B-17 SCID mice were reconstituted with HLA-A*0201 positive human PBL and injected with HIV-1 infected monocyte-derived macrophages MDM in the basal ganglia to provide a mouse model of HIV-1 encephalitis.
- HLA-A*0201 CTL responses were detected by tetramer staining in the spleen in seven days, increased through day 14, and the numbers of productively infected were reduced >85% in the second week.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 LAI)

CTL CD8+

Epitope SLYNTVATL
Epitope name LR23
Subtype B
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade LAI *Adjuvant:* Incomplete Freund's Adjuvant (IFA), Montanide (ISA 720), P30, PLG
Species (MHC) mouse (A*0201)
Keywords binding affinity, vaccine-specific epitope characteristics, immunodominance
References Peter *et al.* 2001

- The stability of peptide binding to HLA-A2.1 was determined for six HLA-A2.1 peptides included in this vaccine study – ILKEPVHGV (RT), SLYNTVATL (p17), SLLNATDIAV (gp41) and LLWKGEGAV (RT) all bound with high affinity comparable to a influenza epitope reference (GILGFVFTL), while RGPGRAFVTI and VIYQYMDDL bound with a lower affinity (relative binding activity = 0.01).
- The four high-affinity peptides formed stable complexes with half-lives ranging between 8 and 32 hours, while the low affinity peptides had half lives of less than an hour.
- HLA-A2.1 transgenic mice were immunized with the six HIV-1 peptides and P30, as a universal T-helper epitope, with IFA or Montanide or microspheres as adjuvants.
- All peptides except VIYQYMDDL induced a stong CTL response in Cr-release assays - stronger responses were observed when peptides were delivered alone, indicating immunodominance when the combination was used.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 LAI)
Epitope SLYNTVATL
Epitope name LR23
Subtype B
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade LAI *Adjuvant:* Incomplete Freund's Adjuvant (IFA), IL-12, P30
Species (MHC) mouse (A*0201)
Keywords vaccine-specific epitope characteristics, immunodominance
References Peter *et al.* 2002

- When HIV-1 peptides were used to vaccinate HLA-A2.1 transgenic A2-Kb mice, strong responses to five peptides were observed when the peptides were given individually, but immunodominance limited the response to some of the peptides when they were given in combination Peter *et al.* [2001]. IL-12 can counteract immunodominance in BALB/c mice, so it was given with the multiple epitope vaccination, and was instead found to specifically eliminate the HLA-A2.1-epitope CTL responses, but not Kb CTL responses. This was possibly a consequence of transient depletion of T-cells, B cells and macropahges in the spleen.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Immunogen computer prediction
Species (MHC) (A*0201)
Keywords subtype comparisons, computational epitope prediction, vaccine-specific epitope characteristics, escape
References Schönbach *et al.* 2002

- Computational methods (artificial neural networks [ANN], hidden Markov models [HMM], binding matrices based on HLA association rates BIMAS) were used to identify HLA-A*0201 and HLA-B*3501 HIV T-cell epitope candidates from 533 Gag, Env and Pol sequences of which 374 were derived from HIV-1, 97 were derived from HIV-2 and 62 from SIV. Comparisons to known epitopes and between clades were made.
- The SLYNTVATL epitope received focused discussion. SLYNTVATL, slFntvatl, slyntvaVl, and syntIaVl are all recognized variants, ANN predicts all four variants would be recognized, while BIMAS only predicts SLYNTVATL and slFntvatl would be recognized. However, Sewell *et al.* [1997] suggested certain substitutions may be antagonistic, including slFntvatl, and vaccines do not stimulate SLYNTVATL responses as well as natural infections. The authors note these kinds of issues complicate the application of computational predictions of epitopes to vaccine design.

HXB2 Location p17 (77–85)
Author Location Gag (76–84)
Epitope SLYNTVATL
Subtype B
Immunogen vaccine
Vector/Type: DNA *HIV component:* HIV-1
Species (MHC) mouse (A*0201)
Keywords epitope processing, vaccine-specific epitope characteristics, immunodominance
References Singh *et al.* 2002; Sykes & Johnston 1999

- C3H (H-2k) transgenic mice carrying a fused HLA-A*0201 alpha1 and alpha2 and H-2Dk alpha3 hybrid class I molecule were immunized using an epidermal gene gun with an ubiquitin expression library of 32 plasmids that spanned the HIV-1 genome. Ubiquitin targets the expressed HIV-1 peptides to the proteasome.
- A single immunization with the UB-HIV-1 library vaccine induced potent, stable and multivalent CTL responses against all library members.
- Immunodominant epitopes SLYNTVATL (Gag), ILKEPVHGV (Pol), RIQRGPGRAFVTIGK (Env) and AFHHVAREK (Nef) elicited strong CD8+/IFN- responses and stimulated CTL that were functional in a Cr-release assay and against wild type antigen.
- The presence of multiple plasmids HLA-A*0201-restricted CTL epitopes did not decrease CTL immunogenicity, and CTL responses to single peptide immunizations were comparable to responses based on mixtures of either 16 or 32 peptides.

HXB2 Location p17 (77–85)
Author Location
Epitope SLYNTVATL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)

Donor MHC A*0202, A*2501, B*1801, B62, Cw*1203, Cw10, DQB1*8, DRB1*1501
Keywords rate of progression, Th1, Th2
References Imami *et al.* 2002b

- 70 patients with chronic disease progression, 10 clinical non-progressors, and 3 immunologically discordant progressors (individuals who controlled viremia but had progressive CD4+ T-cell decline) were analyzed for their T-helper cell responses to p24 and cytokine profile. Long term non-progressors had much stronger Th responses, particularly to p24 peptides, and they tended to be balanced between Th1, IL-2 producing and Th2, IL-4 producing responses.
- One of the immunologically discordant progressors became symptomatic during the course of the study, and he had a rapid drop in proliferative response to all antigens and also a shift from a Th1 to a Th2 response. To find out if the CD8 response also shifted in cytokine production, the CD8+ T-cell response to SLYNTVATL in this patient was also tested. It too was found to shift, from IFNgamma to IL-4 producing in Elispot, and using a bioassay of indicator lines, from IL-2 to IL-4 production.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope `SLYNTVATL`
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Donor MHC A*0201, A11, B51, B61, Cw*14, Cw2
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- Only 1/10 HLA A*02 carrying individuals in this study recognized SLYNTVATL.
- All HIV-1 proteins except Vpu were recognized, and responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

HXB2 Location p17 (77–85)
Author Location
Epitope `SLYNTVATL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Assay type Cytokine production, proliferation, Tetramer binding, Intracellular cytokine staining, Chromium-release assay
References Dagarag *et al.* 2003

- Telomer length is short in the CD8+ T-cell compartment of HIV-1 infected people, indicating excessive CTL activation and premature senescense. Here human telomerase RT (hTERT) transduction of HIV-1-specific CTL was used to study the functional impact of telomerase. Telomerase expression enhanced proliferative capacity, as well as cytolytic and antiviral capabilities; cytokine production was unchanged. hTERT transduced CTLs were 10-fold more efficient in controlling HIV-1 replication in culture. Thus telomerase transduction can restore CTL mediated cytolysis, and may have therapeutic potential.
- Three polyclonal CD8+ T-cell lines derived from an HIV-1, HLA A*0201 positive patient were used in this study, including one specific for this epitope.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope `SLYNTVATL`
Subtype B
Immunogen vaccine
Vector/Type: peptide *HIV component:* p24 Gag
Species (MHC) mouse (A*0201)
Donor MHC A2.1
Assay type Cytokine production, Chromium-release assay
Keywords binding affinity, vaccine-induced epitopes
References Okazaki *et al.* 2003

- Alanine substitutions of VIYQYMDDL were tested for importance of each amino acid for HLA-A2.1 binding. Peptide variant (vLyqymddV) showed an 8 fold higher MHC binding affinity than wild type. YLyqymddV had an even higher binding affinity, but the Y at position one blocked TCR recognition. The higher affinity form of vLyqymddV induced CTL *in vivo* that could protect against a vaccinia virus expressing RT and the wild type epitope.
- SLYNTVATL was included as a control.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope `SLYNTVATL`
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Assay type Tetramer binding
Keywords genital and mucosal immunity
References Shacklett *et al.* 2003

- Lymphocytes from rectal biopsies were used to characterize the CD8+ T cell response to HIV in GALT, Gut-associated lymphoid tissues. Patients were selected on the basis of being HLA-A2+ and having detectable SLYNTVATL and ILKEPVHGV tetramer responses in PBMC. SLYNTVATL frequency was increased in GALT relative to PBMC in 6/7 patients studied, while a control response to a CMV-peptide was diminished in GALT. Only two patients had ILKEPVHGV

CTL CD8+

CD8+ T cell responses, and both had slightly higher frequencies in GALT than PBMC.
- HIV may perturb lymphocyte retention in GALT, suggested by an overall reduction of GALT CD8+ cells expressing alphaEbeta7. GALT HIV-specific CD8+ T cells expressed alphaEbeta7, suggesting mucosal priming.

HXB2 Location p17 (77–85)
Author Location
Epitope SLYNTVATL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, T-cell Elispot, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords epitope processing, escape, variant cross-recognition or cross-neutralization
References Jamieson *et al.* 2003
- Epitope escape mutations in chronically infected individuals developed over several years indicating selective advantage of escape mutants. The maturation state of CTLs appear to affect the rate of epitope mutation and CTL decay.
- In two patients, SL9-specific CTL peaked at 2-4 years post-infection; at that point the escape mutations began to dominate followed by CTL decline with a 6 month lag, suggesting CTL decline resulted as a consequence of escape. In a third patient, the initial response was 1/2 as strong and mutations did not arise until 6-7 years post-infection; in that case the decline in SL9 CTL preceded epitope mutation.
- Two patients HLA-A*0201 started out with a non-consensus sequence, slFntvatl. In one of the patients, a transient reversion to the consensus was observed after 4 years, that did not reappear until the 11th year, suggesting the possibility that a reversion to the consensus form occurred, but a CTL response may have limited it so that this more fit form could not reassert itself until the patient had a more severely compromised immune response.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLYNTVATL
Epitope name SL9
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Country United States
Assay type Cytokine production, Tetramer binding, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords epitope processing, rate of progression, immunodominance, acute/early infection, dendritic cells, TCR usage, memory cells
References Kan-Mitchell *et al.* 2004
- SL9-specific CTLs were shown to be primed by immature DCs and independent of help from CD4+ or exogenous IL2, and sensitive to paracrine IL-2 induced apoptosis. The authors suggest that the reason SL9 responses are not seen during acute infection is the high level of innate immune responses resulting in cytokine-induced apoptosis, but that these CD8+ T-cells would come to dominate later infection when CD4 help is diminished.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Donor MHC A*0201, A*2402, B*52, B75, Cw*03; A*0201, A*31, B*27, B*5101, Cw*02; A*0207, A*2402, B*46, B*52, Cw*01
Country Japan
Assay type Chromium-release assay
Keywords epitope processing, escape
References Yokomaku *et al.* 2004
- Epitope variants escaped from being killed by CTLs in an endogenous expression system although they were recognized when corresponding synthetic peptides were exogenously loaded onto the cells. Escape is thus probably due to changes that occur during the processing and the presentation of epitopes in infected cells.
- Endogenously expressed wild type epitope and slyntIatl variants were recognized by CTL clones while slynLvatl, slFntvaVl and sVyntvatl variants were not. sVyntvatl and slFntvaVl variants were, however, recognized when added exogenously to the cells.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 LAI)
Epitope SLYNTVATL
Epitope name SL9
Subtype B
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost, vaccinia prime DNA boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Protease *Adjuvant:* GM-CSF
Species (MHC) human (A*0201)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Tetramer binding, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords vaccine-specific epitope characteristics, immunodominance, characterizing CD8+ T cells
References Ferrari *et al.* 2004
- Thirteen HLA-A*0201 vaccines with anti-Gag CD8+ CTL reactivities were tested in uninfected HIV vaccine recipients to examine the pattern of SL9 epitope immunodominance. None of the vaccines had a detectable anti-SL9 response, in contrast to 75% of HLA A*0201 chronically infected HIV+ individuals that respond to this epitope.

HXB2 Location p17 (77–85)

Author Location p17
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords review, rate of progression, escape, acute/early infection
References Goulder & Watkins 2004

- This paper is a review of the role of CTL in HIV infection, and it uses SL9 as an example of an epitope that is not responded to early in infection, yet 75% of HIV+ people respond to SL9 during chronic infection. Despite the delay in response, strong SL9 responses have been associated with lower viral loads, and escape mutations arise.

HXB2 Location p17 (77–85)
Author Location (C consensus)
Epitope SLYNTVATL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTIATL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Donor MHC A*0201, A*0301, B*3501, B*51, Cw*04, Cw*06
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords escape, acute/early infection, characterizing CD8+ T cells
References Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- The response to this peptide was not apparent until month 20, by month 32 a T to V change was dominant, but the slyntiVl mutant showed comparable avidity.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection, peptide-HLA interaction, vaccine
Vector/Type: peptide *Strain:* multiple epitope immunogen *HIV component:* mimotopes *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A*0201)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords vaccine-specific epitope characteristics, immunodominance, escape, TCR usage, variant cross-recognition or cross-neutralization, vaccine antigen design, mimics
References Boggiano *et al.* 2005

- A combinatorial library was used to identify epitope mimics of HLA-A2 restricted CTL epitope SL9.
- 19 HIV+ HLA-A*0201 subjects were tested for their ability to bind to peptide variants. 11/19 could bind to SLYNTVATL. Nine epitope mimics were recognized by more than a third of the subjects, and 1 subject recognized 17/20 variants tested. Some SL9 mimics were up to an order of magnitude better at stimulating CTL responses in PBMC than was SL9.
- Compared to the original SL9 sequence, some SL9 variants recognized by HLA-A*0201 patients induced superior SL9 immune responses in HLA-A*0201 transgenic mice.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, TCR usage, characterizing CD8+ T cells
References Killian *et al.* 2005

- A novel technique for subtractive analysis of HIV-1 specific CTLs was developed, including depletion of peptide-specific CTLs by stimulating PBMCs with the specific peptide in the presence of 5-FU, followed by TCR spectratyping for clonal breadth analysis. In analysis of infected individuals using this technique, it was found that HIV-1 specific responses range from two to 10 different T-cell clones per epitope.
- The SL9 responses in one individual were complex, with TCR in multiple families, including: Vbeta12.2, Vbeta17, Vbeta23.3 and Vbeta22.
- This paper provides further evidence for the polyclonal nature of epitope-specific responses. Polyclonal responses may be able to better inhibit escape and may play a beneficial role in progression.

HXB2 Location p17 (77–85)

CTL CD8+

Author Location Gag
Epitope SLYNTVATL
Epitope name S9L
Immunogen vaccine
Vector/Type: measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140ΔV3
Species (MHC) transgenic mouse (A*0201)
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells
References Lorin *et al.* 2005a

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

HXB2 Location p17 (77–85)
Author Location (C consensus)
Epitope SLYNTVATL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- SLYNTVATL is an optimal epitope.

HXB2 Location p17 (77–85)
Author Location p17
Epitope SLYNTVATL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords HAART, ART, responses in children, dendritic cells
References Zhang *et al.* 2006b

- Immune responses in HIV-1 infected children either undregoing HAART or not were analysed. HIV-specific CTLs were lower in children responding to HAART than in non-responders and HAART-naive children. CTL frequency was correlated with myeloid DC frequency in treatment-naive patients, and inversely correlated with duration of virus supression following treatment.
- 11 of the 22 children had significant responses to SL9.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, SLYNTVATL, was found to be 0.006/day (upper bound on rate of escape = 0.008), with SE of 0.001.
- Four variants were shown to confer escape (Y79F, Y79F-V82I, Y79F-T84V, V82I-T84V), and variant A83V was also present but untested for CTL response.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Subtype B
Immunogen peptide-HLA interaction
Species (MHC) human (A*0201)
Assay type Cytokine production, Flow cytometric T-cell cytokine assay
Keywords binding affinity, co-receptor, characterizing CD8+ T cells
References Laugel *et al.* 2007a

- It was found that CD8 co-receptor differentially fine tunes CTL function via cytokine/chemokine production (MCP-1, MIP1-beta, MIP1-alpha, TNF-alpha, RANTES, IFN-gamma, IL-2 and IL-4). Differential CD8 action was controlled by abrogating its engagement using point-mutated HLA Class I molecules in 4 CTL clones specific for 3 different epitopes from HIV-1 and hTERT.
- 2 HLA-A*0201 restricted CTL clones, SLY-10 and 003, specific for HIV-1 Gag eptiope SLYNTVATL were stimulated with cognate antigen and found to have different diversities as well as hierarchies of cyto/chemokine production. Epitope variants 3H (SLHNTVATL), 3S (SLSNTVATL) and 3F (SLFNTVATL) also selectively blocked effector functions for

each clone. CD8 co-receptor requirement was minimally affected for the index ligand SLYNTVATL recognition by CTL, but weaker agonists viz. the epitope variants depended more on co-receptor binding. However, MIP1-beta and IL-2 were consistently the least- and most-CD8 dependent effector secretions.
- This is the first documentation of secretion of MCP-1 by T cells. It seems to require high antigen and co-receptor dependency for release.

HXB2 Location p17 (77–85)
Author Location
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Country Spain
Assay type Tetramer binding
References López *et al.* 2006
- HIV p17 sequence variability and level, phenotype and function of SL9-specific CD8+ T cells were studied in chronic patients.
- SLfNTVATL variant was found in 76% of HLA-A*0201-positive patients and in only 25% of HLA-A*02-negative patients.
- Patients without Tet+ cells had a significantly higher prevalence of mutations in SL9 than patients with Tet+ cells. In patients with Tet+ cells variant SLfNTVATL was associated with lower levels of Tet+ cells.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons, cross-presentation by different HLA, variant cross-recognition or cross-neutralization
References Currier *et al.* 2006
- The pattern of immunodominance and epitope clustering within Gag and Nef proteins in subtype A infected individuals was similar to that seen in subtype B and C infections. An immunodominant HLA-C restricted epitope, YVDRF-FKTL (YL9 from Gag protein) was observed and restricted to Cw0304.
- The sequences SLYNTVATLYC and SLfNTiATL(Y/W)C are associated with HLA-A*0201 and contain the epitope SLYNTVATL. Variable cross-reactivity was seen between subjects with respect to the 2 sequence variants.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, dendritic cells
References Schaubert *et al.* 2007
- CTL responses to the rarely recognized, subdominant HLA-A2-restricted Gag p24 epitope TLNAWKVV (TV9) were studied since its functional sensitivity and viral suppression is relatively high compared to other, dominant HLA-A2-restricted HIV-1 epitopes. Subdominant CTL responses to TV9 were not related to immunogenicity, availability of cognate TCR repertoires or HLA-epitope binding avidity.
- Peptide SL9 had a relative binding to HLA-A*0201 comparable to TV9, TLNAWVKVV. This Gag epitope was unable to stimulate a clone of TV9-specific CTLs that had been preprimed by Gag+Pol transduced DCs, to produce IFN-gamma. SL9-specific CTLs bound tetramers as a single, homogeneous population, indicating distinct avidity to SL9.

HXB2 Location p17 (77–85)
Author Location (77–85)
Epitope SLFNTVATL
Epitope name 3F
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Chromium-release assay, HLA binding
Keywords binding affinity, immunodominance, dendritic cells
References Schaubert *et al.* 2007
- CTL responses to the rarely recognized, subdominant HLA-A2-restricted Gag p24 epitope TLNAWKVV (TV9) were studied since its functional sensitivity and viral suppression is relatively high compared to other, dominant HLA-A2-restricted HIV-1 epitopes. Subdominant CTL responses to TV9 were not related to immunogenicity, availability of cognate TCR repertoires or HLA-epitope binding avidity.
- This epitope, 3F, SLFNTVATL, is the HIV-1 Gag variant of SLYNTVATL. 3F-specific CTLs bound tetramers as a single, homogeneous population, indicating distinct avidity to 3F.

HXB2 Location p17 (77–85)
Author Location (77–85)
Epitope SLYNTVAAL
Epitope name p41 (SL9 agonist)
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Chromium-release assay, HLA binding
Keywords binding affinity, immunodominance, dendritic cells
References Schaubert *et al.* 2007
- CTL responses to the rarely recognized, subdominant HLA-A2-restricted Gag p24 epitope TLNAWKVV (TV9) were studied since its functional sensitivity and viral suppression is relatively high compared to other, dominant HLA-A2-restricted HIV-1 epitopes. Subdominant CTL responses to

CTL CD8+

TV9 were not related to immunogenicity, availability of cognate TCR repertoires or HLA-epitope binding avidity.
- This epitope, p41, SLYNTVAAL, is the HIV-1 Gag agonist of SLYNTVATL. p41-specific CTLs bound tetramers as a single, homogeneous population, indicating distinct avidity to p41.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords class I down-regulation by Nef
References Lewis *et al.* 2008
- To study the role and function of Nef-mediated MHC-I down-regulation in vivo, Nef quasispecies from 11 chronically HIV-1 infected subjects were cloned into reporter viruses and tested for Class I down-regulation ability. Levels of this function varied between individual patients.
- Breadth of CTL response and CD4+ count were found to correlate with Nef down-regulation of MHC I. There was no significant correlation with pVL . This function of Nef one way of HIV-1 coping with CTL immune response.
- A Gag-specific CTL clone recognizing A*0201-restricted epitope SLYNTVATL was used to test CTL antiviral function when presented with wild type Nef-containing NL4-3 or mutant M20A Nef-containing NL4-3 virus.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLYNTVATL
Epitope name SL9
Immunogen virus
Species (MHC) human (A*0201)
Keywords immunotherapy, TCR usage
References Joseph *et al.* 2008
- To circumvent failed adoptive transfer of ex-vivo expanded autologous HIV-1-specific CTLs, the authors use autologous peripheral CTLs with redirected antigen specificities instead. CTLs were transduced with lentiviral vectors encoding TCR-alpha and TCR-beta specific for a control, immunodominant Gag epitope, SL9. Potent and specific in vitro and in vivo activity of the transduced CTLs against SL9-presenting cells was seen.
- The HLA-A*0201-restricted SL9-specific CTL clone had potent effect on HIV replication as plasma viral levels decreased.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLYNTVATL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Country Canada, United States
Assay type proliferation, Tetramer binding, Intracellular cytokine staining, Other
Keywords characterizing CD8+ T cells
References Jones *et al.* 2008
- Tim-3+ T cells form a novel population of dysfunctional CTLs in chronic progressors of HIV infection. Tim-3 surface levels correlate positively with viral load and CD38 expression, but correlates inversely with CD4 T-cell counts.
- Tim-3 expressing CTLs have impaired cytokine production and proliferation in response to antigen, which is restored by blocking Tim-3 signaling pathways using soluble sTim-3.
- Tim-3 expressing CTLs are a distinct population from PD-1 expressing CTLs.
- CTLs specific for HLA-A*0201 restricted Gag epitope SLYNTVATL were used to follow immune response.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Immunogen
Species (MHC) human (A*0202)
Keywords optimal epitope
References Llano *et al.* 2009
- C. Brander notes that this epitope can be presented by A*0201 and A*0202.

HXB2 Location p17 (77–85)
Author Location p17 (SF2)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A*0202)
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a
- The CTL-dominant response was focused on this epitope in 11/25 HLA A2 (A*0201 or A*0202) HIV+ individuals from Boston and in 1/8 HLA A2 HIV+ individuals from Durban.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 LAI)
Epitope SLYNTVATL
Subtype B
Immunogen
Species (MHC) human (A*0205)
Keywords optimal epitope
References Llano *et al.* 2009
- C. Brander notes that this epitope can be presented by A*0201 and A*0202.

HXB2 Location p17 (77–85)
Author Location p17 (subtype A)
Epitope SLYNTVATL
Subtype A
Immunogen HIV-1 exposed seronegative

Species (MHC) human (A*0201, A*0214)
References Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T cell epitopes: DTVLEDINL (3 individuals), SLYNTVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.
- The epitope variants SLYNTVATL and SLFNTVATL were both recognized.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A02)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords subtype comparisons, escape, acute/early infection, variant cross-recognition or cross-neutralization, viral fitness and reversion, HLA associated polymorphism
References Iversen *et al.* 2006

- The evolution of SLYNTVATL epitope was analyzed over 10 to 20 years in 76 patients and it was found that two opposing selective forces act on the epitope in HLA-A2+ patients. One is caused by an effective CTL pressure, resulting in escape. The main escape mutations were in positions 3, 6 and 8 of the epitope. The other force is selection for optimal viral growth, where the wild-type epitope's index amino acids are selected for. These common evolutionary pathways for the epitope were conserved across several HIV subtypes; while the balance between the opposing evolutionary pathways is suggested to determine variants in a patient at any given time. Fitness cost to SL9 variant generation leading to CTL escape also contributes to lower viral loads in such patients.
- Most variation in this epitope affects TCR recognition as shown by binding studies. Heterogenous CTL responses in patients to viral epitope variants also suggest that the advantage of any single mutation in SL9 is host (and HLA) dependent.
- CTL selection can differ between compartments as seen in compartmentalization of epitope variants between blood and cervix samples.

HXB2 Location p17 (77–85)
Author Location Gag (77–85 HXB2)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A02)
Assay type Chromium-release assay, Other
Keywords binding affinity, assay standardization/improvement
References Bennett *et al.* 2007

- Standard assays like ELISpot, ICS and tetramer staining do not measure antiviral activity of HIV-infected CTLs, but use exogenous synthetic peptides on uninfected cells, or HLA tetramers. Similarly, functional avidity assesses CTL activity against uninfected target cells. Here functional avidity is compared to the efficiency of actual infected cells' recognition and killing, revealing a sharp threshold between CTL immune antiviral activity and lack of infected cell recognition.
- As previously shown, epitopes and their variants spanned orders of magnitude of SD50. Likewise, CTL clearance of infected cells varied from 0 to 100% with epitope sequence variation. Moreover, direct suppression of HIV-1 replication by CTLs also varied with epitope variant.
- When killing efficiency (KE) using virus-infected cells was compared to functional avidity using synthetic peptides, there was a narrow threshold separating maximal killing from almost none. Since different SL9-specific clones had similar KEs, which were vastly different from RL10-specific CTL KEs, it was obvious that KEs varied with epitope sequence too. Finally, a strong correlation between KE and inhibition of viral replication was also seen.
- This epitope, SLYNTVATL, showed marked differences in its functional avidity, killing efficiency, as well as inhibition of viral replication when compared to its variants SLfNTVATL, SLfNTiATL, SLYNTiAvL, SLYNTiATL, SLYNaVATL and SLYNlVAvL.

HXB2 Location p17 (77–85)
Author Location
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A02)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope SLYNTVATL elicited a magnitude of response of 335 SFC with a functional avidity of 0.05nM and binding affinity of 9.1nM.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLYNTVATL
Epitope name SL-9
Immunogen HIV-1 infection
Species (MHC) human (A02)
Keywords escape, TCR usage, immune evasion
References Yu *et al.* 2007b

CTL CD8+

- The dependence of TCR clonotype recruitment on genetic background was determined by studying monozygotic twins infected with the same HIV-1 strain. After an early, initial correlation in the magnitude, specificity and immunodominance of CTL response [Draenert et al. J. Exp. Med. 203:529-539(2006)], subsequent disease was mixed with respect to CTL epitopes' mutational escape. TCR alpha and beta chain repertoires were analyzed and it was found that their clonotypes in HIV-specific CTLs were broadly heterogeneous for both concordant and discordant epitope sequence evolution between the twins. Therefore initial TCR recruitment appears to be an entirely random process independent of genetic background of the infected individual.
- This epitope, SL9, showed discordant epitope evolution between the twins, and both alpha and beta TCR chains recruited were entirely different between them.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Subtype B
Immunogen vaccine, in vitro stimulation or selection
Vector/Type: peptide *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A02)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords variant cross-recognition or cross-neutralization
References Blondelle *et al.* 2008

- To identify immunogenically optimized peptide epitopes for use in vaccines, two strategies were used. The first studied rare mutant epitopes that were effective in generating a cross-reactive immune response against a range of mutants. The second method was to use a synthetic combinatorial library of peptides and screen for highly effective responses against one epitope (TV9, TLNAWVKVV) and its mutants. Candidate epitopes were tested in HLA-A2 transgenic mice as well as ex vivo human lymphocytes.
- Mutants of epitope SL9 when tested in transgenic mice, showed that the consensus and most common mutant, SLfNTVATL, were weakly immunogenic or cross-reactive. 3 mutants, SLYNlVATL, SLfNlVATL and SiYNlVATL were highly immunogenic. Peptide SiYNlVATL with the additional L2I change allowed great cross-reactivity to the consensus. Other mutants were SLfNTVATL, SLfNTVAvL, SLYNTVvvL, SLfNlVAvL, SvYNTVATL, SLYNTVAaL, SLYNTiAaL, SLfNTVATp and SLfNTiATi.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLYNTVATL
Subtype B
Immunogen peptide-HLA interaction
Species (MHC) human (A02)
Assay type Chromium-release assay, Other
Keywords TCR usage
References Hofmann *et al.* 2008

- Unlike LTNPs, most patients cannot produce enough conserved-epitope-recognizing, HIV-specific CTLs to curtail infection. Here, primary CTLs are reprogrammed by RNA electroporation of epitope-specific TCRs to produce proinflammatory cytokines and to lyse target cells presenting the appropriate epitope. For the first time functional transfer of epitope-specific TCRs is shown to be feasible.
- T2 cells loaded with epitope SLYNTVATL, were lysed upon contact with the their corresponding TCRs inserted into CTL clones by RNA electroporation.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Subtype A, C, D
Immunogen HIV-1 infection
Species (MHC) human (A02, A68)
Country Tanzania
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, immunodominance
References Geldmacher *et al.* 2007a

- 56 ART-naive subjects were studied to assess whether T-cell responses to Gag and Nef are biased towards infecting subtype recognition, in a setting of epidemic consisting of subtypes A,C and D and their recombinant forms. The infecting subtype was determined by multi-region hybridization assay. Overlapping 15-mer isolate-based Gag and Nef peptide sets representative of local subtypes were used. The best recognized epitope variant in terms of magnitude and breadth corresponded to infecting subtype, in this case usually type-C. Hot spots of CTL recognition in Gag were in p24, p17 and p15; hotspots against Nef were in its central, conserved region.
- Epitope variants SLyNTvATL and SLfNTiATL were studied as peptide sequences SLyNTvATL-YCVHEK (subtypes C, A, D), SLfNTiATL-YCVHEK and SLfNTiATL-WCVHQR with 18% responders. Subtype C sequences were recognized best. Associated HLAs frequently expressed within the studied cohort are listed in the study as A02 and A68.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Immunogen vaccine
Vector/Type: vaccinia
Species (MHC) human (A2)
References Woodberry *et al.* 1999

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2.
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D^d – this transgene is the only MHC molecule expressed in the mice.
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost.

- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFDSRL).
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested.
- SLYNTVATL was recognized by 5/16 HLA-A2 patients.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Immunogen vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Protease
Species (MHC) human (A2)
Keywords immunodominance
References Carruth *et al.* 1999

- The vaccine used was a live recombinant canarypox (CP) virus vaccine containing multiple HIV-1 genes (HIV-1 MN gp120, HIV-1 LAI gp41, HIV-1 LAI Gag, HIV-1 LAI protease).
- CD4+ and CD8+ Gag and Env specific CTL responses were detected in only 1/5 vaccinated volunteers, and were not detectable 1 year after vaccination.
- CTL responses to epitopes SLYNTVATL and TVYYGVPVWK from HIV+ control patients were used as positive controls.
- The study explored why vaccinees were non-responsive – non-response was not due to inherent defects or differences in the ability of these individuals to process and present antigen.
- Lack of response to SLYNTVATL led the authors to speculate that the immunodominance of this epitope in natural infections may not be recapitulated by vaccine antigen.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Birk *et al.* 1998b

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Callan *et al.* 1998

- Included as a negative control in a tetramer study of A2-EBV CTL response.

HXB2 Location p17 (77–85)
Author Location p17
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Wagner *et al.* 1998a

- CTL specific for HIV epitopes were used to show that the mediators of both the cytolytic (granzyme A was used as the marker) and non-cytolytic (HIV-1 inhibitory chemokines MIP-1 α and RANTES were used as markers) anti-viral responses are localized within the CTL's cytotoxic granules.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 HXB2)
Epitope SLYNTVATL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Collins *et al.* 1998

- Two CTL clones recognize this epitope, but not the NL4-3 form of the epitope SLYNTIAVL.
- Nef down-regulates MHC class I molecules, which inhibits CTL killing, and this down-regulation can be partially compensated for by adding excess soluble peptide.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords subtype comparisons
References Durali *et al.* 1998

- Cross-clade CTL response was studied by determining the CTL activity in seven patients from Bangui, (6 A subtype, and 1 AG recombinant infections) and one A subtype infection from a person living in France originally from Togo, to different antigens expressed in vaccinia.
- Pol reactivity: 8/8 had CTL to A subtype, and 7/8 to B subtype, and HIV-2 Pol was not tested.
- Gag reactivity: 7/8 reacted with A or B subtype gag, 3/8 with HIV-2 Gag.
- Nef reactivity: 7/8 reacted with A subtype, and 5/8 with B subtype, none with HIV-2 Nef.
- Env reactivity: 3/8 reacted with A subtype, 1/8 with B subtype, none with HIV-2 Env.
- Patient B18 had the greatest breadth and diversity of response, and recognized Gag SLYNTVATL and Nef PLTFGWCFKL.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords dendritic cells
References Kundu *et al.* 1998b

CTL CD8+

- Allogeneic dendritic cells (DCs) were obtained from HLA-identical siblings, pulsed with rgp160 MN or A2-restricted HIV-1 epitope peptides, and infused monthly into six HIV-infected patients.
- 1/6 showed increased env-specific CTL and increased lymphoproliferative responses, 2/6 showed increase only in proliferative responses, and 3/6 showed no change – pulsed DCs were well tolerated.
- SLYNTVATL is a conserved HLA-A2 epitope included in this study – 3/6 patients had this sequence as their HIV direct sequence, one had the form SLYNTVAVL and all four of these had a detectable CTL response – the other two had either the sequence SLFSAVAVL or SLFSAVAAL and no detectable CTL response.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 IIIB)
Epitope `SLYNTVATL`
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Sipsas *et al.* 1997

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB.
- SLYNTVAVL, a variant found in HIV-1 MANC, was also recognized.
- SLFNTVAVL, a variant found in HIV-1 NY5CG, was also recognized.

HXB2 Location p17 (77–85)
Author Location p17
Epitope `SLYNTVATL`
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords subtype comparisons, HIV exposed persistently seronegative (HEPS)
References Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A subtype consensus is SLfNtvatL.
- The D subtype consensus is SLyNTvATL.

HXB2 Location p17 (77–85)
Author Location p17
Epitope `SLYNTVATL`
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords binding affinity
References Sewell *et al.* 1997

- Naturally occurring variants of this epitope escaped killing and acted as antagonists.
- The following variants were found in HIV-1 infected patients who mounted a strong response against this epitope: –F——, –F—-V-, –S——, -SF——, –L——, —–I—, —–I-V-, –F–I—, –F–I-V-, –F-A—-
- All variants bound to A2 with at least half the affinity of SLYNTVATL except the triple mutant: –F–I-V-
- Antagonism could be observed at low concentrations, abrogating lysis at an antagonist:agonist ratio of 1:10 – the antagonism was observed in one SLYNTVATL-specific CTL line but not another.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 HXB2)
Epitope `SLYNTVATL`
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords kinetics
References Yang *et al.* 1997b

- A chimeric universal T cell receptor was created by linking CD4 or an HIV-specific anti-gp41 Ig sequence to the signaling domain of the T cell receptor chain ζ, and transduced into CD8+ cells.
- The response using universal-receptor-bearing CD8+ cells to lyse infected cells *in vitro* was comparable to the natural occurring responses of CTL-clones from HIV+ individuals in terms of kinetics and efficiency.
- A CTL clone specific for this epitope was used for the comparison.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope `SLYNTVATL`
Epitope name SL9
Immunogen in vitro stimulation or selection
Species (MHC) human (A2)
References Stuhler & Schlossman 1997

- Keyhole limpit hemocyanin or tetanus toxoid Th epitope co-expression with peptide CTL epitopes on the same APC was required for induction of peptide-specific CTL.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope `SLYNTVATL`
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Yang *et al.* 1996

- CD4+ cell lines acutely infected with HIV were studied to determine their susceptibility to lysis by CTL.
- Clones specific for RT lysed HIV-1 infected cells at lower levels than Env or Gag specific clones.
- The distinction was thought to be due to lower expression of RT relative to Env and Gag.
- CTL can lyse infected cells early after infection, possibly prior to viral production.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)

Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CTL suppression of replication
References Yang *et al.* 1997a

- CTL inhibit HIV-1 replication at effector cell concentrations comparable to those found *in vivo*.
- CTL produced HIV-1-suppressive soluble factors – MIP-1α, MIP-1β, RANTES, after antigen-specific activation.
- CTL suppress HIV replication more efficiently in HLA-matched cells.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 LAI)
Epitope SLYNTVATL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Parker *et al.* 1992; Parker *et al.* 1994

- Examined in the context of motifs important for HLA-A2 binding.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 LAI)
Epitope SLYNTVATL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords review
References McMichael & Walker 1994

- Review of HIV CTL epitopes.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Tsomides *et al.* 1994

- CTL clones recognize naturally processed peptide.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen in vitro stimulation or selection
Species (MHC) human (A2)
References Stuhler & Schlossman 1997

- A three cell-type cluster consisting of APCs, Th, and CTLs is the minimal regulatory unit required for Th cell-dependent induction of CTLs.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords subtype comparisons
References Cao *et al.* 1997a

- The consensus peptides of B and D clade viruses and some Cs have the sequence SLYNTVATL.
- The consensus peptide of A, and some C strains have SLFNT-VATL, a form that is cross-reactive.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Dyer *et al.* 1999

- CTL specific responses were measured over a 1.3 to 1.5 year period in members of the Sydney Blood Bank Cohort (SBBC) who had been infected with a natural attenuated strain of HIV-1 which was Nef-defective.
- Some of these patients had prolonged high levels of CTL effector and memory cells despite low viral load.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords escape
References Harrer *et al.* 1998

- Two overlapping epitopes were recognized in a long-term survivor, restricted by two different HLA molecules, HLA-A11(TLYCVHQR) and -A2 (SLYNTVATL)
- Viral sequence substitutions were present in this individual which did not affect viral replication and did not alter CTL-recognition of the A2 epitope, but reduced recognition of the A11 epitope, indicative of immune escape.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 SF2)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords acute/early infection
References Altfeld *et al.* 2001a

- The relative contribution of CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- Individuals with long-term nonprogressive and treated chronic HIV-1 infection targeted Vpr more frequently than individuals with treated acute infection.
- Vpr is a frequent target of HIV-1 specific CD8+ T-cells – a response was detected in 45% of individuals tested and Vpr and p17 were the most preferentially targeted proteins per unit length by CD8+ T-cells.
- The A2 epitopes Vpr AIIRLLQQL and p17 SLYNTVATL do not account for the dominance of Vpr and p17, the result holds even when HLA-A2+ individuals are excluded.

HXB2 Location p17 (77–85)

Author Location p17 (BRU)
Epitope SLYNTVATL
Epitope name SL9
Immunogen in vitro stimulation or selection
Species (MHC) human (A2)
Keywords epitope processing, dendritic cells
References Buseyne *et al.* 2001

- Exogenous presentation or cross-presentation of epitopes by antigen presenting cells (APC) without protein synthesis is an alternative pathway for CTL epitope processing that may be important in the initial generation of viral specific CTL.
- Dendritic cells treated with AZT to inhibit protein synthesis were able to elicit a strong specific CTL response in SLYNTVATL specific CTL line EM71-1 without protein synthesis, while macrophages demonstrated a decreased presentation efficiency.
- Exogenous Gag epitope presentation was Env-dependent and required receptor-dependent fusion.

HXB2 Location p17 (77–85)
Author Location p17
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Kostense *et al.* 2001

- HLA tetramers to six epitopes were used to study HLA-A2, B8 and B57 CTL in 54 patients – HIV-specific tetramer positive cells were inversely correlated with viral load in patients with high CD4, but in patients with CD4 T-cells below 400 high tetramer frequencies were found despite high viral load.
- Most patients have high levels of HIV-specific T-cell expansions, but many of these cells aren't functional.
- In 15 of the patients, the proportion of IFN gamma producing tetramer cells correlated with AIDS-free survival.
- In one patient with a SLYNTVATL response, no SLYNTVATL mutations were found among 21 clones despite high viral load (260,000 RNA copies/ml serum), suggesting low *in vivo* efficacy of the SLYNTVATL response.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p17 (77–85)
Author Location p17
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HAART, ART, immunodominance
References Seth *et al.* 2001

- CTL responses were studied by tetramer staining in 41 patients with combination therapy – activated CD8+ T-cells decline as the viral load drops in response to therapy, but the overall level of antigen-specific cells capable of differentiating into effectors stays constant and new epitopes may be recognized.
- 6/10 A*0201+ individuals had HIV-specific tetramer staining cells, and 5 of these declined upon successful therapy.
- 4/10 A*0201+ individuals with chronic HIV-1 infection recognized this epitope.
- Prior to therapy, the mean percentage of CD8+ cells that recognized the immunodominant epitope SLYNTVATL was six-fold greater than the percentage recognizing the epitope ILKEPVHGV.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HAART, ART, TCR usage
References Islam *et al.* 2001

- Transcript frequencies were followed for four CTL clones from patient 115, with a chronic and stable HIV-1 infection, and tracked in a longitudinal study of samples collected 6-11 years post infection: clone M21 and E15 recognize ERYLKDQQL, and clone D87 recognizes variant ERYLQDQQL, and clone p175b recognizes the A2 epitope SLYNTVATL.
- This epitope sequence from clone p175b uses the Vβ5, CDR3 (FDS), Jβ2.7 TCR beta gene.
- Responses were stable even through HAART with undetectable viral loads, but frequencies varied over time by 100-fold, ranging from 0.012% of the total population for SLYNTVATL at its lowest point to 3.78% for M21, with the relative frequencies of clones shifting over time.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 SF2)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.

- Number of HLA-A2+ individuals that had a CTL response to this epitope broken down by group: 1/10 group 1, 2/6 group 2, and 2/4 group 3.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLFNTVATL
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A2)
Keywords subtype comparisons, HIV exposed persistently seronegative (HEPS), immunodominance
References Kaul *et al.* 2001a

- Variants SL(F/Y)NTVATL are A/B clade specific.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-A2 women, 1/10 HEPS and 22/26 HIV-1 infected women recognized this epitope, likelihood ratio 18.3, p value < 0.003, and ILK(D/E)PVHGV tended to be more reactive in HEPS women, SL(F/Y)NTVATL in infected women.
- The dominant response to this HLA allele was to this epitope in the 1/10 HEPS case and in 18 of the 22/26 HIV-1 infected women that responded.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.
- Subject ML 1250 had an A2 response to ILK(D/E)PVHGV prior to seroconversion, which switched to SL(F/Y)NTVATL post-seroconversion.
- Subjects ML 1575 and ML 1592 had no response to SL(F/Y)NTVATL prior to seroconversion, but made responses post-seroconversion.
- Subject ML 1760 had an A2 response to ILK(D/E)PVHGV prior to seroconversion, and gained responses to epitopes A2 SL(F/Y)NTVATL and B27 KRWII(L/M)GLNK post-seroconversion.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 93TH253 subtype CRF01)
Epitope SLYNTIATL
Epitope name G77-85
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HIV exposed persistently seronegative (HEPS)
References Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV positive controls, and 0/9 HIV negative women that were not exposed.
- This epitope was reactive in HIV+ control study subjects 125 and 144 who carried HLA-A2.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 93TH253 subtype CRF01)
Epitope SLYNTIATL
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords subtype comparisons
References Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- 2/4 tested FSWs recognized the E clade version of this epitope, SLYNTIATL, the B clade version is SLYNTVATL.
- This epitope was only conserved in CRF01 and subtypes B and D, and exact matches were uncommon.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- SLYNTVATL was the dominant A2 epitope recognized in patients with chronic infection, except for Subject 11841 who recognized 5/8 epitopes.
- Three subjects had an A2 response only to SLYNTVATL.
- The two subjects with acute infection did not respond to SLYNTVATL.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords mother-to-infant transmission, escape
References Goulder *et al.* 2001c

CTL CD8+

- Immune escape variants in this epitope where transmitted both horizontally and vertically in two families.
- Eight transmitting mothers and 14 non-transmitting mothers were studied and variation within the SL9 epitope was associated carrying HLA-A2 (P=0.04), but no link between variation from the SL9 consensus and vertical transmission was established.

HXB2 Location p17 (77–85)
Author Location p17 (SF2)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined.

HXB2 Location p17 (77–85)
Author Location
Epitope SLYNTVATL
Epitope name Gag-SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A02, 17/30 (57%) recognized this epitope.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 LAI)
Epitope SLYNTVATL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HAART, ART, epitope processing, immunodominance
References Kelleher *et al.* 2001a

- Ritonavir (RTV) inhibits chymotryptic activity in the 20S proteasome *in vitro*, as does Saquinavir (SQV) to a lesser extent; Indinavir (IDV) does not. Thus there is concern protease inhibitors may adversely effect CTL epitope processing, but this paper indicates that processing is not inhibited at therapeutically relevant concentrations of RTV when the proteasome is functioning in an intracellular context.
- RTV did not reduce antigen presentation and concentration of the two immunodominant Gag CTL epitopes (KRWIIMGLNK (B27) and SLYNTVATL (A2)).
- RTV did not inhibit the processing and assembly of HLA-B35 or -A2, which are assembled with a rapid and moderate time course, respectively, or of HLA-A3, -B27 and -B39.

HXB2 Location p17 (77–85)
Author Location p17
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2002

- Neisseria gonorrhea cervititis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
- Ghonorrhea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 NL43)
Epitope SLYNTVATL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords class I down-regulation by Nef
References Yang *et al.* 2002

- Nef down-modulates class I protein expression, and this study demonstrates directly that Nef-deleted HIV-1 NL-43 can be more effectively killed *in vitro* than NL-43 with an intact Nef. The effect was shown to be specific for class I presentation of epitopes, and unlike Nef, deleting Vpr did not alter CTL susceptibility of NL-43. The CTL clone 18030D23, specific for the class I A2 presented SLYNTVATL epitope, was one of four used in this study.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 BRU)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords epitope processing
References Cohen *et al.* 2002

- The antigen presentation of two A2-restricted epitopes was compared, SLYNTVATL (p17) and ILKEPVHGV (RT). HIV-1 infected cells were more sensitive to lysis by SLYNTVATL-specific CTL than by ILKEPVHGV-specific CTL, because of a higher density of SLYNTVATL-A2 resulting from differences in processing.
- Incubation with a T1-cell proteolytic extract showed that by four hours, 25% of a p17 peptide had a C-term Leu-85 and were SLYNTVATL-precursors, while ILKEPVHGV-precursors were far less frequent (6.8%) even with four times more proteolytic extract after 30 hours.
- p17 was preferentially cleaved between Leu85 and Tyr86, while appropriate Val484 and Tyr485 cleavage was minor for RT.
- In a competition experiment, RSLYNTVATL bound TAP 3.7-fold more efficiently than RT peptides.
- No difference in CTL avidity was detected in six patients with HLA-A2-restricted responses to these epitopes.
- No significant difference in HLA-A2 binding to p17 or RT epitopes was observed.

HXB2 Location p17 (77–85)

Author Location p17 (77–85)
Epitope SLYNTVATL
Immunogen vaccine
Strain: B clade IIIB *HIV component:* Gag, Pol *Adjuvant:* IL-12
Species (MHC) mouse (A2)
References Kmieciak *et al.* 2001

- Transgenic mice expressing a HLA-A2/Kb chimeric protein were vaccinated with either a p17-p24-p51 fusion protein (vG/P-92) or the Gag-Pol precursor protein (vVK1).
- Compared to vVK1, vG/P-92 induced a significant increase in Gag and Pol induced IFNgamma production and CTL responses, and to the epitopes SLYNTVATL and ILKEPVHGV, as determined by Elispot and 51Cr-release assays.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, A3, B7, Bw6
Keywords HAART, ART
References Appay *et al.* 2002

- Four HIV patients with prolonged clinically successful antiviral therapy but with ongoing evidence of replication and Nef mRNA transcription, showed specific T-cell responses by Elispot and Tetramer staining, maintained for 2-4 years after initiation of HAART.
- Nef epitope recognition was detected in all 4 subjects, gp120, Pol and Gag-specific in 1 or 2 subjects.
- The HIV-specific CD8+ T-cells had an intermediate maturation phenotype characterized by low levels of perforin and high levels of CD27 expression.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 NL-43)
Epitope SLYNTVATL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords class I down-regulation by Nef, escape
References Ali *et al.* 2003

- NL43 was passaged in the presence of Nef KEKGGLEGL-specific CTL clones STD11 and KM3, giving rise to rapid selection of escape mutations, including E93G, E93K, K94N+G99R, G95R+G99R, E98K, E98D, G99R, G99E, L100P, and L100I; insertions, deletions, frameshifts and an early stop codon. 34/36 (94%) of sequences carried mutations in the epitope by seven days, 36/36 (100%) by 14 days.
- Several mutations selected by KEKGGLEGL-specific CTL were shown to impair the down regulation of class I MHC by Nef, in particular E93G, E93K, and a truncation mutation at position 51.
- Nef deletion mutants increased 100-fold NL-43 susceptibility to inhibition by CTL specific for epitopes in other proteins, the A2 epitopes ILKEPVHGV in RT and SLYNTVATL in p17 Gag.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords class I down-regulation by Nef
References Bobbitt *et al.* 2003

- Nef, through Nef-mediated MHC-1 down-regulation, is not the only viral protein to influence levels of HIV-specific CTL recognition. The Rev L60F mutation, a common natural variant, can decrease CTL recognition of late gene products. The Rev mutation impacts the early to late gene switch, reducing late gene product production (Gag, Pol, Env, Vpu, Vpr and Vif), while increasing Nef production, both of which reduce the impact CTL recognition of late gene products. As expected, Rev L60F rendered HIV infected cells more resistant to CTL that recognized epitopes from the late proteins Env and Gag. Gag expression is reduced more than Env, and Gag-specific CTL were more profoundly affected. Conversely CTL against an epitope in an early gene product, Tat, were more effeciently recognized when infected with viruses carrying the Rev L60F mutation.
- Patients in the asymptomic phase with active immune responses had more CTL resistant viruses, with lower Rev activity, lower Gag expression and greater resistance to Gag-specific CTL killing, while viruses isolated from people with AIDS were more sensitive to CTL killing.

HXB2 Location p17 (77–85)
Author Location Gag (77–)
Epitope SLYNTVATL
Epitope name Gag77
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* Gag *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This epitope was one of the previously identified HLA-A2 epitopes studied.
- 10/17 HIV-infected HLA-A2+ people in this study recognized this epitope, and CTL and CD8+ T cells responses were elicted by immunization of transgenic mice with this peptide.

HXB2 Location p17 (77–85)
Author Location p17
Epitope SLYNTVATL
Immunogen HIV-1 infection

CTL CD8+

Species (MHC) human (A2)
Assay type Intracellular cytokine staining
Keywords immunodominance, genital and mucosal immunity
References Kaul *et al.* 2003

- Predefined immunodominant peptide responses were used to compare CD8+ T-cell responses in the blood and cervix of 16 HIV+ Kenyan sex workers. Cervical responses were detected in 8/10 women from whom adequate samples could be obtained. The frequency of the CD8+ T-cell response in the genital tract was comparable to the blood, with a trend toward being slightly higher.
- The immunodominant response was to this epitope in the PBMC of 1/16 patients (Kaul *et al.* 2001, AIDS, 107:1303).

HXB2 Location p17 (77–85)
Author Location p17
Epitope `SLYNTVATL`
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, A24, B38, B60, Cw12, Cw2
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), early treatment
References Montefiori *et al.* 2003

- HIV-1 + patient AC10 underwent early HAART treatment, which was discontinued 1.5 years later. At this timepoint potent NAb responses against autologous virus were detected. Treatment interruption initially induced weak CD8+ responses directed against 5 epitopes. By days 873d and 923d the CTL response had broadened to target 22 epitopes; of these six were fully characterized. Eventually the virus escaped the NAb response, but escape was not accompanied by a rise in viral load, and the authors suggest the virus was contained by the CTL response.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope `SLYNTAVTL`
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords responses in children
References Sandberg *et al.* 2003

- 65 vertically HIV-1 infected children, ages 1-16, the majority undergoing ART, were analyzed in regard to their plasma viremia and CD4+ and CD8+ T-cell counts, and CD8+ T-cell responses.
- Using vaccina expressed Gag, Pol, Env, Rev, Nef in target cells in an Elispot assay, 85% of the children recognized at least one HIV antigen. Strong CD8+ T-cell responses were directed against Pol, followed by Gag and Nef. Children younger than 4 had significantly weaker responses (7/14 had no reponse) than older children (only 1/32 had no response, and responses were greater in magnitude).
- SLYNTVATL and ILKEPVHGV tetramers were used to quantitate specific responses. 49 chlidren in an expanded cohort carried HLA-A2. 1/11 children under 3 years of age had detectable CD8+ T-cell responses to SLYNTVATL, 2/11 to ILKEPVHGV. Among children over 3, 11/38 recognized SLYNTVATL and 9/38 recognized ILKEPVHGV.
- Older children that maintained a CD4 count greater than 400 cells/ul tended to have stronger CTL reponses.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope `SLYNTVATL`
Immunogen HIV-1 infection
Species (MHC) (A2)
Donor MHC A2, A3, B27, B51; A2, A3, B27, B57; A2, A23, B57
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining
Keywords assay standardization/improvement, memory cells
References Sun *et al.* 2003

- This study compares assay methods for testing CTL responses using samples from 20 HIV+ patients. The study compares ELISpot, tetramer-binding, and intracellular IFN-γ. Tetramer-bidning analysis was performed with Gag (SLYNTVATL) or Pol (ILKEPVHGV) tetramers. Antigen presentation using recombinant vaccinia viruses (rVVs) encoding HIV-LAI Gag, Pol, Env, Nef, Tat and Vif proteins was compared to peptide panels. HIV antigen recognition in memory CTLs was measured by chromium release assay and compared to effector/memory CD8+ T-cells in an IFN-γ ELISpot assay.
- Results: IFN-γ Elispot and flow cytometry gave similar frequencies of HIV specific CD8+ T-cells. Tetramer-binding analysis was most sensitive. Pools of peptides and the sum of frequencies of individual peptides were comparable. Elispot assays using peptides were more sensitive than assays using vaccinia expressed proteins. Cr release and Elispot against rVVs gave comparable memory cell responses 2/3s of the time.
- 3/7 HLA-A2+ patients recognized this epitope.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 NL43)
Epitope `SLYNTVATL`
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type Chromium-release assay, CTL suppression of replication
Keywords escape, TCR usage
References Yang *et al.* 2003a

- Virus was cultured in the presence of CTL lines specific for 5 different epitopes (SLYNTVATL, ILKEPVHGV, IEIKDTKEAL, SEGATPQDL, and KEKGGLEGL) to study the emergence of escape mutations. Escape varied between clones for the same epitope, and between different epitopes. Gag and RT epitope escape, if it occurred at all, tended to be monoclonal and within the epitope, indicating strong fitness constraints, while the Nef epitope escape was rapid, polyconal, and sometimes the result of upstream frameshifts.

- Three CTL clones were studied that recognized SLYNTVATL, 161JxA14, 18030D23, and 115DEC4. The different TCR usage on the CTL clones resulted in different patterns of recognition and escape. 161JxA14 suppressed the variant slFntvatl, 18030D23 did not; conversely the variants slfntIaVl and slFntIatl were suppressed by 18030D23, but not 161JxA14.
- After two weeks of passage the predominant escape mutant from 161JxA14 was slyntIatl. Amino acid residues flanking SL9 were unchanged. Escape mutations did not occur within two weeks for the two additional SL9-specific CTL clones 18030D23 and 115DEC4.

HXB2 Location p17 (77–85)
Author Location p17 (43)
Epitope `SLYNTVATL`
Epitope name SL9
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (A2)
Assay type CTL suppression of replication
Keywords class I down-regulation by Nef, early-expressed proteins, kinetics
References Ali *et al.* 2004

- Translocation of the gag SLYNTVATL epitope into the early expressed Nef protein resulted in increased antiviral efficiency of SL9 specific CTLs in culture and the loss of MHC-I down-regulation by Nef, indicating that both the timing of epitope expression and reduction of MHC-I affect the ability of CTLs to supress HIV-1.

HXB2 Location p17 (77–85)
Author Location Gag (77–85 B con)
Epitope `SLYNTVATL`
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Draenert *et al.* 2004c

- CD8+ T-cell responses that persisted in individuals with advanced disease were studied; most of the optimal epitopes defined were recognized with intermediate to high avidity. On average 13 (range, 2-39) epitopic regions were targeted in an average of 6 proteins (range, 1-8). HAART resulted in decrease in antigen and reduction in gamma IFN EliSpot responses, suggesting active responses to autologous virus. The lack of mutations within most viral epitopes suggest that persistent CTL through late disease do not exert strong immune selection pressure, yet the Elispot assays show robust responses, suggesting to the authors that gamma IFN-based screening methods may not reveal functional CD8+ T-cell impairment in patients with AIDS.
- 3 subjects recognized this epitope with high functional avidity. Relative to consensus, 2 individuals that had the SLYNTVATL epitope carried a R -> K mutation proximal to but outside the epitope; possible processing implications were not studied here.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope `SLYNTVATL`
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords HIV exposed persistently seronegative (HEPS)
References Koning *et al.* 2004

- A high-risk seronegative group of 29 patients showed reduced in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A*11, A*31 and Cw*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
- 2/11 HLA A2+ infection-resistant men, compared to 7/9 men pre-seroconversion who went on to become infected, reacted to this epitope.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope `SLYNTVATL`
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 14/19 patients recognized this epitope, it was the most commonly recognized of 9 HLA A*02 epitopes tested.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope `SLYNTVATL`
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type Chromium-release assay
Keywords binding affinity, TCR usage, characterizing CD8+ T cells
References Yang *et al.* 2003b

CTL CD8+

- Killing efficiency of CTLs and their ability to suppress viral replication is shown to depend more on epitope specificity than to antigenic avidity. Different clones recognizing the same epitope had similar killing efficiency despite their variation in avidity. Nef specific CTL clones tended to be most inhibitory, followed by Gag, then by RT specific clones, regardless of avidity.
- 3/14 CTL T-cell clones tested were specific for Gag/p17-SL9. Under conditions of excess peptide (100ug/ml), there was no difference in their lytic potential; all possessed similar effector capacity. Avidity was measured as the sensitizing dose of peptide required for 50% of maximal killing (SD50), which varied from 20 pg/ml to 100 ng/ml, over four orders of magnitude for all 14 epitopes. The SD50 range for Gag/p17-SL9 was 1,000 - 20,000 pg/ml.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope `SLYNTVATL`
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type Cytokine production, proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, memory cells, characterizing CD8+ T cells
References Daniel *et al.* 2004

- CD4+ and CD8+ responses in chronically HIV-1 infected patients on HAART were weak with decreased polyclonality. Only 33% of patients had CD4+ T-cells that could proliferate, and only 22% had HIV-specific CD8+ T-cell responses, and those rare responses showed low perforin levels and persistent expression of CD27, indicating incomplete differentiation and loss of lytic function.

HXB2 Location p17 (77–85)
Author Location p17
Epitope `SLYNTVATL`
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type proliferation, Tetramer binding, T-cell Elispot
Keywords acute/early infection, characterizing CD8+ T cells, immune dysfunction
References Lichterfeld *et al.* 2004a

- HIV-1 specific CD8+ T-cells in acute and long-term nonprogressive HIV-1 infection show strong ex-vivo proliferative capacities which are rapidly lost in chronic HIV-1 infection. The loss of CD8+ T-cell function is closely linked with the loss of HIV-1 specific, IL2 secreting CD4+ T-cells. The function can be rescued in vitro and in vivo by restoring the specific CD4+ T-cell help.
- Despite being detectable at high frequencies, CD8+ T-cells specific for SL9 epitope were shown to entirely lose their proliferative capacity in chronic HIV-1 infection. This activity could be restored by co-stimulation with CD4+ T cells isolated from acute infection in an IL-2 dependent manner.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope `SLYNTVATL`
Epitope name gag 77-85
Subtype B
Immunogen HIV-1 infection, HIV-2 infection
Species (MHC) human (A2)
Country Gambia
Assay type Tetramer binding, Intracellular cytokine staining
Keywords escape, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells, HIV-2
References Lopes *et al.* 2003

- CD8+ T cells from HIV-2 infected patients had more polyclonal TCR responses than HIV-1 infected patients, who tended to have oligoclonal responses. This results in limited plasticity of T cell responses to amino acid substitutions within epitopes in HIV-1 infections. HIV-2-specific CD8+ T-cells showed a more diverse TCR usage associated with enhanced CD8 expansion and IFN-gamma production on cross-recognition of variant epitopes.
- Responses to this epitope were characterized in detail. One patient's response to SL9 A2-SLYNTVATL tetramers was shown to have only Vbeta5.1 clonotypes. The naturally-occurring HIV-2 variant: slFntvCVI, was not recognized well by this response or by the SLYNTVATL reactive CD8+ T cells in four additional A2+ HIV infected asymptomatic individuals. The subtype A variant, slFntvatl was also poorly recognized, and 4/5 Ala substitutions abrogated responses. All variants bound to HLA-A2 with higher affinity than the index peptide except slyntAatl, which was slightly reduced, so the lack of cross-reactivity must have been due to the TCR.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope `SLYNTVATL`
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type Chromium-release assay
Keywords assay standardization/improvement
References Lubong *et al.* 2004

- Using IL7 or IL15 in culturing of HIV-1-specific CTL clones was inferior to using IL-2 alone; the addition of these cytokines to IL-2 did not show any advantage. Neither proliferation, survival, nor lytic capacity of HIV-1-specific CTLs was significantly enhanced by addition of IL7 or IL15.

HXB2 Location p17 (77–85)
Author Location p17
Epitope `SLYNTVATL`
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A2)
Donor MHC A*02, A*30, B*15, B*4402
Assay type Tetramer binding, T-cell Elispot
Keywords HIV exposed persistently seronegative (HEPS)

References Missale *et al.* 2004

- HIV-specific T-cell response was tested in patients exposed to blood from a patient with highly replicating HIV; these patients were nosocomially infected with HBV, but uninfected with HIV. HIV-specific T-cell responses were directed to structural and non-structural HIV proteins in 2 patients, suggesting that the virus replicated in these patients sufficiently to prime a cell-mediated immune response that protected them from HIV infection.
- This patient responded to 4/8 HIV epitopes tested in an IFNgamma EliSpot assay or tetramer assay. Responses were detected 8 and 28 weeks after exposure. No response to SLYNTVATL was detected by either assay.

HXB2 Location p17 (77–85)
Author Location p17
Epitope `SLYNTVATL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United Kingdom
Assay type Tetramer binding, T-cell Elispot, Intracellular cytokine staining
Keywords rate of progression, acute/early infection, characterizing CD8+ T cells, immune dysfunction
References Papagno *et al.* 2004

- Acute HIV-1 infection induces massive activation of HIV-specific and non-HIV-specific CD8+ T-cells resulting in differentiation of these cells. High differentiation of CD8+ T-cells is correlated with disease progression. Differentiation is a natural process but it can be driven by elevated immune activation, such as in HIV infection.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope `SLFNTVATL`
Epitope name SLF
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, A68.1, B*07, B*3503, Cw*0401, Cw*0702, DQ2, DQ6, DR15, DR17, DR51, DR52
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, CD4 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, escape
References Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses, and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relatively efficiency of the variant eptiopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- This epitope was one of six epitopes found to be under positive selection for escape mutations and was completely replaced by escape variants between days 327 and 635 (slYntvatl and slYnAvatl).

HXB2 Location p17 (77–85)
Author Location Gag
Epitope `SLYNTVATL`
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Two escape mutations, at positions 3 and 8, slFntvatl and slyntvaVl, were found in the most polymorphic residues in the epitope. These were shared between clades B and C. One escape mutation, at position 6, slyntIatl, was found not to correspond to the most polymorphic residue in the epitope.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope `SLYNTVATL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords acute/early infection, optimal epitope
References Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This is the most commonly recognized A2 epitope in chronic infection, recognized in 62% of 74 A2+ people, but it is rarely recognized in acute infection (in only 1/14 cases).

HXB2 Location p17 (77–85)
Author Location p17 (77–85 HXB2)
Epitope `SLYNTVATL`
Epitope name 17A
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* multiple epitope immunogen *HIV component:* p17/p24 Gag, Pol *Adjuvant:* IL-12
Species (MHC) transgenic mouse (A2)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-specific epitope characteristics, vaccine antigen design

CTL CD8+

References Bolesta *et al.* 2005

- Immunization of transgenic mice with a codon-optimized hGagp17p24-Polp51 DNA plasmid, consisting of clusters of highly conserved CTL epitopes presented by multiple MHC class I alleles, induced 2- to 5-fold higher CD8+ T-cell responses than the corresponding full-length proteins. The modified proteins had the ribosomal frameshift deleted, as well as the potentially immunosuppressive p15, and protease and integrase. This correlated with higher protection against challenge with Gag and Pol expressing recombinant vaccinia virus. Mice immunized with the hGagp17p24-Polp51 also showed an elevated level of type 1 cytokine production as well as an increased titer of p24- and RT-specific IgG2 antibody responses.
- This was 1 of 4 A2 gag/pol epitopes tested. Transgenic mice immunized with the deleted construct induced more potent EliSpot reactions to this epitope than those immunized with full length Gag/Pol.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2A2, B44, B70; A2, A31, B51, B58w4
Country United States
Assay type Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, escape, variant cross-recognition or cross-neutralization
References Casazza *et al.* 2005

- Evidence of continued viral evolution during HAART therapy despite low viral load was found in 1/5 patients studied.
- This epitope was recognized in 2 individuals and was invariant in both prior to HAART (20/20 clones in each).

HXB2 Location p17 (77–85)
Author Location
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, variant cross-recognition or cross-neutralization, optimal epitope
References Harrer *et al.* 2005

- An HLA-B13-restricted optimal epitope was defined in Nef, RI9. The frequency of CTLs specific for this epitope in B13-positive patients exceeded the number of CTLs against other epitopes, indicating that this is a dominant epitope in B13-positive subjects. Three B13-positive patients who had an immunodominant response to this epitope were good controllers of their infection, with low viral loads over long periods.
- Five A2+ B13+ patients were found to make an immunodominant response to the B13 epitope RI9. 0/5 recognized ILKEPVHGV, and only 1/5 recognized SLYNTAVTL, with a much lower frequency than the B13 response.

HXB2 Location p17 (77–85)
Author Location Gag (77–85 BRU)
Epitope SLYNTVATL
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 3/9 CRF02_AG-infected patients, and by 2/9 B-infected patients.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Netherlands
Assay type Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords binding affinity, rate of progression, escape, characterizing CD8+ T cells
References Jansen *et al.* 2005

- HLA-B57 has been associated with long term non-progression in HIV+ people. The number and responsiveness of CD8 T-cells directed to different Gag peptides presented by HLA-A2, -B8 and B57 were compared. T cells specific for the HLA-B57 epitope KAFSPEVIPMF responded to a higher extent and more readily to antigenic stimulation than those specific for the A2 epitope SLYNTVATL and the B8 epitope EIYKRWII.
- In 3/4 A2 subjects that were sequenced, epitope variants dominated: 2 subjects carried slFntvatl, and the other syntIatl.
- Tetramer decay experiments indicate that the HLA-B57 peptide has a higher half-life than the A2 and B8 peptides. The authors point out that CD8+ T cells with high binding affinity may require less help.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A*02, A*68, B*14, B*52, Cw*08, Cw*12
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords escape, optimal epitope
References Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- Elispot responses to the consensus form of this epitope, SLYNTVATL, were much more intense than to the most common variants of the epitope found over time in this individual, SLfNTiATL and SLfNTVAvL; these may be escape variants. The strong response to the consensus form persisted, despite the fact it was not observed among the autologous sequences during 6 years of chronic infection.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope `SLYNTVATL`
Epitope name SL9
Subtype B
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A2)
Country Canada
Assay type CD8 T-cell Elispot - IFNγ
Keywords HIV exposed persistently seronegative (HEPS), immunodominance, genital and mucosal immunity, characterizing CD8+ T cells
References Makedonas *et al.* 2005

- CD8 T-cell responses were studied in individuals who remained seronegative in spite of being mucosally (group 1) or intravenously (group 2) exposed to HIV-1. A similar proportion of subjects from each group recognized at least 1 HIV peptide, and they recognized peptides with similar cumulative intensity. The proportion of responding individuals in both groups was significantly greater than in a low-risk, negative control group. One exposed uninfected subject recognized 7 epitopes.
- HLA-A*0201 epitopes that are immunodominant in chronically infected individuals were rarely stimulatory in exposed uninfected individuals. SLYNTVATL was recognized by one HLA A2+ individual in each group (1/11 vs 1/5), while none of the exposed uninfected individuals tested responded to ILKEPVHGV. In contrast, chronically infected subjects recognized these epitopes at a frequency of 69% and 31%, respectively.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope `SLYNTVATL`
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Germany
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords HAART, ART, characterizing CD8+ T cells, optimal epitope
References Schmitt-Haendle *et al.* 2005

- CTL responses to 3 HLA-A2-restricted epitopes were investigated in 51 HIV-1 infected HLA-A2+ individuals. The most prevalent response was seen for IV9, followed by SL9. The VL9 epitope was not recognized. There was a significant correlation of CTL activity to the CD8 counts in peripheral blood, but no correlation to CD4 counts, viral load, or antiviral therapy.
- SL9 was only recognized in 13.7% of the individuals tested.

HXB2 Location p17 (77–85)
Author Location p17
Epitope `SLYNTVATL`
Epitope name A2-SL9(p17)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope `SLYNTVATL`
Epitope name SL9
Subtype B
Immunogen peptide-HLA interaction
Species (MHC) human (A2)
Assay type Chromium-release assay, HLA binding
Keywords escape, TCR usage, structure, optimal epitope
References Martinez-Hackert *et al.* 2006

- Several natural SL9 variants were shown to bind comparably well to soluble HLA-A2 and D3 TCR. All variants had remarkably similar peptide conformations as evidenced by high resolution crystal structures of soluble interacting proteins. These structures were shown to differ from other peptide-MHC-TCR structures. SL9 variation was shown to be partially restricted by its context in the HIV p17 matrix protein, and the preservation of peptide conformation despite epitope variation may contribute to the persistence of SL9-mediated immune responses.

- 11 Natural variants of SLYNTVATL were tested. They were SLYNTiATL (SL9-6I), SLYNTiAvL (SL9-6I/8V), SLYNTVAvL (SL9-8V), SLfNTVATL (SL9-3F), SLfNTiAvL (SL9-3F/6I/8V), SLfNTiATL (SL9-3F/6I), SLfNTVAvL (SL9-3F/8V), SLYNaVATL (SL9-5A), SLYNsVATL (SL9-5S), SLYNaiATL (SL9-5A/6I), SLYNlVAvL (SL9-5L/8V). Only variants at P5 where Threonine is substituted by Alanine or Leucine abrogated activity, while all others variants were active. No natural variants had substitutions at P4, while P1, P2 and P9 were also conserved. 9 synthetic variants were also tested.
- This degenerate recognition of the HIV Gag epitope by CTL is different from other viral peptide-degeneracies in that several CTL clones can perform equally well in recognition of the SL9 pMHC, and there is not necessarily one dominant recognition.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen in vitro stimulation or selection
Species (MHC) human, mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords TCR usage, variant cross-recognition or cross-neutralization
References Kan-Mitchell *et al.* 2006

- A synthetic combinatorial nonapeptide library was screened with ex-vivo-primed SL9-specific T-cells and an agonist variant of the SL9, p41 SLYNTVAaL, was identified. p41 immunized SL9-cross-reactive CTLs from donors ex vivo and double knockout mice expressing a chimeric HLA I molecule. p41-primed CTLs were also found to require less costimulation from APCs and (unlike SL9-CTLs, they required exogneous IL-2 to proliferate, suggesting they would have better immune memory) less need for exogenous IL-2 to proliferate. The loss of SL9 T-cells was minimized with p41, and the TCR clonotype was shown to be able to develop into either help-dependent or help-independent CTLs.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Epitope name Peptide 7027
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, A3, B44, B7
Country United Kingdom
Assay type Flow cytometric T-cell cytokine assay, Other
Keywords HAART, ART, immunodominance, TCR usage, memory cells
References Weekes *et al.* 2006

- The effect of HAART on the population size, phenotype and function of HIV- and HCMV-specific CTL clones was analyzed. It was determined that the clonal composition of gag and env HIV-specific CD8 T-cells did not change after HAART. Following HAART, the size of immunodominant HIV-specific CD8 T-cell clones was found to diminish even with the relative preservation of functional memory responses. Maintainance of such strong functional responses implied the preferential loss of HIV-specific cells that have reduced cloning efficiency in vitro. HCMV-specific CTL clones had different kinetics and phenotypes than HIV-specific CTL clones in the same subject.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope SLYNTVATL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, subtype comparisons, acute/early infection
References Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (ANC) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- This epitope, SLYNTVATL, is invariant across CON A, B, C and M-Group sequences, as well as clade B COT and ANC sequences. HLA-A02 restriction was inferred based on subject possessing appropriate HLA class I allele and prior publication.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLYNTVATL
Epitope name A2-SL9 Gag (77-85)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, A32, B27, B39
Country France
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, immunodominance, TCR usage, characterizing CD8+ T cells
References Almeida *et al.* 2007

- Since it is suggested that a single response to B27-KK10 epitope may be responsible for the association of HLA-B*2705 patients with AIDS-free survival, B27-KK10-specific CTLs were compared to other HLA-specific CTLs in phenotype, function, clonal diversity, and antigen sensitivity in 47 treatment-naive infected slow or nonprogressing patients.
- cVL, the cell-associated viral load (number of infected cells harboring HIV DNA) correlated inversely with Gag-specific CTLs. This was most significant in HLA-B27 donors, and

KK10 was identified as the peptide generating strongest CTL responses.
- SLYNTVATL was a dominant epitope found in non-B27-KK10 CTL responses.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLFNTVATL
Epitope name A2-SL9 Gag (77-85)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, A3, B60, B7
Country France
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, immunodominance, TCR usage, characterizing CD8+ T cells
References Almeida *et al.* 2007
- Since it is suggested that a single response to B27-KK10 epitope may be responsible for the association of HLA-B*2705 patients with AIDS-free survival, B27-KK10-specific CTLs were compared to other HLA-specific CTLs in phenotype, function, clonal diversity, and antigen sensitivity in 47 treatment-naive infected slow or nonprogressing patients.
- cVL, the cell-associated viral load (number of infected cells harboring HIV DNA) correlated inversely with Gag-specific CTLs. This was most significant in HLA-B27 donors, and KK10 was identified as the peptide generating strongest CTL responses.
- SLFNTVATL was a dominant epitope found in non-B27-KK10 CTL responses.

HXB2 Location p17 (77–85)
Author Location Gag (77–85 Henan isolate)
Epitope SLYNTVAVL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006
- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- SLYNTVAVL was recognized by 61% HLA-A2-positive individuals.

HXB2 Location p17 (77–85)
Author Location
Epitope SLYNTVATL
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a
- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A*0201, A*2402, B*4001, B*5001, Cw03, Cw04
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords immunodominance, escape, variant cross-recognition or cross-neutralization
References Draenert *et al.* 2006
- HIV-specific cellular and humoral immune responses were examined in monozygotic male twins infected simultaneously with the same virus. 15 of 17 targeted epitopes were identical in the twins, including two immunodominant responses. 3 of 4 declining responses in the twins showed mutations at the same residue. Evolving antibody responses cross-neutralized the other twin's virus. The results were compared with a third brother, infected by the twins' virus 13 months after their seroconversion. The data show similarity in disease course in persons of identical genetic background infected with the same strain of HIV-1.
- This epitope, SLYNTVATL (SL9), is restricted by HLA-A02. A variant that arose was SLYNTVAvL.

HXB2 Location p17 (77–85)
Author Location
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States, South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords memory cells
References Wherry *et al.* 2006

CTL CD8+

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

HXB2 Location p17 (77–85)
Author Location
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining
Keywords responses in children, rate of progression
References Chakraborty *et al.* 2005

- A study of long-term surviving children in Kenya revealed CD8 T-cell responses in all progression groups. The most striking atttribute of long term surviving children was strong CD4 T-cell responses, which may be significant in delaying disease progression.
- Response detected in 1 long-term surviving progressive child.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLYNTVATL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords rate of progression, acute/early infection, memory cells
References Sabbaj *et al.* 2007

- CD127 hi memory CTLs were correlated with different patient groups - subjects with chronic HIV-1 infection or controllers or those treated early with ART. For patients with chronic infection, CD127 hi CTL levels decrease greatly. Early ART treatment alone maintained these long-lived memory T cells.
- In response to epitope SL9, SLYNTVATL, a patient with oscillating ART had IFN-gamma secretion by CD127 lo cells during viremia and CD127hi cell-IFN-gamma production during viremic control. Shortly after ART cessation, CD127 mixed cells secreted IFN-gamma. HLA-restriction was to -A2.

HXB2 Location p17 (77–85)
Author Location
Epitope SLYNTVATL
Epitope name Gag 77
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords immunodominance, escape, variant cross-recognition or cross-neutralization
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- The exact sequence of Gag 77 SLYNTVATL epitope (used as an immunodominant control), was found in only 2 patients but 6 patients had a CTL immune response to it. Thus known immunodominant epitopes were less conserved but frequently targeted.
- In most patients, this epitope sequence was different by 1 or more amino acids between positions 3-8.
- Frequent mutations in immunodominant Gag 77 may represent escape mutants emerging during infection.

HXB2 Location p17 (77–85)
Author Location
Epitope SLFNTVATL
Immunogen peptide-HLA interaction
Species (MHC) human (A2)
Keywords cross-presentation by different HLA
References Li *et al.* 2008a

- Degenerate CTL recognition of pMHC if predictable may be used to broaden vaccine reactivity. A series of epitope-position specific substitution matrices (EPSSMs) were derived by comparing observed- versus chance-amino acid substitution frequencies.
- EPSSMs showed position-specific preferences: anchor position substitutions and substitutions to P at position 1 are not well tolerated while a change to W at position 3 is favored.
- All possible single mutations in Gag SLFNTVATL were experimentally checked for tolerated versus escape substitutions. EPSSMs predicted tolerated variants very well, but in the middle region of epitopes escape mutation prediction was poor.
- From a dataset of cross-reactive variant epitopes, substitution types were identified. Variation in certain amino acid types were tolerated with strong position-preference. At anchor position 2, substitutions between basic amino acids are tolerated and at anchor 9, changes between aromatic and small hydrophobic amino acids. At all positions, the best tolerated substitutions were small hydrophobic residues for hydrophilic, suggesting spatial constraint and supporting use of side-chain volume as a predictor of degenerate recognition by CTLs.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLYNTVATL
Subtype A, B, C
Immunogen HIV-1 infection
Species (MHC) human (A2)

Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- The immunodominant HLA-A2-restricted epitope SLYNTVATL (SL9) of HIV-Gag p17 was used in a peptide pool to stimulate PBMCs from 31 HIV-1 + subjects by ELISpot assay. Patients were infected with several HIV subtypes.

HXB2 Location p17 (77–85)
Author Location p17
Epitope `SLYNTVATL`
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- Epitope SLYNTVATL varied to SLYNTVAvL in an untreated patient. Previously published HLA-restriction for SL9 is HLA-A2.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope `SLYNTVATL`
Epitope name SL9-A02
Subtype B, F
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Argentina
Keywords dynamics, escape, HLA associated polymorphism
References Dilernia *et al.* 2008

- Dynamics of CTL escape mutations was studied theoretically by analyzing plasma samples from 302 subjects (collected over 20 years). HLA associated polymorphisms accumulated in a subtype-specific manner.
- Epitope SLYNTVATL has an anchor residues at SL(Y)NTVAT(L). One mutation to SLYNTVvTL is a known escape, diminishing affinity for the restricting HLA molecule. This epitope tends to the consensus in subtype B. Another mutation, SLYNTVAvL increases over time in subtype F.

HXB2 Location p17 (77–85)
Author Location p17 (77–85)
Epitope `SLYNTVATL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Switzerland
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords HAART, ART
References Rehr *et al.* 2008

- By following T-cell function in ART-regimented patients over time, it was shown that ART resulted in reduced viral replication and the restoration of CTLs to polyfunctionality. It is concluded that in vivo antigenic exposure during declining viremia has a positive influence on CTL function.
- Epitope SLYNTVATL was used to interrogate CTL function in 37 chronically infected HIV-1 positive subjects, with respect to cytokine production.

HXB2 Location p17 (77–85)
Author Location Gag (77–)
Epitope `SLYNTVATL`
Epitope name Gag77
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.

CTL CD8+

- Despite carrying HLA A2, DK1 did not respond to HLA-A2 control epitope SLYNTVATL, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope SLYNTVATL
Subtype B
Immunogen HIV-2 infection, HIV-1 or HIV-2 infection
Species (MHC) human (A2)
Country Gambia
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, HIV-2
References Ondondo *et al.* 2008

- To comprehensively compare Gag-specific cellular immunity against HIV-1 versus HIV-2, 20 subjects each infected with HIV-1 or -2, and with similar CD4+ counts were tested for CTL response to Gag peptide pools. No significant difference was seen in magnitude/breadth of CTL response, immunodominance and frequency of targeted Gag peptides, and cross-recognition.
- HIV-1 subtype B SL9 epitope, SLYNTVATL, and its HIV-2 equivalent, SLFNTVCIW, were hardly recognized by these Gambian patients, as opposed to most HIV-C positive Southern African subjects as well as HIV-B positive subjects. A2 restriction of this epitope is previously published.

HXB2 Location p17 (77–85)
Author Location p17
Epitope SLYNTVATL
Epitope name SL9
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A*0202, A2)
Keywords subtype comparisons
References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among B and D clade viruses.
- The Clade A version of the epitope, SLFNTVATL, was preferentially recognized by CTL.
- This epitope was recognized by two different exposed seronegative prostitutes.

HXB2 Location p17 (77–85)
Author Location p17
Epitope SLYNTVATL
Immunogen HIV-1 infection
Species (MHC) human
Keywords review, escape
References Sewell *et al.* 2000

- Review of the impact of CTL on viral immunity and escape that notes that SLYNTVATL-tetramer binding cells in individuals that react to this epitope inversely correlate with plasma viral load.

HXB2 Location p17 (77–85)
Author Location (SF2, HXBc2/Bal chimeric)
Epitope SLYNTVATL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC)
Keywords rate of progression, escape
References Douek *et al.* 2002

- Seven HIV-positive subjects tended to make their strongest CD8+ T-cell response against Gag; these responses had varying breadth and magnitude that were unrelated to disease progression.
- Patient TX7 primarily recognized SL9 during a three year study period and used six T-cell clonotypes for this recognition.
- SLYNTVATL was the only form of the epitope found initially, but three alternate forms eventually appeared: SLYNTVAVL, SLYNTIATL, and most commonly SLYNTIAVL. These distinct forms bind A2, but have distinct abilities to stimulate different T-cell clonotypes.
- In subject TX7, the observed mutations of SL9 failed to escape overall CTL recognition, presumably because the six T-cell clonotypes allowed a more flexible response.
- The BV17 T-cell clone recognized SL9 but not SLYNTIAVL, and BV17 became undetectable at week 20 when SLYNTIAVL predominated. Subsequently BV17 became the second most common clone. Thus the relative frequency of the T-cell clonotypes varied with respect to each other and to epitope variation.

HXB2 Location p17 (77–85)
Author Location p17 (77–85 LAI)
Epitope SLYNTVATL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0201
Keywords HAART, ART, responses in children
References Luzuriaga *et al.* 2000

- Longitudinal study of 8 infants with prolonged viral suppression due to combination antiretroviral therapy showed no HIV-1 specific CTL responses in peripheral blood cells. 6/8 were studied using a Chromium release assay and no response was detected using Gag expressed in vaccinia in the target cells. Three HLA-A*0201 children were tested using SLYNTVATL or ILKEPVHGV HLA A*0201 tetramers and again no HIV-specific response was detected, either using PBMC specimens, or PBMC which had been stimulated *in vitro* for a week.
- In contrast, one of the children with therapy suppressed HIV viral replication who was co-infected with HIV and EBV, while HIV-tetramer negative, had EBV-tetramer staining cells at a frequency of 0.14% in the PBMC.

HXB2 Location p17 (77–85)
Author Location Gag (77–85)
Epitope SLYNTVATL
Subtype B
Immunogen peptide-HLA interaction
Species (MHC) human

CTL CD8+

Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Degranulation, CD107a and b cell surface mobilization, HLA binding
Keywords binding affinity, co-receptor
References Laugel *et al.* 2007b

- To interrogate why epitope variant-related T-cell activations differ in degree of CD8 coreceptor dependence, the authors set up a system to examine pMHCI/CD8 interactions upon binding of antigenic ligands by CTLs. 2 previous hypotheses to explain coreceptor dependence are those of Holler and Kranz suggesting it is inversely correlated to TCR/pMHCI affinity, or it is related to the geometry of TCR engagement. The former hypothesis was supported, since the CD8 coreceptor may optimize T-cell polyspecificity by improving low to intermediate binding affinities of pMHCI for TCR.
- Most studies were performed using clones specific for an hTERT or HTLV-1 peptide. SLYNTVATL was used with clones 003 and SLY-10, both derived from HIV-infected donors, to show that binding to pMHCI tetramers was greater in the presence of WT rather than null CD8 coreceptors.

HXB2 Location p17 (77–85)
Author Location
Epitope `SLYNTVATL`
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A*0201, A*1101; B*4002, B*5101
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it both before and after infection.
- PBMCs from reacting individual failed to bind the HLA-A2/SLYNTVATL tetramer. The optimal epitope turned to be newly defined LYNTVATL, restricted by HLA-C14, not previously shown to restrict HIV-1 epitopes, and T cells recognizing LYNTVATL were of high avidity.

HXB2 Location p17 (77–85)
Author Location p17
Epitope `SLYNTVATL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References Willberg *et al.* 2007

- In order to detect CTL responses using fewer PBMCs and sets of peptides, the authors select pools of peptides that correspond to epitopes which are most likely to elicit HIV-1-specific immunogenic response in the population under study i.e. epitopes that interact with the major HLA of the population. This approach is of benefit to in-field therapeutic and vaccine studies and also under resource-limiting conditions.
- Peptide panels for the following proteins were also generated and tested - p17, p24, p2p7p2p6, Protease, RT, Integrase, Tat, Rev, Vif, Vpr, Vpu, Env and Nef.

HXB2 Location p17 (77–85)
Author Location p17
Epitope `SLFNTVATL`
Epitope name SL9(p17)
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope SLFNTVATL elicited an immune response as part of peptide TGSEELRSLFNTVATLY. The tested sequence corresponds to previously described HLA-A2-restricted epitope SLYNTVATL, differing from this epitope, SLfNTVATL, at one residue.
- 11 of the 55 HLA-A2 carriers responded to SLfNTVATL-containing peptide with average magnitude of CTL response of 227 SFC/million PBMC.

HXB2 Location p17 (77–85)
Author Location Gag
Epitope `SLYNTVATL`
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Garrison *et al.* 2007

- The study examined the influence of HIV-1 infection on human endogenous retroviruses (HERVs) activity and explored T cells cross-reactivity in regions of HIV-1/HERV similarity.
- T cell responses to HERV peptides were identified in HIV-1 positive individuals. There was an inverse correlation between anti-HERV T cell responses and HIV-1 viral load.
- HIV-1 epitope SLYNTVATL has a corresponding HERV peptide PMVSTPATL. These 2 peptides were used in measuring IFN-γ ELISPOT responses in HIV-1-positive and -negative individuals.

HXB2 Location p17 (77–86)
Author Location p17 (77–85)
Epitope SLYNTVATLY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, SLYNTVATLY, was detected within overlapping peptides TGSEELRSLYNTVATLY and SLYNTVATLYCVHQRIEV as well as overlapping peptide QLQPSLQTGSEELRSLY.

HXB2 Location p17 (77–86)
Author Location Gag
Epitope SLYNTVATLY
Epitope name 1261
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A01, A02, B08, Cw16; A02, A30, B35, B49, Cw04, Cw07; A02, A03, B58, B7, Cw07; A02, A03, B08, B51, Cw01, Cw07
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for SLYNTVATLY: 78%

HXB2 Location p17 (77–86)
Author Location
Epitope SLYNTVATLY
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining
Keywords responses in children, rate of progression
References Chakraborty *et al.* 2005

- A study of long-term surviving children in Kenya revealed CD8 T-cell responses in all progression groups. The most striking atttribute of long term surviving children was strong CD4 T-cell responses, which may be significant in delaying disease progression.
- Response detected in 1 LTNP child and 1 early nonprogressive child.

HXB2 Location p17 (77–86)
Author Location Gag (82–92)
Epitope SLFNTVATLY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p17 (77–89)
Author Location Gag
Epitope SLYNIVATLWCVH
Subtype CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide SLYNIVATLWCVH from subtype CRF02_AG.

HXB2 Location p17 (77–91)
Author Location p17 (77–85)
Epitope SLYNTVATLYCVHQR
Subtype A, D
Immunogen HIV-1 infection
Species (MHC) human (A*0201, A*3002)
Donor MHC A*3002, A*6801, B*5703, B*5802; A*0201, A*2902, B*1402, B*1503
Country Uganda

Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References Barugahare *et al.* 2005

- T-cell immune responses were examined in HIV-1 infected Ugandans. Similar levels of cross-clade responses for Gag, Env and Nef were observed. Higher frequencies of responses in conserved regions were found for Gag within a single clade, while areas with higher viral sequence variation had fewer detectable responses. Differential interclade sequence homologies between the Gag regions did not affect the respective level of cross-clade recognition.
- The sequence contains a known A2 epitope and a known A*3002 epitope, and the subjects recognizing it each carry an HLA with a previously-defined restriction. The viral sequence isolated from the subjects was slFntvatlycvhqr, and was reactive.

HXB2 Location p17 (77–91)
Author Location
Epitope `SLYNTVATLYCVHQR`
Immunogen HIV-1 infection
Species (MHC) human (A2, B44, B60)
Donor MHC A11, A2, B60, B7; A2, A32, B44, B7; A2, A24, B15, B40; A11, A2, B44, B60; A2, A31, B27, B44
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 20 (NIH ARRP Cat# 7891), SLYNTVATLYCVHQR, which contains epitopes restricted by HLA-A*02, -B*44 and -B*60 in different patients elicited the following CTL responses: (1) >2000 sfc/ million PBMC in a living non-progressor for 22+ years; (2) in another living non-progressor, responses upto 22+ years; (3) responses of >1000 sfc/million PBMC upto 22+ years for yet another living non-progressor; (4) ∼100 sfc/million PBMC upto 12 years in a low-viremic former non-progressor who succumbed to non-AIDS death; and (5) >1000 sfc/million PBMC upto 22+ years in a deceased former non-progressor who lost viremic control.

HXB2 Location p17 (77–91)
Author Location Gag (77–91)
Epitope `SLYNTVATLYCVHQR`
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized by mice co-immunized with Gag and Tat, but not by mice immunized with Gag alone.

HXB2 Location p17 (77–94)
Author Location p17
Epitope `SLYNTVATLYCVHQRIEV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.

CTL CD8+

- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, SLYNTVATLYCVHQRIEV, had an overall frequency of recognition of 25.3% - 30.5% AA, 26.9% C, 22.7% H, 9.5% WI. This peptide is included in a 34 aa Gag-p17 highly reactive region to be used for vaccine design.

HXB2 Location p17 (78–85)
Author Location p17
Epitope LYNTVATL
Subtype D
Immunogen HIV-1 infection
Species (MHC) human (A24)
Donor MHC A23, A24, B35, B58, Cw4, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on a patient with an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

HXB2 Location p17 (78–85)
Author Location
Epitope LYNTVATL
Immunogen
Species (MHC) human (Cw*14)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an Cw14 epitope.

HXB2 Location p17 (78–85)
Author Location
Epitope LYNTVATL
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human (Cw*14)
Donor MHC A*0201, A*1101; B*4002, B*5101
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it both before and after infection.
- This epitope was contained in SLYNTVATL epitope, but PBMCs from reacting individual failed to bind the HLA-A2/SLYNTVATL tetramer. The optimal epitope turned to be newly defined LYNTVATL, restricted by HLA-C14, not previously shown to restrict HIV-1 epitopes, and T cells recognizing LYNTVATL were of high avidity.

HXB2 Location p17 (78–85)
Author Location p17 (78–85)
Epitope LYNTVATL
Epitope name LL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*14)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-C*14-associated substitutions within optimally defined epitope LYNTVATL are at positions Y2 and T4, LyNtVATL.

HXB2 Location p17 (78–85)
Author Location Gag (78–85 SF2)
Epitope LYNTVATL
Epitope name LYN
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF2 *HIV component:* Gag, Tat *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse (H-2^d)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes
References Cellini *et al.* 2008

- In order to increase the known number of epitopes in Gag protein so that they can be assayed for reactivity in vaccine studies, BALB/c mice were inoculated with Gag or Gag+Tat. OLPs were used to elicit T-cell immune responses from mouse splenocytes, tested for by cytotoxicity or ELISpot assays. 5 novel predicted optimal CTL epitopes, 2 novel predicted CD4 epitopes and 2 immune response eliciting peptides were found.
- Predicted epitope LYNTVATL was found in reactive Peptide 20, SLYNTVATLYCVHQR.

HXB2 Location p17 (78–86)
Author Location (C consensus)
Epitope LYNTVATLY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*29)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the Y2 residue of LYNTVATLY are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location p17 (78–86)
Author Location p17 (78–86)
Epitope LYNTVATLY
Epitope name LY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*29)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-A*29-associated substitutions within optimally defined epitope LYNTVATLY are at positions Y2 and Y9, LyNTVATLy.

HXB2 Location p17 (78–86)
Author Location p17 (78–86)
Epitope LYNTVATLY
Immunogen
Species (MHC) human (A*2902)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an A*2902 epitope.

HXB2 Location p17 (78–86)
Author Location (78–86)
Epitope LFNTVATLY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2902)
Assay type Other
Keywords HLA associated polymorphism
References Boutwell & Essex 2007

- Publicly available HIV-1 subtype C sequences from South Africa and Botswana were analyzed, and 94 HLA-associated amino acid polymorphisms were found. Many polymorphisms were associated with multiple HLA allele classes. 12% associations were negative: association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles accounted for 50% of associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes.
- LFNTVATLY was a previously defined A*2902 presented epitope that encompassed an A*29 associated polymorphism, LfNTVATLY,in the second position.

HXB2 Location p17 (78–86)
Author Location Gag
Epitope LYNTVATLY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2902)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Chopera *et al.* 2008

- Transmission of HIV-1-escape variants from individuals with protective HLA-B*57/-B*5801 alleles to those without these alleles was studied to determine if infection with such replication-deficient mutants offered any advantage to the new host. Dependency between slower rate of disease progression in the newly infected subject and protective genotype of the infecting individual was suggested.
- HLA-A*2902-restricted epitope LYNTVATLY, within peptide TGTEELRSLYNTVATLY was able to elicit CTL response in a wild type virus-carrying subject.

HXB2 Location p17 (78–86)
Author Location p17
Epitope LYNTVATLY
Epitope name LY-9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2902, B*4403)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay

CTL CD8+

Keywords subtype comparisons, epitope processing, immunodominance, cross-presentation by different HLA
References Masemola *et al.* 2004b

- Highly targeted regions in Gag for CD8+ T-cells were defined for individuals with C clade infections in South Africa. 9 specific epitopes within the most reactive regions were characterized. This is 1 of 5 novel epitopes that were found among subtype C HIV-1 from African patients who hadn't previously been identified in B clade infections. Some epitopes were shown to be promiscuous, presented by multiple class I restricting alleles.
- LYNTVATLY was presented by A*2902 and B*4403. B*44 is more common among Caucasians than Zulus (allele frequency 0.149 versus 0.107), while A*29 is more common in Zulus (0.045 versus 0.125).

HXB2 Location p17 (78–86)
Author Location (C consensus)
Epitope LYNTVATLY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A29)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p17 (78–86)
Author Location
Epitope LYNTVATLY
Immunogen
Species (MHC) human (B*4403)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B*4403 epitope.

HXB2 Location p17 (78–86)
Author Location p17
Epitope LFNTVATLY
Epitope name LY9(p17)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope LFNTVATLY elicited an immune response as part of peptides TGSEELRSLFNTVATLY and SLFNTVATLYCVHQRIEI. This epitope differs from the previously described HLA-A29 and -B44-restricted epitope, LYNTVATLY, at 1 residue, LfNTVATLY.
- 1 of the 8 HLA-A29 carriers responded to LfNTVATLY-containing peptide #11 with a magnitude of CTL response of 415 SFC/million PBMC and 3/8 of the HLA-A29 carriers responded to peptide #12 with average magnitude of CTL response of 95 SFC/million PBMC. 1 of the 6 HLA-B44 carriers responded to peptide #11 with a magnitude of CTL response of 50 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p17 (79–90)
Author Location Gag
Epitope YNIVATLWCVHQ
Subtype CRF02_AG, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide YNIVATLWCVHQ from subtype CRF02_AG and to peptide YNtVATLWCVHQ from subtype CRF01_AE.

HXB2 Location p17 (80–88)
Author Location Gag (80–)
Epitope NTVATLYCV
Epitope name Gag80
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* p17 Gag *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction

References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was an intermediate A2 binder, and induced CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 1/17 HIV+ HLA-A2 subjects.

HXB2 Location p17 (80–88)
Author Location
Epitope NTVATLYCV
Epitope name Gag 80
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Gag 80 NTVATLYCV natural epitope was found in 6 patients but only 1 had a CTL immune response to it.

HXB2 Location p17 (80–88)
Author Location Gag (77–)
Epitope NTVATLYCV
Epitope name Gag80
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Gag epitope NTVATLYCV, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients.

HXB2 Location p17 (81–95)
Author Location Gag (81–95)
Epitope TVATLYCVHQRIEVK
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized by mice co-immunized with Gag and Tat, but not by mice immunized with Gag alone.

HXB2 Location p17 (82–91)
Author Location p17 (82–91 93TH253 subtype CRF01)
Epitope IATLWCVHQR
Epitope name G82-91
Subtype CRF01_AE
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A11)
Keywords HIV exposed persistently seronegative (HEPS)
References Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was weakly reactive in the HEPS study subject 265 who was HLA A2/A11.
- This epitope was strongly reactive in HIV+ study subject 053 who carried HLA-A11.

HXB2 Location p17 (82–91)
Author Location p17 (82–91 93TH253 subtype CRF01)
Epitope IATLWCVHQR
Subtype CRF01_AE

CTL CD8+

Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords subtype comparisons
References Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This epitope was predicted by the EpiMatrix method to be likely to bind to A11, and it served as an epitope in the FSWs, it was one of the six A11 epitopes that had been previously defined.
- 3/8 tested FSWs recognized this epitope.
- This epitope was not conserved in other subtypes, and exact matches were uncommon.

HXB2 Location p17 (83–91)
Author Location p17 (84–91)
Epitope ATLYCVHQR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*11)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This putative epitope, ATLYCVHQR, was detected and confirmed within overlapping peptides TGSEELRSLYNTVATLY and SLYNTVATLYCVHQRIEV.

HXB2 Location p17 (83–91)
Author Location Gag (Henan isolate)
Epitope AVLYCVHQR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p17 (83–94)
Author Location Gag
Epitope ATLWCVHQRIDI
Subtype CRF02_AG, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide ATLWCVHQRIDI from subtype CRF02_AG and to peptide ATLWCVHQRIev from subtype CRF01_AE.

HXB2 Location p17 (83–103)
Author Location p17
Epitope ATLYCVHEKIEVRDTKEALDK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- A sequence polymorphism at residue E in Gag reacting peptide, ATLYCVHEKIeVRDTKEALDK, was associated with HLA-B*41. No known HLA-B*41-restricted epitope was in this sequence.

HXB2 Location p17 (84–91)
Author Location p17 (84–91)
Epitope TLYCVHQK
Immunogen HIV-1 infection
Species (MHC) human (A*1101)

Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an A*1101 epitope.

HXB2 Location p17 (84–91)
Author Location Gag (83–90)
Epitope TLYCVHQR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Keywords subtype comparisons, TCR usage
References Fukada *et al.* 2002

- Counterparts for eight known clade B HLA A*1101 epitopes were generated for clade E (CRF01). Three epitopes, identical among clade A-E, were cross-reactive and recognized by clade E infected individuals. The clade E and B analogs to three more HLA A*1101 epitopes was recognized in a clade specific manner. Two other HLA A*1101 clade B defined epitopes were found not to have stimulated a response in clade E infected individuals.
- TLYCVHQR was found to elicit clade-specific responses in clade B (TLYCVHQR is most common, and is also common in clade A – the variant tlycvhqK is common in clade B) and clade E (tlWcvhqr is most common). TLYCVHQR was not recognized by any CTL, tlycvhqK was recognized by CTL from 1/5 B clade infected Japanese subjects, and tlWcvhqr was not recognized by CTL from infected Thai subjects, so this seems to be a B clade exclusive epitope.
- The binding of the variant peptides to HLA A*1101 was comparable, but CTL that recognized tlycvhqK did not cross-recognize the other forms, implicating TCR interaction differences.

HXB2 Location p17 (84–91)
Author Location p17 (83–91)
Epitope TLYCVHQR
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords escape
References Harrer *et al.* 1998

- Two overlapping epitopes were recognized in a long-term survivor, restricted by two different HLA molecules, HLA-A11(TLYCVHQR) and HLA-A2 (SLYNTVATL)
- Viral sequence substitutions were present in this individual which did not affect viral replication and did not alter CTL-recognition of the A2 epitope, but reduced recognition of the A11 epitope, indicative of immune escape.
- A Q90E substitution resulted in a loss of the ability of the peptide to induce lysis, a R91K substitution was still reactive, and a R91Q substitution showed a reduced ability to stimulate lysis.

HXB2 Location p17 (84–92)
Author Location p17 (84–92)
Epitope TLYCVHQRI
Epitope name TI9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*11)
Country Australia, Canada, Germany, United States
Keywords escape, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-A*11-associated substitution within optimally defined epitope TLYCVHQRI is at position R8, TLYCVHQrI. While TI9 recognition frequency is very low, escapes increased after 6 months.

HXB2 Location p17 (84–92)
Author Location Gag (83–91 SUMA)
Epitope TLYCVHQKI
Epitope name Gag TI9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*1103)
Donor MHC A*1103, A*2402, B*1402, B*1501, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, acute/early infection, characterizing CD8+ T cells
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T-cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape muations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

HXB2 Location p17 (84–92)
Author Location p17 (84–92)
Epitope TLYCVHQRI
Immunogen HIV-1 infection
Species (MHC) human (A11)

CTL CD8+

Keywords responses in children, mother-to-infant transmission
References Brander & Walker 1995
- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.

HXB2 Location p17 (84–92)
Author Location p17 (84–92)
Epitope `TLYCVHQRI`
Immunogen HIV-1 infection
Species (MHC) human (A11)
References Birk *et al.* 1998b
- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

HXB2 Location p17 (84–92)
Author Location p17 (84–92)
Epitope `TLYCVHQRI`
Immunogen HIV-1 infection
Species (MHC) human (A11)
References Ferrari *et al.* 2000
- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p17 (84–92)
Author Location p17 (84–92 SF2)
Epitope `TLYCVHQRI`
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b
- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with preseroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A11+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 0/0 group 2, and 1/2 group 3.

HXB2 Location p17 (84–92)
Author Location p17 (84–92)
Epitope `TLYCVHQRI`
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A11)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location p17 (84–92)
Author Location Gag
Epitope `TLYCVHQRI`
Epitope name TI9-A11
Subtype B, F
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country Argentina
Keywords dynamics, HLA associated polymorphism
References Dilernia *et al.* 2008
- Dynamics of CTL escape mutations was studied theoretically by analyzing plasma samples from 302 subjects (collected over 20 years). HLA associated polymorphisms accumulated in a subtype-specific manner.
- Epitope TLYCVHQRI with anchor residues at TLYCVHQ(R)I and a polymorphism tLYCVHQRI, mutates to variant vLYCVHQRI which increases in time.

HXB2 Location p17 (84–92)
Author Location p17
Epitope `TLYCVHQRI`
Epitope name TI9(p17)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008
- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A11-restricted epitope TLYCVHQRI elicited an immune response in Chinese HIV-1 positive subjects as part of peptide SLFNTVATLYCVHQRI.
- 4 of the 28 HLA-A11 carriers responded to TLYCVHQRI-containing peptide with average magnitude of CTL response of 145 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p17 (84–92)
Author Location Gag (Henan isolate)
Epitope `VLYCVHQRI`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p17 (85–92)
Author Location p17
Epitope `LYCVHQKI`
Subtype D
Immunogen HIV-1 infection
Species (MHC) human (A24)
Donor MHC A23, A24, B35, B58, Cw4, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on a patient with an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

HXB2 Location p17 (85–92)
Author Location Gag (85–92 SF2)
Epitope `LYCVHQRI`
Epitope name LYC
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF2 *HIV component:* Gag, Tat *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse (H-2^d)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes
References Cellini *et al.* 2008

- In order to increase the known number of epitopes in Gag protein so that they can be assayed for reactivity in vaccine studies, BALB/c mice were inoculated with Gag or Gag+Tat. OLPs were used to elicit T-cell immune responses from mouse splenocytes, tested for by cytotoxicity or ELISpot assays. 5 novel predicted optimal CTL epitopes, 2 novel predicted CD4 epitopes and 2 immune response eliciting peptides were found.
- Predicted epitope LYCVHQRI was found in reactive Peptide 21, TVATLYCVHQRIEVK.

HXB2 Location p17 (86–96)
Author Location Gag (92–103)
Epitope `YCVHAGIEVRD`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p17 (86–101)
Author Location p17 (SF2)
Epitope `YCVHQRIEIKDTKEAL`
Immunogen HIV-1 infection
Species (MHC) human
References Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined.

HXB2 Location p17 (86–101)
Author Location p17 (SF2)
Epitope `YCVHQRIEIKDTKEAL`
Immunogen HIV-1 infection
Species (MHC) human
References Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined.

HXB2 Location p17 (87–95)
Author Location Gag (Henan isolate)
Epitope `CVHQRIEIK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p17 (87–105)
Author Location p17 (91–105 SF2)
Epitope CRIDVKDTKEALEKIE
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

HXB2 Location p17 (88–115)
Author Location p17 (88–115 ARV)
Epitope VHQRIEIKDTKEALDKIEEEQNKSKKKA
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Achour *et al.* 1990

- B cell epitope HGP-30 also serves as a CTL epitope.

HXB2 Location p17 (88–115)
Author Location p17 (88–115 ARV)
Epitope VHQRIEIKDTKEALDKIEEEQNKSKKKA
Immunogen vaccine
Vector/Type: peptide *HIV component:* CD4BS, HPG30, V3 *Adjuvant:* IL-12
Species (MHC) mouse (H-2^d)
References Hamajima *et al.* 1997

- B cell epitope HGP-30 also serves as a CTL epitope.
- Vaccine combined HGP-30, V3 loop peptide variants, and CD4 binding site peptide.
- IL-12 expression plasmid included with the vaccination enhanced the CTL response.

HXB2 Location p17 (89–98)
Author Location Gag (Henan isolate)
Epitope HQRIEIKDTK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p17 (91–101)
Author Location p17 (SF2)
Epitope RIDVKDTKEAL
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in an HIV+ Haitian living in Boston, who was A23/68 B45/72 Cw2/16 – this epitope fell outside the most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

HXB2 Location p17 (91–105)
Author Location p17 (91–105 SF2)
Epitope RIDVKDTKEALEKIE
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A3, A24, B8, B55.

HXB2 Location p17 (92–101)
Author Location p17 (92–101)
Epitope IEIKDTKEAL
Epitope name IL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*40)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*40-associated substitution within optimally defined epitope IEIKDTKEAL is at positions E2, IeIKDTKEAL.

HXB2 Location p17 (92–101)
Author Location p17 (92–101)
Epitope IEIKDTKEAL
Immunogen HIV-1 infection
Species (MHC) human (B*4001)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*4001 epitope.

HXB2 Location p17 (92–101)
Author Location Gag (92–101)
Epitope IDIKDTKEAL
Epitope name IL10
Immunogen HIV-1 infection
Species (MHC) human (B*4001)
Donor MHC A*0201, A*2402, B*4001, B*5001, Cw03, Cw04
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords immunodominance, escape, variant cross-recognition or cross-neutralization
References Draenert *et al.* 2006

- HIV-specific cellular and humoral immune responses were examined in monozygotic male twins infected simultaneously with the same virus. 15 of 17 targeted epitopes were identical in the twins, including two immunodominant responses. 3 of 4 declining responses in the twins showed mutations at the same residue. Evolving antibody responses cross-neutralized the other twin's virus. The results were compared with a third brother, infected by the twins' virus 13 months after their seroconversion. The data show similarity in disease course in persons of identical genetic background infected with the same strain of HIV-1.
- This epitope, IDIKDTKEAL (IL10) was restricted by HLA-B*4001.

HXB2 Location p17 (92–101)
Author Location p17
Epitope IEIKDTKEAL
Epitope name B40-IL10(p17)
Immunogen HIV-1 infection
Species (MHC) human (B40)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p17 (92–101)
Author Location
Epitope IEIKDTKEAL
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (B40)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location p17 (92–101)
Author Location Gag
Epitope IEIKDTKEAL
Epitope name IL10-B40
Subtype B, F
Immunogen HIV-1 infection
Species (MHC) human (B40)
Country Argentina
Keywords dynamics, HLA associated polymorphism
References Dilernia *et al.* 2008

- Dynamics of CTL escape mutations was studied theoretically by analyzing plasma samples from 302 subjects (collected over 20 years). HLA associated polymorphisms accumulated in a subtype-specific manner.
- Epitope IEIKDTKEAL with anchor residues at I(E)IKDTKEAL mutates to variant IEIrDTKEAL. The consensus epitope IEIkDTKEAL and a polymorphism IEIkDTKEAL increases over time.

HXB2 Location p17 (92–101)
Author Location p17
Epitope IEIKDTKEAL
Epitope name IL10(p17)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B40)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.

CTL CD8+

- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B40-restricted epitope IEIKDTKEAL elicited an immune response in Chinese HIV-1 positive subjects as part of peptides LYCVHQRIEIKDTKEAL and IEIKDTKEALEKIEEEQNK.
- 3 of the 20 HLA-B40 carriers responded to a IEIKDTKEAL-containing peptide with average magnitude of CTL response of 363 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p17 (92–101)
Author Location p17
Epitope IEIKDTKEAL
Immunogen HIV-1 infection
Species (MHC) human (B60)
References Wagner *et al.* 1998a

- CTL specific for HIV epitopes were used to show that the mediators of both the cytolytic (granzyme A was used as the marker) and non-cytolytic (HIV-1 inhibitory chemokines MIP-1 α and RANTES were used as markers) anti-viral responses are localized within the CTL's cytotoxic granules.

HXB2 Location p17 (92–101)
Author Location p17 (92–101 SF2)
Epitope IEIKDTKEAL
Immunogen HIV-1 infection
Species (MHC) human (B60)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B60+ individuals that had a CTL response to this epitope broken down by group: 0/2 group 1, 1/1 group 2, and 0/0 group 3.

HXB2 Location p17 (92–101)
Author Location p17 (SF2)
Epitope IEIKDTKEAL
Immunogen HIV-1 infection
Species (MHC) human (B60)
References Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes.
- B60 is present in 10-20% of the Caucasoid and very common in Asian populations.

HXB2 Location p17 (92–101)
Author Location Gag (92–101)
Epitope IEIKDTKEAL
Immunogen HIV-1 infection
Species (MHC) human (B60)
Keywords class I down-regulation by Nef
References Yang *et al.* 2002

- Nef down-modulates class I protein expression, and this study demonstrates directly that Nef-deleted HIV-1 NL-43 can be more effectively killed *in vitro* than NL-43 with an intact Nef. The effect was shown to be specific for class I presentation of epitopes, and unlike Nef, deleting Vpr did not alter CTL susceptibility of NL43 infected cells. The CTL clone 161JD27, specific for the class I B60 presented epitope IEIKDTKEAL, was one of four used in this study.

HXB2 Location p17 (92–101)
Author Location p17 (92–101 NL43)
Epitope IEIKDTKEAL
Epitope name IL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B60)
Assay type Chromium-release assay, CTL suppression of replication
Keywords escape
References Yang *et al.* 2003a

- Virus was cultured in the presence of CTL lines specific for 5 different epitopes (SLYNTVATL, ILKEPVHGV, IEIKDTKEAL, SEGATPQDL, and KEKGGLEGL) to study the emergence of escape mutations. Escape varied between clones for the same epitope, and between different epitopes. Gag and RT epitope escape, if it occurred at all, tended to be monoclonal and within the epitope, indicating strong fitness constraints, while the Nef epitope escape was rapid, polyconal, and sometimes the result of upstream frameshifts.
- There was one cloned cell line that recognized IEIKDTKEAL, 161JD27. After 2 weeks of passaging HIV-1 in the presence of 161JD27, no mutations were observed within the epitope in 10 sequences; one of the 10 had a single E -> K substitution 6 amino acids beyond the C-terminal end of the epitope.

HXB2 Location p17 (92–101)
Author Location Gag (92–101 B consensus)
Epitope IEIKDTKEAL
Epitope name IL10
Subtype B
Immunogen vaccine
Vector/Type: adeno-associated virus (AAV)
HIV component: gp120
Species (MHC) human (B60)
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords dynamics, immune evasion
References Brainard *et al.* 2004

- HIV-1 gp120 is shown to suppress the ability of antigen-specific CTLs to migrate or remain at sites of high viral replication by concentration-dependent chemotaxis and fugetaxis. Directional T-cell movement is shown to depend on the interaction of the V2 and V3 loops with the CXCR4 receptor. X4

HIV-1 gp120 causes the migration of T-cells, including HIV-1 specific CTL, away from infected target cells, another potential mechanism for immune evasion.

HXB2 Location p17 (92–101)
Author Location p17 (92–101)
Epitope IEIKDTKEAL
Epitope name Gag/p17-IL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B60)
Assay type Chromium-release assay
Keywords binding affinity, epitope processing, TCR usage, characterizing CD8+ T cells
References Yang *et al.* 2003b

- Killing efficiency of CTLs and their ability to suppress viral replication is shown to depend more on epitope specificity than to antigenic avidity. Different clones recognizing the same epitope had similar killing efficiency despite their variation in avidity. Nef specific CTL clones tended to be most inhibitory, followed by Gag, then by RT specific clones, regardless of avidity.
- 1/14 CTL T-cell clones tested were specific for Gag/p17-IL10. Under conditions of excess peptide (100ug/ml), there was no difference in their lytic potential; all possessed similar effector capacity. Avidity was measured as the sensitizing dose of peptide required for 50% of maximal killing (SD50), which varied from 20 pg/ml to 100 ng/ml, over four orders of magnitude for all 14 epitopes. The SD50 value for the Gag/p17-IL10 clone was 8,000 pg/ml.

HXB2 Location p17 (92–101)
Author Location p17 (92–101)
Epitope IEIKDTKEAL
Immunogen HIV-1 infection
Species (MHC) human (B60, B61)
Keywords immunodominance
References Day *et al.* 2001

- No immunodominant responses were detected to five B61-restricted epitopes tested.
- All five B60-restricted epitopes were reactive in another subject, and the B60-restricted responses together contributed over one-third of the total CTL response.

HXB2 Location p17 (93–101)
Author Location Gag (93–101)
Epitope EVKDTKEAL
Epitope name EL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*08)
Donor MHC A*01, A*02
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- A minor response was detected against an E93D variant of this epitope, dVKDTKEAL. However, CTL responses effectively eliminated cells with this viral variant. Upstream of this epitope, EVKDTKEAL, an R91G mutation was seen that is suggested to affect processing of this EL9 epitope, such that this mutant viral population evaded immune responses restricted by HLAs A*01, A*02 and B*08. Other variants detected were EiKDTKEAL, kVKDTKEAL and EVKDTKgAL.

HXB2 Location p17 (93–101)
Author Location Gag (99–107 WEAU)
Epitope EVKDTKEAL
Epitope name Gag EVL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Donor MHC A*2902, B*0801, B*4403
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, immunodominance, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.
- There was a weak response to this epitope during acute and early infection, and the epitope sequence did not vary during the first year of the infection.

CTL CD8+

HXB2 Location p17 (93–101)
Author Location p17
Epitope EVKDTKEAL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Donor MHC A*0101, A*0301, B*0801, B*5101; A*0101, B*0801
Country United Kingdom
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords escape, acute/early infection, variant cross-recognition or cross-neutralization
References Milicic *et al.* 2005

- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient. In an early acute infection of the donor, the precise timing of transmission determines the viral variants transmitted.
- The second donor in the study shares A*0101 and B*0801 with his partner. The epitope EVKDTKEAL has an escape variant in the donor that does not react in an Elispot assay, DvkGtkeal, but the Dvkdtkeal form was the transmitted variant. The transmitted form and EVKDTKEAL bind with equal affinity to B*0801.
- The recipient mounted a response to the Dvkdtkeal form of the epitope. The variant DvRdtkeal was detected by 32 weeks post infection.

HXB2 Location p17 (93–101)
Author Location p17 (93–101)
Epitope EIKDTKEAL
Immunogen peptide-HLA interaction
Species (MHC) human (B8)
References DiBrino *et al.* 1994b

- Examined in the context of motifs important for HLA-B8 binding, predicted epitope based on Achour *et al*.

HXB2 Location p17 (93–101)
Author Location p17 (93–101)
Epitope EIKDTKEAL
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Birk *et al.* 1998b

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

HXB2 Location p17 (93–101)
Author Location p17 (93–101 B1 and B2)
Epitope EIKDTKEAL
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A3, A32, B62, B8, Cw3
Country Netherlands
Assay type Other
Keywords subtype comparisons, computational epitope prediction, superinfection
References Kozaczynska *et al.* 2007

- The influence of superinfection upon changes in HIV-1 strains was studied in a triple infected subject. While continuous expression of all three strains was observed, the LTR promoters of subtype AE had highest activity of all 3 strains, and subtype B2 had the lowest. Env-V3 sequences were present in higher numbers in strains B2 and CRF01_AE. Recombination was seen between viruses B1/B2 in gag and vpr genes.
- This HLA-B08 restricted epitope, EIKDTKEAL, varied to EvKDTKEAL in 83% of viruses in B1 within 4 years, dvKDTKEAL at the earliest time point taken in B2 with no changes over time, and EIlDTKEAL in AE at the earliest time point taken, with no changes over time. A reversion was seen in B1 to dIKDTKEAL i.e. v to I, suggesting a lack of CTL pressure on this sequence.

HXB2 Location p17 (93–101)
Author Location p17 (93–101)
Epitope EIKDTKEAL
Epitope name EL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords rate of progression, immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-B8-restricted autologous epitope EIKDTKEAL was able to elicit CTL response only by the last time point. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location p17 (93–101)
Author Location p17 (93–101 LAI)
Epitope EIKDTKEAL
Subtype B
Immunogen
Species (MHC) human (B60, B8)
References Brander & Walker 1997

- Pers. comm. from A. Trocha and S. Kalams to C. Brander and B. Walker.

HXB2 Location p17 (93–101)
Author Location p17 (SF2)
Epitope DVKDTKEAL
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a HIV+ Caucasian from Boston, who was A1/*0201 B8/63 Cw7/- – this epitope fell outside the most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

HXB2 Location p17 (103–112)
Author Location Gag (Henan isolate)
Epitope KIEEEQNKSK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p17 (114–122)
Author Location Gag
Epitope KTQQAAADK
Subtype B, F
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Argentina
Keywords dynamics, escape, HLA associated polymorphism
References Dilernia *et al.* 2008

- Dynamics of CTL escape mutations was studied theoretically by analyzing plasma samples from 302 subjects (collected over 20 years). HLA associated polymorphisms accumulated in a subtype-specific manner.
- Epitope KTQQAAADK with anchor residues at KTQQAAAD(K) mutates to KTQQkAADK, KTQQmAADK, KTQQtAADK and KTQQvAADK. These mutations are strongly supported as escape by phylogenetic correction.

HXB2 Location p17 (119–127)
Author Location Gag (119–127 BORI)
Epitope AADTGNSSQ
Epitope name Gag AQ9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*2902, B*1402, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, immunodominance, escape, acute/early infection, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient BORI had high viral loads and rapid CD4 decline. BORI mounted 8 detected responses. BORI did not control viral replication well, and escape mutations occurred early and in most epitopes, 6/7 that were precisely identified.
- 20 variants in the AADTGNSSQ epitope were found in the patient BORI, the first appearing at day 35 with new variants continuing to arise through day 556. This is an extremely variable epitope, and changed not only by base substitution but by insertion and deletion. All variants tested conferred escape, at high concentrations of peptide.

HXB2 Location p17 (119–127)
Author Location p17 (119–127)
Epitope AADTGNSSQ
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*2902, B*1402
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.

- The best estimate of escape rate for this epitope, AADTGNSSQ, was found to be 0.119/day, with SE of 0.021.
- A number of mutations in this epitope (Gag AQ9) abolished recognition completely. Gag AQ9 overlapped with a second epitope (Gag NP10), and a number of mutations conferring escape from the AQ9 directed response were shown to confer escape from NP10 responses as well. This will lead to an overestimate of the importance of a single CTL response. Escape at NP10 was not quantified separately on the grounds that it was insufficiently independent from escape at AQ9.

HXB2 Location p17 (121–132)
Author Location p17 (121–132 HXB2R)
Epitope `DTGHSNQVSQNY`
Immunogen HIV-1 infection
Species (MHC) human (A33)
References Buseyne *et al.* 1993b

- Clustering of Gag p24 CTL epitopes recognized in 29 HIV-infected people.

HXB2 Location p17 (121–132)
Author Location Gag (121–132 LAI)
Epitope `DTGHSNQVSQNY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A33)
References Buseyne *et al.* 1993a

- Vertical transmission of HIV ranges from 13% to 39%.
- Primary assays showed that cytotoxic activity against at least one HIV protein was detected in 70% of infected children.
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
- Patient EM17 (CDC P2A+C+D2) had a CTL response to two epitopes in Gag.

HXB2 Location p17 (123–132)
Author Location Gag
Epitope `GNSSQVSQNY`
Epitope name GY10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 2, gKssqvsqny, was found not to correspond to the most polymorphic residues in the epitope. This is a novel partially mapped epitope.

HXB2 Location p17 (124–132)
Author Location p17 (124–132 LAI)
Epitope `NSSKVSQNY`
Subtype B
Immunogen HIV-1 or HIV-2 infection
Species (MHC) human (B*3501)
Keywords optimal epitope
References Llano *et al.* 2009

- Noted by Brander to be B*3501 epitope.

HXB2 Location p17 (124–132)
Author Location p17
Epitope `NSSQVSQNY`
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Keywords binding affinity
References Dorrell *et al.* 2001

- The crystal structure of this epitope bound to HLA-B*3501 shows that a serine can fit into the B pocket, which is shared between B35 and B53, with the hydroxyl group of the P2 serine occupying a position almost identical to the P2 proline that was previously considered the anchor motif.
- Novel B53 epitopes (DTINEEAAEW and QATQEVKNM) were defined in this study that showed that A and T can also serve as P2 anchor residues for the B pocket of HLA-B35 and B53 – while S, T, and P could all fit into the B pocket and form a hydrogen bond, A would not form a bond, so the authors propose compensatory interactions account for the high affinity of QATQEVKNM for B53.

HXB2 Location p17 (124–132)
Author Location p17 (124–132 LAI)
Epitope `NSSKVSQNY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords review
References McMichael & Walker 1994

- Review of HIV CTL epitopes.

HXB2 Location p17 (124–132)
Author Location
Epitope `NSSKVSQNY`
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords dynamics, acute/early infection
References Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load.
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B2705; and A*0201, A*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK.
- The subject with A*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705.
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

HXB2 Location p17 (124–132)
Author Location p17 (124–132)
Epitope `NSSKVSQNY`
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Birk *et al.* 1998b

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

HXB2 Location p17 (124–132)
Author Location p17 (124–132 LAI)
Epitope `NSSKVSQNY`
Subtype B
Immunogen HIV-1 or HIV-2 infection
Species (MHC) human (B35)
Country Gambia
Keywords HIV exposed persistently seronegative (HEPS), HIV-2
References Rowland-Jones *et al.* 1995

- Established by titration. HIV-1infected and HIV-2-infected B35+ subjects recognized both the HIV-1 (NSSKVSQNY) and HIV-2 forms (PPSGKGGNY).

HXB2 Location p17 (124–132)
Author Location p17 (124–132 LAI)
Epitope `NSSKVSQNY`
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (B35)
References Lalvani *et al.* 1997

- A peptide-based protocol was optimized for restimulation of CTLp using optimized peptide and IL-7 concentrations – importantly this protocol does not stimulate a primary response, only secondary – peptide-specific CTLp counts could be obtained via staining with peptide-Class I tetramers.
- This peptide was one of the B35 presented test peptides used in control experiments showing that the assay gave no activity using lymphocytes from 21 healthy B35 seronegative donors.

HXB2 Location p17 (124–132)
Author Location p17
Epitope `NSSKVSQNY`
Immunogen
Species (MHC) human (B35)
References Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive.
- HIV-2 version of this epitope is not conserved: PPSGKGGNY, but the CTLs are cross-reactive – this is one of five B35 CTL epitopes that are cross-reactive, see also Rowland-Jones *et al.* [1995].

HXB2 Location p17 (124–132)
Author Location p17
Epitope `NSSKVSQNY`
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords HAART, ART
References Seth *et al.* 2001

- CTL responses were studied by tetramer staining in 41 patients with combination therapy – activated CD8+ T-cells decline as the viral load drops in response to therapy, but the overall level of antigen-specific cells capable of differentiating into effectors stays constant and new epitopes may be recognized.

HXB2 Location p17 (124–132)
Author Location p17 (124–132 SF2)
Epitope `NSSKVSQNY`
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with preseroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 0/2 group 1, 0/2 group 2, and 1/1 group 3.

HXB2 Location p17 (124–132)

CTL CD8+

Author Location
Epitope NSSKVSQNY
Epitope name Gag-NY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B35, 1/21 (5%) recognized this epitope.

HXB2 Location p17 (124–132)
Author Location p17 (124–132)
Epitope NSSKVSQNY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2/9 patients recognized this epitope.

HXB2 Location p17 (124–132)
Author Location
Epitope NSSKVSQNY
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (B35)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location p17 (124–132)
Author Location p17
Epitope NSSQVSQNY
Epitope name NY9(p17)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope NSSQVSQNY elicited an immune response in Chinese HIV-1 positive subjects as part of peptide AADTGNSSQVSQNYPIV. This epitope differs from the previously described HLA-B35-restricted epitope, NSSKVSQNY, at 1 residue, NSSqVSQNY.
- 2 of the 17 HLA-B35 carriers responded to an NSSqVSQNY-containing peptide with average magnitude of CTL response of 80 SFC/million PBMC.

II-B-2 Gag p17-p24 CTL/CD8+ epitopes

HXB2 Location p17-p24 (119–3)
Author Location p17-p24
Epitope AADTGNSSQVSQNYPIV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.

- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This overlapping peptide, AADTGNSSQVSQNYPIV, was differentially targeted across ethnic groups and had an overall frequency of recognition of 2.7% - 0% AA, 15.4% C, 0% H, 0% WI (P value = 0.001). HLA-A11 and -A25 were the most commonly present HLA alleles among individuals with responses to this peptide.

HXB2 Location p17-p24 (124–1)
Author Location Gag (124–133 BORI)
Epitope NSSQVSQNYP
Epitope name Gag NP10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*2902, B*1402, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, immunodominance, escape, acute/early infection, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient BORI had high viral loads and rapid CD4 decline. BORI mounted 8 detected responses. BORI did not control viral replication well, and escape mutations occurred early and in most epitopes, 6/7 that were precisely identified.
- 10 variants in the NSSQVSQNYP epitope were found in the patient BORI, the first appearing at day 35, NgSQVSQNYP, with new variants continuing to arise through day 556. This is an extremely variable epitope, and changed not only by base substitution but by insertion and deletion. All variants tested conferred some degree of escape by diminishing the CTL response.

HXB2 Location p17-p24 (125–3)
Author Location Gag (133–143)
Epitope GKKVSQNYPIV
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p17-p24 (126–11)
Author Location (C consensus)
Epitope GKVSQNYPIVQNLQGQMV
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B13)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location p17-p24 (126–11)
Author Location Gag
Epitope SQVSQNYPIVQNLQGQMV
Epitope name GAG-03
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, EKIRLRPGGKKkYrLKHL differs from the consensus C sequence KIRLRPGGKKhYmLKHL at 2 amino acid positions, i.e. by 11.1%.

CTL CD8+

HXB2 Location p17-p24 (127–3)
Author Location p17-p24 (127–135 subtype D)
Epitope QVSQNYPIV
Subtype D
Immunogen
Species (MHC) human (A*6802)
References Dong 1998
- Epitope starts in p17 and ends in p24.
- Predicted on binding motif, no truncations analyzed.

HXB2 Location p17-p24 (127–3)
Author Location p17
Epitope QVSQNYPIV
Epitope name A68-QV9(p17)
Immunogen HIV-1 infection
Species (MHC) human (A68)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006
- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p17-p24 (127–3)
Author Location p17
Epitope QVSQNYPIV
Epitope name A68-QV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A68)
Donor MHC A2, A68, B14, B44, Cw5, Cw8
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape, acute/early infection, antibody generation, co-receptor, immune evasion
References Streeck *et al.* 2007b
- A subject with acute and rapid disease progression to AIDS showed no neutralizing antibody activity and rapid decline in HIV-specific CTL response by 6 months post-infection. Virus from this rapid progressor was resistant to neutralization by plasma from a long-term progressor. Viral epitopes did not vary much. This suggests viral immune evasion in the absence of viral sequence variation.
- This epitope, QVSQNYPIV, elicited a sub-dominant CTL response, not detectable after 6 months post-infection. QV9 and its flanking sequences NSSQVSQNYPIVQNL showed one escape mutation in the flanking sequence to sSSQVSQNYPIVQNL by 6 months post-infection.

HXB2 Location p17-p24 (127–3)
Author Location p17
Epitope QVSQNYPIV
Epitope name QV9(p17)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A68)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008
- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A68-restricted epitope QVSQNYPIV elicited an immune response in Chinese HIV-1 positive subjects as part of peptide SQVSQNYPIVQN-LQGQMV.

HXB2 Location p17-p24 (129–7)
Author Location Gag (129–139)
Epitope SQNYPIVQNIQ
Epitope name Gag 7.3
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade *HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu
Species (MHC) macaque
Assay type T-cell Elispot, Intracellular cytokine staining
Keywords subtype comparisons, variant cross-recognition or cross-neutralization, memory cells
References Amara *et al.* 2005
- A clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02_AG consensus Gag in macaques. The activity was better conserved for CD8 than CD4 T cells.
- All 5 CD8 and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation of a CD8 T cell epitope previously reported for humans as NYPIVQNL. HLA restriction: A*2402.
- The response elicited to the B clade epitope SQNYPIVQNIQ does not cross-react with the CRF02 form SQNYPIVQNaQ. Other clades either most commonly carry an A or L in this position, SQNYPIVQN[a/l]Q.

HXB2 Location p17-p24 (131–6)

Author Location p17-p24 (132–140 SF2)
Epitope NYPIVQNL
Epitope name Gag133-8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Country Japan
References Ikeda-Moore *et al.* 1997

- The epitope starts in p17 and ends in p24.
- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402.
- This peptide induced CTL in 1/4 HIV-1 + people tested.
- NYPIVQNL bound to A*2402 with medium strength, and the epitope can be processed in a vaccinia construct and presented – no CTL clone was obtained.

HXB2 Location p17-p24 (131–6)
Author Location Gag (133–141 NL-432 or NL-M20A)
Epitope NYPIVQNL
Epitope name Gag133-8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Donor MHC A*2402
Country Japan
Assay type Chromium-release assay, CTL suppression of replication, HLA binding
References Fujiwara *et al.* 2008

- To clarify mechanisms of escape mutation accumulation in the population, the Japanese Nef138-10 (RYPLTFGWCF) epitope was studied amongst hemophiliacs and others, to determine replication suppression abilities of both the wild type and 2F (RfPLTFGWCF) mutant virus. This mutant is conserved due to reduced CTL suppression of viral replication, also preventing viral reversion to WT upon transfer to a new host.
- Epitope Gag133-8, NYPIVQNL, was used as a comparison for positive cytolytic activity of epitope-specific HLA-A*2402 clones against target cells prepulsed with corresponding peptide. These clones partially suppressed NL-M20A viral replication.

II-B-3 Gag p24 CTL/CD8+ epitopes

HXB2 Location p24 (3–11)
Author Location Gag (135–143)
Epitope VQNLQGQMV
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*13)
Donor MHC A*0301, A*3001, B*1301, B*1402, Cw*0602, Cw*0802
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords epitope processing, immune evasion, viral fitness and reversion, HLA associated polymorphism
References Honeyborne *et al.* 2007

- To determine whether HLA-B*13-restricted CTL responses could partially explain low viremic loads in patients, a cohort of chronic C-clade infected subjects was studied. 6 novel B*13-restricted CTL epitopes were defined from both C- and B-clade viruses, 3 of which were within Gag. B*13-restricted CTL responses correlated with lower viremia, with most immunity targeted against Gag epitopes (p15, p17, p24). Gag epitope escape variants may exact a high viral fitness cost, mutations being seen within and around the optimal epitope.
- Variants of this epitope, VQNLQGQMV, were seen at positions 4, 7 and 9. A closer look at sequences just upstream and downstream of the optimal epitope, QNPIVQNLQGQMVHQaiSPRTLNAWVKVEE, show that residues 146 and 147 show most change. In association with HLA-B*57/5801, the epitope ISPRTLNAW (Gag, 147-155)may vary; whilst the HLA-B*1510-restricted epitope VHQAISPRTL (Gag, 143-152) varies at A146P to VHQpISPRTL. Such mutations may be seen >= 4 residues downstream of the epitope C terminus.

HXB2 Location p24 (3–11)
Author Location
Epitope VQNLQGQMV
Epitope name VV9
Immunogen
Species (MHC) human (B13)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B13 epitope.

HXB2 Location p24 (3–11)
Author Location p24
Epitope VQNLQGQMV
Epitope name VV9(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B13)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B13-restricted epitope VQNLQGQMV elicited an immune response in Chinese HIV-1 positive subjects as part of peptide IVQNLQGQMVHQPISPR.
- 7 of the 29 HLA-B13 carriers responded to VQNLQGQMV-containing peptide with average magnitude of CTL response of 189 SFC/million PBMC (author communication and Fig.1).

CTL CD8+

HXB2 Location p24 (8–17)
Author Location Gag (140–149)
Epitope GQMVHQAISP
Subtype A, C, D
Immunogen HIV-1 infection
Species (MHC) human (B*5802)
Country Tanzania
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, immunodominance
References Geldmacher *et al.* 2007a

- 56 ART-naive subjects were studied to assess whether T-cell responses to Gag and Nef are biased towards infecting subtype recognition, in a setting of epidemic consisting of subtypes A,C and D and their recombinant forms. The infecting subtype was determined by multi-region hybridization assay. Overlapping 15-mer isolate-based Gag and Nef peptide sets representative of local subtypes were used. The best recognized epitope variant in terms of magnitude and breadth corresponded to infecting subtype, in this case usually type-C. Hot spots of CTL recognition in Gag were in p24, p17 and p15; hotspots against Nef were in its central, conserved region.
- Epitope variants GQMVHQaiSP, GQMVHQslSP and GQMVHQalSP were studied as peptide sequences GQMVHQaiSP-RTLNA (subtypes C and D), NLQ-GQMVHQslSP-RT (subtype A) and NAQ-GQMVHQalSP-RT with 16% responders. Associated HLA frequently expressed within the studied cohort is listed in the study as B*5802.

HXB2 Location p24 (8–17)
Author Location p24 (140–149)
Epitope GQMVHQAISP
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the A2+ individuals was HLA A*0201, A1, B57 and responded to four B57 epitopes and two others.

HXB2 Location p24 (8–17)
Author Location Gag
Epitope GQMVHQAISP
Epitope name GP10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- GP10, GQMVHQAISP, is a known HLA-B57-restricted epitope used as a positive control for eliciting CTL IFN-gamma response.

HXB2 Location p24 (8–20)
Author Location p24 (140–152 IIIB)
Epitope GQMVHQAISPRTL
Immunogen HIV-1 infection
Species (MHC) human (Cw3)
References Littaua *et al.* 1991

- Fine specificity of human Cw3 restricted Gag CTL epitope.

HXB2 Location p24 (8–20)
Author Location p24 (8–20)
Epitope GQMVHQAISPRTL
Immunogen HIV-1 infection
Species (MHC) human (Cw3)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these eptiopes, but this increased over time.

HXB2 Location p24 (8–21)
Author Location p24 (8–21 B1 and B2)
Epitope GQMVHQAISPRTLN
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A3, Cw3)
Donor MHC A3, A32, B62, B8, Cw3
Country Netherlands
Assay type Other
Keywords subtype comparisons, computational epitope prediction, superinfection
References Kozaczynska *et al.* 2007

- The influence of superinfection upon changes in HIV-1 strains was studied in a triple infected subject. While continuous expression of all three strains was observed, the LTR promoters of subtype AE had highest activity of all 3 strains, and subtype B2 had the lowest. Env-V3 sequences were present in higher

numbers in strains B2 and CRF01_AE. Recombination was seen between viruses B1/B2 in gag and vpr genes.
- This HLA-A03-supertype, -Cw3 restricted epitope, GQMVHQAISPRTLN, varied to GQMVHQpISPRTLN in B1, GQMVHQpISPRTLN in B2 and GQMVHQpvSPRTLN in AE by the earliest time point taken, with no changes over time.

HXB2 Location p24 (8–27)
Author Location p24 (140–159)
Epitope `GQMVHQAISPRTLNAWVKVV`
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Musey *et al.* 1997
- CTL specific for this epitope were found in the peripheral blood but not in the cervical mucosa of one donor.

HXB2 Location p24 (9–18)
Author Location Gag (173–182)
Epitope `QMVHQAISPR`
Immunogen HIV-1 infection
Species (MHC) human (A3 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001
- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801).

HXB2 Location p24 (9–23)
Author Location p24 (16–24)
Epitope `QMVHQSLSPRTLNAW`
Subtype A, D
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*3002, A*6801, B*5703, B*5802; A*3001, A*6601, B*5801, B*5802
Country Uganda
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References Barugahare *et al.* 2005
- T-cell immune responses were examined in HIV-1 infected Ugandans. Similar levels of cross-clade responses for Gag, Env and Nef were observed. Higher frequencies of responses in conserved regions were found for Gag within a single clade, while areas with higher viral sequence variation had fewer detectable responses. Differential interclade sequence homologies between the Gag regions did not affect the respective level of cross-clade recognition.
- The sequence contains a known B7/B8 epitope, but the subjects recognizing it are B7- and B8-negative. The viral sequences isolated from the subjects were qmThqNlsprtlnaw and qmvhqAlsprtlnaw, and the peptide was recognized.

HXB2 Location p24 (9–23)
Author Location Gag (141–155)
Epitope `QMVHQAISPRTLNAW`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008
- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the Progressor. Both patients had A146P, I147L substitutions.

HXB2 Location p24 (10–18)
Author Location Gag (144–152 SF2)
Epitope `MVHQAISPR`
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (A*3303)
Assay type Chromium-release assay
Keywords binding affinity, computational epitope prediction
References Hossain *et al.* 2003
- HLA-A*3303 is a common HLA allele in east and southeast Asia. Pol, Gag and Nef SF2 proteins were scanned for potential A*3303 epitopes. 99 potential epitopes were synthesized, and 52/99 bound to A*3303. Six of these served as peptide-targets for lysis by PBMC from infected individual, and clones derived from 4 of these 6 could lyse HIV-vaccinia infected target cells, indicating proper processing.
- This epitope is one of the 4 that are properly processed.

HXB2 Location p24 (10–18)
Author Location Gag (174–182)
Epitope `MVHQAISPR`
Immunogen HIV-1 infection
Species (MHC) human (A3 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 5/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801).

HXB2 Location p24 (10–23)
Author Location Gag
Epitope MVHQSMSPRTLNAW
Subtype A, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 2 subjects responded to peptide MVHQSMSPRTLNAW from subtype CRF02_AG, and 1 of the 2 responded to peptide MVHQplSPRTLNAW from subtype A.

HXB2 Location p24 (11–20)
Author Location (C consensus)
Epitope VHQAISPRTL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p24 (11–20)
Author Location (C consensus)
Epitope VHQAISPRTL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- VHQAISPRTL is an optimal epitope.

HXB2 Location p24 (11–20)
Author Location p24
Epitope VHQAISPRTL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- VHQAISPRTL is a previously described HLA-B*1510-restricted epitope (part of reacting peptide QNLQGQMVHQAISPRTLNAWV) that contains a B*1510-associated reversion at residue A (VHQaISPRTL).

HXB2 Location p24 (11–24)
Author Location p24 (SF2)
Epitope VQHAISPRTLNAWV
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in an HIV+ Haitian living in Boston, who was A34/68 B57/71 Cw3/7 – this epitope fell outside the most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24

161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

HXB2 Location p24 (11–25)
Author Location p24 (11–25 HXB2)
Epitope `VHQAISPRTLNAWVK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 29% of the study subjects, and it was the third most frequently recognized peptide.

HXB2 Location p24 (11–32)
Author Location p24 (143–164 BH10)
Epitope `VHQAISPRTLNAWVKVVEEKAF`
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Johnson *et al.* 1991

- Gag CTL response studied in three individuals.

HXB2 Location p24 (12–20)
Author Location p24 (144–152)
Epitope `HQAISPRTL`
Epitope name HL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*15)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*15-associated substitution within optimally defined epitope HQAISPRTL is at positions I4, HQAiSPRTL.

HXB2 Location p24 (12–20)
Author Location
Epitope `HQAISPRTL`
Immunogen
Species (MHC) human (B*1510)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B*1510 epitope.

HXB2 Location p24 (12–20)
Author Location Gag (146–154)
Epitope `HQAISPRTL`
Immunogen HIV-1 infection
Species (MHC) chimpanzee (Patr-B*02)
References Balla-Jhagjhoorsingh *et al.* 1999b

- Certain HLA-alleles have been associated with long-term survival – among them are HLA-B*27 and HLA-B*57.
- Of more than 150 chimpanzees that have been reported to be infected with HIV-1, only one has developed AIDS.
- CTL responses were studied in two HIV-1 infected chimpanzees that have strong CTL responses, and they were found to respond to highly conserved epitopes that are recognized in humans in the context of HLA-B*27 and HLA-B*57.
- The human HLA protein which presents this Patr-B*02 epitope is HLA-B*5701 but the amino acid sequences in the binding pockets of HLA-B*5701 and Patr-B*02 are distinctive.

HXB2 Location p24 (12–20)
Author Location p24
Epitope `HQPISPRTL`
Epitope name HL9(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.

- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope HQPISPRTL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide QMVHQPISPRTLNAWVKV. This epitope differs from the previously described HLA-B15-restricted epitope, HQAISPRTL, at 1 residue, HQpISPRTL.
- 3 of the 21 HLA-B15 carriers responded to HQpISPRTL-containing peptide with average magnitude of CTL response of 750 SFC/million PBMC.

HXB2 Location p24 (13–20)
Author Location p24 (13–20)
Epitope QAISPRTL
Epitope name QL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*07)
Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords rate of progression, immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-Cw*07-restricted autologous epitope QAISPRTL only elicited a CTL response at the first time point. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location p24 (13–20)
Author Location p24 (145–152)
Epitope QAISPRTL
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (Cw3)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location p24 (13–23)
Author Location p24 (145–155)
Epitope QAISPRTLNAW
Epitope name QW11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*25)
Country United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-A*25-associated substitution within optimally defined epitope QAISPRTLNAW is at positions 3I, QAiSPRTLNAW.

HXB2 Location p24 (13–23)
Author Location p24 (145–155 LAI)
Epitope QAISPRTLNAW
Subtype B
Immunogen
Species (MHC) human (A*2501)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an A*2501 epitope.

HXB2 Location p24 (13–23)
Author Location p24 (13–23 HXB2)
Epitope QAISPRTLNAW
Epitope name QW11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2501)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- Amino acid site in the third position potentially experienced positive selection. QAlSPRTLNAW CTL escape mutant was found.

HXB2 Location p24 (13–23)
Author Location p24 (145–155 LAI)

CTL CD8+

Epitope QAISPRTLNAW
Subtype B
Immunogen
Species (MHC) human (A25)
References Kurane & West 1998

HXB2 Location p24 (13–23)
Author Location p24 (145–155 SF2)
Epitope QAISPRTLNAV
Immunogen HIV-1 infection
Species (MHC) human (A25)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with preseroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A25+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/2 group 2, and 1/3 group 3.

HXB2 Location p24 (13–23)
Author Location Gag (145–155 IIIB)
Epitope QAISPRTLNAW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A25)
Assay type Chromium-release assay
References Kurane *et al.* 2003

- Three CD8+ CTL cell clones were derived from 2 HIV-1 positive asymptomatic patients, and their epitope specificities and HLA presenting proteins were defined.

HXB2 Location p24 (13–23)
Author Location
Epitope QAISPRTLNAW
Immunogen HIV-1 infection
Species (MHC) human (A25)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- Based on a prediction of the minimum number of HLA alleles needed to cover the HLA representation in all responders to this epitope, a minimum set of 6 alleles was found: 1 allele previously known to be associated (A25) and 5 additional alleles (A23, A68, B44, Cw04, Cw07).

HXB2 Location p24 (13–23)
Author Location p24 (145–155)
Epitope QAISPRTLNAW
Immunogen HIV-1 infection
Species (MHC) human
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the A2+ individuals was HLA A*0201, A1, B57 and responded to QAISPRTLNAW noted previously to be A25.

HXB2 Location p24 (13–23)
Author Location
Epitope QAISPRTLNAW
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A*0202, A*8001; B*1801, B*5301
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location p24 (14–23)
Author Location Gag
Epitope AISPRTLNAW
Epitope name IW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

CTL CD8+

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Two escape mutations, at positions 1 (A146P) and 2 (I147L), were found in the most polymorphic residue in the epitope. Both were shared between clades B and C. Both were significantly more variable in persons expressing HLA-B57.

HXB2 Location p24 (14–23)
Author Location p24
Epitope `AISPRTLNAW`
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B57, B63)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, cross-presentation by different HLA, optimal epitope
References Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This epitope was recognized by 30% of B63-positive subjects and 29% of B57/58-positive subjects.

HXB2 Location p24 (15–23)
Author Location p24 (147–155)
Epitope `ISPRTLNAW`
Epitope name IW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*15, B*57)
Country Australia, Canada, Germany, United States
Keywords escape, viral fitness and reversion, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- Escape (and reversion) rates for B*57-restricted epitopes were highest for Gag-TW10 (TSTLQEQIGW) > RT-IW9 (IVLPEKDSW) > Nef-YY9 (YTPGPGIRY) > Nef-HW9 (HTQGYFPDW) > Gag-IW9 (ISPRTLNAW) > Gag-KF11 (KAFSPEVIPMF) .
- HLA-B*15 and B*57-associated substitution within optimally defined epitope ISPRTLNAW is at positions I1, iSPRTLNAW. With a recognition frequency of > 20%, IW9 is also the 7th most rapidly escaping and its escape mutations at position 242 are most rapidly reverting.

HXB2 Location p24 (15–23)
Author Location p24
Epitope `LSPRTLNAW`
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2002

- Neisseria gonorrhea cervititis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
- Ghonorrhea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

HXB2 Location p24 (15–23)
Author Location Gag
Epitope `ISPRTLNAW`
Epitope name IW9
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- There was nearly equivalent IFN-γ response to [i/m]SPRTLNAW and to [i/l]SPRTLNAW in several subjects, compared to the wild type.

HXB2 Location p24 (15–23)
Author Location Gag (147–155)
Epitope `ISPRTLNAW`
Epitope name IW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- One patient showed an I147L mutation in the HLA-B57 restricted epitope ISPRTLNAW, to lSPRTLNAW.

HXB2 Location p24 (15–23)
Author Location p24 (15–23)
Epitope `ISPRTLNAW`
Epitope name IW9
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country United Kingdom, Kenya
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance, TCR usage, structure, characterizing CD8+ T cells
References Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B*57-peptide complexes were studied.
- In addition, immunodominance of the previously mapped B*57 epitopes during chronic infection was assessed. KGFNPEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

HXB2 Location p24 (15–23)
Author Location Gag
Epitope `ISPRTLNAW`
Epitope name IW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Donor MHC A*310102, A*6603, B*440302, B*570301, Cw*040101, Cw*07
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords escape, viral fitness and reversion, drug resistance
References Bailey *et al.* 2007

- In this study the entire HIV-1 genome was analyzed before and after virologic escape for the first time and escape mutations were temporarily associated with an increased viremia in an otherwise B*57-elite controller of viral load. It is suggested that HLA-B*57-restricted CTL mutations were the major cause of escape because other multiple drug resistance mutations in Pol and RT (M184V and T215Y) did not result in a marked increase in viral replication capacity in vitro.
- CTLs detecting this Gag epitope, ISPRTLNAW, were detectable and levels remained unchanged over 20 months. Most clones developed an A-P mutation in the position preceding IW9 which is a well-characterized processing escape mutation.

HXB2 Location p24 (15–23)
Author Location Gag
Epitope `ISPRTLNAW`
Epitope name IW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country Canada
Keywords HLA associated polymorphism
References Brumme *et al.* 2008b

- A large chronically infected, treatment naïve cohort was studied to identify and organize HLA I-associated polymorphisms in Gag into an immune escape map. Insertion polymorphisms at p17 C-terminus were associated with HLA-B*44, -A*32, -C*05. Inverse correlations were found between number to HLA-associated sites and pVL as well as escaped Gag residues and pVL. pVL positively correlates with CD4 T-cell count. No enrichment for HLA-associated polymorphisms are seen at anchor residues, showing that CTL escape is primarily not through abrogation of peptide-HLA binding.
- Gag p24 IW9 is B*57-restricted and an HLA-B*57-associated escape mutation at codon 147 resides within it.

HXB2 Location p24 (15–23)
Author Location p24 (147–155)
Epitope `ISPRTLNAW`
Epitope name IW9
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country Kenya
Keywords epitope processing, escape
References Peters *et al.* 2008a

- Gag sequences from 468 HIV-1 positive sex workers from the Kenyan Pumwani cohort were analyzed to bioinformatically identify positively selected residues that could be related to antigen processing. Mutation effects on disease progression were followed by mean CD4 counts. This method is also one way of identifying potential CTL epitopes and classifying them.
- A Gag positive selection map was generated and sites were classified as beneficial or harmful to HIV. They were correlated to antigen processing (proteasomal cleavage), antigen presentation (TAP transport efficiency) and T-cell receptor binding.
- p17 and p24's structural constraints limited their diversity, while p7-p1-p6 showed a higher average entropy.

CTL CD8+

- HLA-B*57-restricted IW9, ISPRTLNAW, has mutation A146P i.e. ISPRTLNpW, that prevents N-terminal trimming by ER aminopeptidase I. Another mutation, I147L, i.e. lSPRTLNAW, is significantly associated with dropping CD4 counts. Double mutants, lSPRTLNpW, occured in 11% of the patients who were HLA-B*5703 progressors.

HXB2 Location p24 (15–23)
Author Location Gag (147–155)
Epitope ISPRTLNAW
Epitope name ISW9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*57, B*5801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, viral fitness and reversion, compensatory mutation
References Chopera *et al.* 2008

- Transmission of HIV-1-escape variants from individuals with protective HLA-B*57/-B*5801 alleles to those without these alleles was studied to determine if infection with such replication-deficient mutants offered any advantage to the new host. Dependency between slower rate of disease progression in the newly infected subject and protective genotype of the infecting individual was suggested.
- 2 Gag polymorphisms in epitopes ISW9 (ISPRTLNAW) and TW10 (TSTLQEQIAW) associated with low viral loads and high CD4+ counts during acute and chronic infection were followed in HLA-B*57 and HLA-B*5801 negative subjects for minimum 12 months. A correlation was suggested between rate of disease progression and genotype of the individual HLA-B*57/-B*5801 positive) from whom virus was contracted.
- Epitope ISW9, ISPRTLNAW, was found with A146X mutation adjacent to ISW9, an epitope processing mutation in 9/21 subjects. 2 of 9 individuals carrying substitutions A146X and T242N had compensating H219Q to partially restore replicative fitness. While A146X/T242N+ subjects show no significant difference from A146X/T242N- subjects in magnitude or breadth of CTL response to other Gag-epitope-containing peptides, they do have lower viremia.
- Other variations found in ISW9 were (p)mSPRTLNAW(V), (p)ISPRTLNAW(V), (p)lSPRTLNAW(V) and (s)lSPRTLNAW(V).

HXB2 Location p24 (15–23)
Author Location p24 (147–155 IIIB)
Epitope ISPRTLNAW
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*5701 epitope.

HXB2 Location p24 (15–23)
Author Location
Epitope ISPRTLNAW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords rate of progression, immunodominance
References Migueles & Connors 2001

- HLA B*5701 was found in a very high frequency in HIV-1 infected non-progressors, 11/13 (85%) versus 19/200 (9.5%) of progressors. Non-progressors tended to have an immune response that was highly focused on four p24 epitopes that were presented by B*5701, ISPRTLNAW, KAFSPEVIPMF, TSTLQEQIGW, and QASQEVKNW.

HXB2 Location p24 (15–23)
Author Location
Epitope ISPRTLNAW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords rate of progression, immunodominance
References Migueles & Connors 2001

- CTL activity was monitored in 27 individuals, including 10 LTNP with an over-expression of HLA B*5701 – these individuals have viral loads below the threshold of infection without therapy, and their immune response tends to be focused on peptides that contain B*5701 epitopes ISPRTLNAW, KAFSPEVIPMF, TSTLQEQIGW, and QASQEVKNW.
- CTL responses are broader in B*5701+ individuals with progressive viremia than those that control viremia.
- The HLA-A*0201 SLYNTVATL epitope response was not as strong in individuals that carried both A2, B57.

HXB2 Location p24 (15–23)
Author Location
Epitope ISPRTLNAW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Assay type Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Migueles *et al.* 2003

- cDNA Gag sequences from a set of 17 HLA-B*5701+ progressors and 10 LTNPs were obtained, and the variation in four p24 B*5701 epitopes examined. Sequence variants were more common ($p < 0.01$) in the epitopes in the progressors (median 3, range 1-7) than LTNPs (median 2, range 0-4).
- In general use of the autologous protein in a target cell did not diminish the overall CD8+ T-cell responses.

HXB2 Location p24 (15–23)
Author Location p24
Epitope ISPRTLNAW
Immunogen peptide-HLA interaction
Species (MHC) human (B*5701)
Assay type Tetramer binding
Keywords binding affinity
References Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, ISPRTLNAW (MHC Class I restriction, serotype Bw4Ile80) complexed with MHC B*5701 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C.

HXB2 Location p24 (15–23)
Author Location p24 (15–23)
Epitope ISPRTLNAW
Epitope name ISP
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells
References Turnbull *et al.* 2006

- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.
- This epitope, B57-ISP, is very strongly associated with delayed progression to AIDS, and its natural variants were less efficiently cross-recognized. Its alanine-substituted variants were poorly cross-recognized.

HXB2 Location p24 (15–23)
Author Location Gag (147–155 LAI)
Epitope ISPRTLNAW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701, B*5801)
Keywords rate of progression
References Klein *et al.* 1998

- B57 has been associated with long-term non-progression in the Amsterdam cohort.
- The most pronounced CTL responses in HLA B*5701 LTS were to RT and Gag.

HXB2 Location p24 (15–23)
Author Location Gag
Epitope LSPRTLNAW
Immunogen HIV-1 infection
Species (MHC) human (B*5703)
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons, cross-presentation by different HLA, variant cross-recognition or cross-neutralization
References Currier *et al.* 2006

- The pattern of immunodominance and epitope clustering within Gag and Nef proteins in subtype A infected individuals was similar to that seen in subtype B and C infections. An immunodominant HLA-C restricted epitope, YVDRFFKTL (YL9 from Gag protein) was observed and restricted to Cw0304.
- The sequence QSLSPRTLNAW is associated with HLA-B*5703 and contains the epitope LSPRTLNAW.

HXB2 Location p24 (15–23)
Author Location p24 (15–23)
Epitope LSPRTLNAW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5801)
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope LSPRTLNAW showed its greatest conservation at $\sim$ 60% to subtype A. It was shown to be HLA-B*5801-restricted.

HXB2 Location p24 (15–23)
Author Location p24 (147–155)
Epitope ISPRTLNAW
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.

CTL CD8+

- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the A2+ individuals was HLA A*0201, A1, B57 and responded to four B57 epitopes and two others, but not SLYNTVATL.

HXB2 Location p24 (15–23)
Author Location Gag (SF2)
Epitope ISPRTLNAW
Epitope name IW9
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords acute/early infection
References Goulder *et al.* 2001a

- This epitope elicited the second strongest CTL response in patient PI004 during acute infection, and maintained the response.
- Three CTL responses, to epitopes TSTLQEQIGW, ISPRTLNAW, and KAFSPEVIPMF, were evident early after infection; CTL responses to SLYNTVATL, QASQEVKNW, EIYKRWII, and FLKEKGGL were detectable at 5 months post-infection and beyond.

HXB2 Location p24 (15–23)
Author Location p24 (147–155)
Epitope ISPRTLNAW
Epitope name ISP
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords HAART, ART, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- None of the 8 study subjects recognized this epitope but none were HLA B57+.

HXB2 Location p24 (15–23)
Author Location p24 (15–23)
Epitope ISPRTLNAW
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (15–23)
Author Location p24 (147–155 SF2)
Epitope ISPRTLNAW
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B57+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/0 group 2, and 2/2 group 3.

HXB2 Location p24 (15–23)
Author Location
Epitope ISPRTLNAW
Epitope name Gag-IW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B57, 2/5 (40%) recognized this epitope.
- Among HIV+ individuals who carried HLA B58, 0/4 (0%) recognized this epitope.

HXB2 Location p24 (15–23)
Author Location
Epitope ISPRTLNAW
Epitope name ISP
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords HAART, ART, supervised treatment interruptions (STI)
References Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFN? Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

HXB2 Location p24 (15–23)
Author Location Gag (147–155)
Epitope ISPRTLNAW
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A28, A3, B53, B57; A31, B57, B7
Assay type Chromium-release assay
Keywords TCR usage, genital and mucosal immunity
References Musey *et al.* 2003

- CTL clones from blood, semen, cervix and rectum samples from 12 individuals were compared. CTL clones derived from blood and mucosal samples had similar high lysis efficiency, primarily perforin dependent, and TCRβ VDJ region sequencing revealed cases of expansion of the same clone in different compartments.
- CD8+ T cell clones directed at this epitope were derived from blood and semen of one male subject, and blood and cervix of one female subject.
- From the male patient, six clones that recognized this epitope had three different patterns of TCRβ usage: 2 from the blood and 1 from the semen used Vβ6S2DJ2S2; 1 from the blood and 1 from the semen used Vβ6S2DJ1.1; and 1 from the semen used Vβ7S1DJ2.3.
- From the female patient, five clones that recognized this epitope had different TCRβ usage. Blood derived clones were Vβ6S7DJ2.7, Vβ6.4DJ2.3, and Vβ6S3DJ2.1. Cervix derived clones were Vβ6S3DJ1.4 and Vβ6S5DJ2.5.

HXB2 Location p24 (15–23)
Author Location Gag (147–155)
Epitope `ISPRTLNAW`
Epitope name ISW9
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords epitope processing, escape
References Draenert *et al.* 2004b

- The A146P mutation flanking the ISW9 epitope (Pisprtlnaw) is positively selected in HLA-B57+ persons and it prevents trimming of the optimal epitope by the endoplasmic reticulum aminopeptidase I. The A146P processing escape mutation does not influence replicative capacity of the virus in vitro and is accumulated over time in the human population.

HXB2 Location p24 (15–23)
Author Location p24 (15–23)
Epitope `ISPRTLNAW`
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 3/7 patients recognized this epitope.

HXB2 Location p24 (15–23)
Author Location (147–155 B consensus)
Epitope `ISPRTLNAW`
Epitope name IW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Allen *et al.* 2004

- This study characterizes an escape mutation in a C-terminal flanking residue of the HLA-A3 gag p17 KK9 epitope that inhibits processing, and is embedded in the overlapping HLA-A3 RK9 epitope.
- The immune response was tracked in subject AC-38. The acute immunodominant response was to the B57 TW10 epitope; this response declined following viral escape (tsNlqeqigw) by day 64. The p17 KK9 and RK9 became immunodominant, but then declined as the escape mutation arose. IW9 is 1 of 3 other strong responses that persisted, along with 1 sub-dominant response.

HXB2 Location p24 (15–23)
Author Location p24
Epitope `ISPRTLNAW`
Epitope name ISW9
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords review, epitope processing, escape
References Goulder & Watkins 2004

- This paper is a review of the role of CTL in HIV infection, and it uses the ISW9 epitope as an example of an epitope that escapes due to a mutation before the N-terminal end of the epitope. The insertion of a proline prevents the aminopeptidase ERAAP from cleaving the glutamine from the precursor, qPisrptlnaw, preventing processing of ISRPTLNAW.

HXB2 Location p24 (15–23)
Author Location Gag
Epitope `ISPRTLNAW`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, epitope processing, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Characteristic changes in B57 epitopes in B57+ people were mapped: ISPRTLNAW often has the substitution Lsprtlnaw, as well as the proximal A->P substitution Pisprtlnaw.

HXB2 Location p24 (15–23)
Author Location p24 (147–155)

Epitope ISPRTLNAW
Epitope name IW9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Ethiopia
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance, escape, variant cross-recognition or cross-neutralization
References Currier *et al.* 2005

- Epitope sequence variation and CD8 T-cell responses were analyzed in C subtype infected HLA-B57-positive individuals from Ethiopia. KF11 was the immunodominant response.
- ISPRTLNAW had a variant lSPRTLNAW in 7/10 B57+ subjects, and 4/9 B57- subjects; 2 other variants were observed, but there was no apparent sequence selection in this epitope.

HXB2 Location p24 (15–23)
Author Location Gag (147–155)
Epitope LSPRTLNAW
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Canada
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords mimics
References Mason *et al.* 2005

- CTL responses against the human IP-30 signal peptide sequence LLDVPTAAV were shown to be elicited by stimulation of PBMCs from HIV-1 infected individuals with HIV protease peptide 76-84, LVGPTPVNI. In vitro stimulation with HIV PR 76-84 or the IP-30 signal peptide was shown to activate a comparable population of cross-reactive effector cells. None of the peptides activated CTL in non-HIV-infected individuals. IP-30 signal peptide was shown to have lower avidity T-cell interactions than the HIV peptide.
- As a control, responses to A2-restricted HIV epitopes ALVEICTEM, EELRQHLLRW, and LSPRTLNAW were shown not to give IP-30 responses.

HXB2 Location p24 (15–23)
Author Location Gag (147–155)
Epitope ISPRTLNAW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A*3001, A*66, B*4201, B*5802, Cw*0602, Cw*1701; A*66, A*68, B*57, B*5802, Cw*0602, Cw*0701
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords epitope processing, responses in children, mother-to-infant transmission, escape, acute/early infection
References Pillay *et al.* 2005

- HIV-specific CTLs in infants were shown to be able to select for viral escape variants early in life, despite a lack of escape with the same CTL specificity in the mother. Infant CTL responses may be compromised by transmission of escape variants that arose in the mother and also those that arose in the father, if the father was the source of the mother's infection.
- ISPRTLNAW is the C consensus form of the epitope and was the autologous form in the mother, and was transmitted to her infant. By 33 weeks a new dominant form of the epitope had emerged in the infant, mSPRTLNAW, and two additional variants had arisen, one with a substitution proximal to the epitope, plSPRTLNAW, and lSPRTLNAW.

HXB2 Location p24 (15–23)
Author Location p24 (15–23)
Epitope ISPRTLNAW
Epitope name IW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, subtype comparisons, acute/early infection
References Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (ANC) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- Epitope sequences for this eptiope, IW9 are invariant between CON B, COT B, ANC B and M-group. Cross-recognition is seen with both C- and A-clades. Anchor residues are at positions 2 and 9; while the A-clade variant contains a change at position 1 to lSPRTLNAW. HLA-B57 restriction was inferred based on subject possessing appropriate HLA class I allele and prior publication.

HXB2 Location p24 (15–23)
Author Location p24 (15–23)
Epitope ISPRTLNAW
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is

made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate reversion rate for this epitope, ISPRTLNAW, was found to be -0.005/day with a SE of 0.
- An A14P substitution in the flanking region of this B57-restricted epitope prevented correct processing of the epitope and conferred CTL escape. On transfer of this variant to an HLA-B57- individual, the frequency of the escape mutant actually increased giving a negative reversion rate of -0.005/day. This is consistent with in vitro replication and competition assays as well as with the accumulation of this mutation in the population, suggesting that A14P does not carry a fitness cost.

HXB2 Location p24 (15–23)
Author Location
Epitope ISPRTLNAW
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location p24 (15–23)
Author Location Gag
Epitope ISPRTLNAW
Epitope name IW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- IW9(Gag), ISPRTLNAW, is a known HLA-B57-restricted epitope used as a positive control for eliciting CTL IFN-gamma response.

HXB2 Location p24 (15–23)
Author Location p24 (147–155 IIIB)
Epitope ISPRTLNAW
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Keywords rate of progression
References Goulder *et al.* 1996b

- Five slow progressors made a response to this epitope, and in two it was the dominant response.
- Peptide defined on the basis of B*5801 binding motif, yet not cross-restricted except at high concentrations.

HXB2 Location p24 (15–23)
Author Location Gag
Epitope ISPRTLNAW
Epitope name ISW9
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords epitope processing, responses in children, mother-to-infant transmission, escape
References Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.
- ISPRTLNAW was recognized more often in children than in adults, and was the most frequently recognized B57 epitope in children. Escape variants of this epitope arose in 2 children: an A->P change proximal to the epitope, pISPRTLNAW, and and I1L change, lSPRTLNAW. In both cases the mother carried AISPRTLNAW.

HXB2 Location p24 (15–23)
Author Location p24 (subtype A)
Epitope LSPRTLNAW
Subtype A

CTL CD8+

Immunogen HIV-1 exposed seronegative
Species (MHC) human (B57, B58)
References Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T cell epitopes: DTVLEDINL (3 individuals), SLYNTVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

HXB2 Location p24 (15–23)
Author Location p24 (147–155)
Epitope `LSPRTLNAW`
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B57, B58)
Keywords HIV exposed persistently seronegative (HEPS), immunodominance
References Kaul *et al.* 2001a

- Variants (L/I)SPRTLNAW are specific for the A/B clades.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B57/B58 women, 4/6 HEPS and 14/17 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in 2 of the 4/6 HEPS cases and in 7 of the 14/17 responsive HIV-1 infected women.

HXB2 Location p24 (15–23)
Author Location Gag (144–152)
Epitope `ISPRTLNAW`
Subtype A, C
Immunogen HIV-1 infection
Species (MHC) human (B57, B58)
Country Tanzania
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, immunodominance
References Geldmacher *et al.* 2007a

- 56 ART-naive subjects were studied to assess whether T-cell responses to Gag and Nef are biased towards infecting subtype recognition, in a setting of epidemic consisting of subtypes A,C and D and their recombinant forms. The infecting subtype was determined by multi-region hybridization assay. Overlapping 15-mer isolate-based Gag and Nef peptide sets representative of local subtypes were used. The best recognized epitope variant in terms of magnitude and breadth corresponded to infecting subtype, in this case usually type-C. Hot spots of CTL recognition in Gag were in p24, p17 and p15; hotspots against Nef were in its central, conserved region.
- Epitope variants iSPRTLNAW and lSPRTLNAW were studied as peptide sequences HQA-iSPRTLNAW-YKV (subtype C), QMVHQS-lSPRTLNAW (subtype A) and QMVHQA-lSPRTLNAW (subtype A) with 20% responders. Associated HLAs frequently expressed within the studied cohort are listed in the study as B57, B58.

HXB2 Location p24 (15–23)
Author Location p24
Epitope `ISPRTLNAW`
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human (B58)
Donor MHC A23, A24, B35, B58, Cw4, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence had an I1L change, lSPRTLNAW.

HXB2 Location p24 (15–23)
Author Location
Epitope `ISPRTLNAW`
Immunogen
Species (MHC) human (B63)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B63 epitope.

HXB2 Location p24 (15–23)
Author Location Gag
Epitope `ISPRTLNAW`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*0602)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- I->L (Lsprtlnaw) is associated with HLA C*0602.

HXB2 Location p24 (15–23)
Author Location
Epitope LSPRTLNAW
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- ISPRTLNAW was consistently recognized by 1/22 HEPS sex worker controls (ML1250), and LSPRTLNAW was recognized by 2 additional HEPS sex worker controls (ML1693 and ML1589).

HXB2 Location p24 (15–23)
Author Location Gag (147–155)
Epitope ISPRTLNAW
Epitope name IW9
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human
Country Canada, South Africa
Keywords escape
References Carlson *et al.* 2008

- A statistical model, the phylogenetic dependency network (PDN), was developed to differentiate the confounding effects of codon variation, linkage disequilibrium of HLA alleles and HIV phylogeny from HLA-associated evolution including HIV selection by HLA-pressure and codon evolution.
- This approach was applied to 2 cohorts of 1144 Gag sequences from HIV-infected individuals, generating associations between HIV codons themselves and codons with HLA alleles. Results generated predicted escapes that confirmed that escape kinetics and compensating mutations are consistent across clades. General patterns of covariation and CTL adaptation were determined. Some clade-based differences were identified.
- HLA-B*57-restricted IW9, ISPRTLNAW, escapes from AISPRTLNAW to pISPRTLNAW (A146P), an antigen processing mutation, in the context of escape substitutions T242N in TW10 (TSTLQEQIGW).
- A putative epitope, pSG9, showed escape that was correlated with escape at this epitope, IW9 (as well as epitopes TW10, TSTLQEQIGW, and QW9, Gag 308-316).

HXB2 Location p24 (15–24)
Author Location p24
Epitope ISPRTLNAWV
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5702, B*5703)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- ISPRTLNAWV is a previously described HLA-B*5702 and -B*5703-restricted epitope (part of Gag reacting peptides QNLQGQMVHQaISPRTLNAWV and NLQGQMVHQAiSPRTLNAWVK) that contains a B*5702-associated reversion at residue I (iSPRTLNAWV).

HXB2 Location p24 (16–24)
Author Location p24 (148–156)
Epitope SPRTLNAWV
Immunogen
Species (MHC) human (B*0702)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*0702 epitope.
- Optimal peptide mapped by titration.

HXB2 Location p24 (16–24)
Author Location p24 (16–24)
Epitope SPRTLNAWV
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords computational epitope prediction, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction.

Thus, the CTL response was less degenerate than peptide binding to MHC.

- In addition to published restriction above, epitope SPRTLNAWV was predicted to be restricted by HLA B*0702, B*3501, B*5102, B*5103, B*5301, B*5401 and B*5502 as well.

HXB2 Location p24 (16–24)
Author Location
Epitope SPRTLNAWV
Immunogen HIV-1 infection
Species (MHC) human (B07)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B07), an additional HLA (B42) was statistically predicted to be associated with this epitope.

HXB2 Location p24 (16–24)
Author Location p24 (148–156)
Epitope SPRTLNAWV
Immunogen
Species (MHC) human (B7)
References Brander & Walker 1997

- Optimal peptide mapped by titration, pers. comm. from D. Lewinsohn to C. Brander and B. Walker.

HXB2 Location p24 (16–24)
Author Location p24 (148–156)
Epitope SPRTLNAWV
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Brodie *et al.* 2000

- Study tracks and quantifies *in vivo* migration of neo-marked CD8 HIV-specific CTL.
- Adoptively transferred gene-marked HIV-specific CTL homed to specific lymph node sites, colocalizing within the parafollicular regions of the lymph node adjacent to cells expressing HIV tat-fusion transcripts, indicative of viral replication.
- The CTL clones expressed CCR5 and localized among HIV-1 infected cells expressing MIP-1alpha and MIP-1beta, CC-chemokines produced at sites of viral replication, suggesting a possible homing mechanism.
- This study provides a methodology for tracking and studying antigen specific CTL *in vivo*.

HXB2 Location p24 (16–24)
Author Location p24 (148–156)
Epitope SPRTLNAWV
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B7)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Subject ML 1203 started with CTL responses to A*6802 DTVLEDINL and to B7 FPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A*6802 ETAYFILKL which became dominant, B7 TPGPGVIRYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV.

HXB2 Location p24 (16–24)
Author Location p24 (16–24)
Epitope SPRTLNAWV
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP).
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes.
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

HXB2 Location p24 (16–24)
Author Location
Epitope SPRTLNAWV
Epitope name Gag-SW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B07, 1/9 (11%) recognized this epitope.

- Among HIV+ individuals who carried HLA B81, 1/6 (17%) recognized this epitope.

HXB2 Location p24 (16–24)
Author Location p24 (16–24)
Epitope SPRTLNAWV
Epitope name B7-SV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 1/11 HLA-B7 positive individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 1/4 individuals had detectable responses to this epitope after STI.

HXB2 Location p24 (16–24)
Author Location p24 (16–24)
Epitope SPRTLNAWV
Epitope name B7-SV9 Gag
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), escape, early treatment, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response, but in this case the epitope did not vary.

HXB2 Location p24 (16–24)
Author Location p24 (148–156)
Epitope SPRTLNAWV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords characterizing CD8+ T cells
References Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- None of seven patients responded to this peptide with GzB producing cells or IFN-gamma producing cells.
- The authors describe the epitope as SPRTLNNQWV – the double N's may be a typo or an unusual form of the epitope; it is atypical and may be why there was no response.

HXB2 Location p24 (16–24)
Author Location p24 (16–24)
Epitope SPRTLNAWV
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 7 patients recognized this epitope.

HXB2 Location p24 (16–24)
Author Location p24
Epitope SPRTLNAWV
Epitope name B7-SV9(p24)
Immunogen HIV-1 infection
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (16–24)
Author Location p24
Epitope SPRTLNAWV

Epitope name SV9(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B7-restricted epitope SPRTLNAWV elicited no immune response in Chinese HIV-1 positive subjects as part of peptide QMVHQPISPRTLNAWVKV.
- Although the tested peptide sequence contains the exact sequence of a previously described HLA-B7 optimal epitope, SPRTLNAWV, none of the 9 HLA-B7 carriers responded to it.

HXB2 Location p24 (16–24)
Author Location p24 (subtype B)
Epitope `SPRTLNAWV`
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B*8101, B7)
References Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T cell epitopes: DTVLEDINL (3 individuals), SLYNTVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

HXB2 Location p24 (16–24)
Author Location Gag (subtype B)
Epitope `SPRTLNAWV`
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B*8101, B7)
Keywords subtype comparisons
References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among A, B, and D clade viruses.

HXB2 Location p24 (16–24)
Author Location p24
Epitope `SPRTLNAWV`
Immunogen HIV-1 infection
Species (MHC) chimpanzee
References Santra *et al.* 1999

- 3/4 animals displayed HIV-1 Gag-specific CTL activity.
- Effector cells from two chimpanzees were able to recognize epitopes also recognized by human HIV-1 Gag-specific CTL (SPRTLNAWV, HLA-B7, and DLNTMLNTV, HLA-B14)
- No chimpanzee CTL were detected to the following human HIV-1 specific Gag epitopes, although they were embedded within 20mer peptides that contained a reactive epitope: ISPRTLNAW, HLA-B57; KRWIILGLNK, HLA-B27; and DRFYKTLRA, HLA-B14.

HXB2 Location p24 (16–26)
Author Location Gag
Epitope `SPRTLNAWVKV`
Subtype A, D
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-B7-restricted epitope SPRTLNAWVKV is from a subtype A library, and is reactive in a subtype D-carrying subject. This epitope is part of reacting peptide VTSPRTLNAWVKVIE.

HXB2 Location p24 (17–31)
Author Location
Epitope `PRTLNAWVKVVEEKA`
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, A31, B27, B44
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS.

- Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 38 (NIH ARRP Cat# 7909), PRTLNAWVKVVEEKA, which contains an epitope restricted by HLA-A2 elicited CTL response for 20+ years in a deceased former non-progressor who lost viremic control of disease.

HXB2 Location p24 (18–26)
Author Location Gag (150–)
Epitope `RTLNAWVKV`
Epitope name Gag150
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* p24 Gag *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was an intermediate A2 binder, and induced CTL responses in mice. Responses were detected in 1/17 HIV+ HLA-A2 subjects.

HXB2 Location p24 (18–26)
Author Location
Epitope `RTLNAWVKV`
Epitope name Gag 150
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords variant cross-recognition or cross-neutralization
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Gag 150 RTLNAWVKV, a very conserved epitope, was found in all 11 patients but only 1 had a CTL immune response to it. It was anchor-optimized to Gag150 (2L)mod, RlLNAWVKV, resulting in a strong immunogen with cross-reaction to the natural form.

HXB2 Location p24 (18–26)
Author Location Gag (150–)
Epitope `RTLNAWVKV`
Epitope name Gag150
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Gag epitope RTLNAWVKV, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients.

HXB2 Location p24 (19–26)
Author Location Gag
Epitope `TLNAWVKW`
Epitope name T9V
Immunogen vaccine
Vector/Type: measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140ΔV3
Species (MHC) transgenic mouse (A*0201)
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells
References Lorin *et al.* 2005a

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

HXB2 Location p24 (19–27)
Author Location p24 (151–159)
Epitope `TLNAWVKVV`
Immunogen HIV-1 infection
Species (MHC) human (A*02)

CTL CD8+

Keywords HAART, ART, immunodominance
References Huang *et al.* 2000

- The single cell ELISPOT assay was optimized and highly specific, and found to work well even after the primary cells had been frozen and thawed.
- Increases in gamma interferon producing cells were observed in response to anti-retroviral therapy using single cell IFN-gamma-production ELISPOT.
- In 3/3 HLA-A*02, -B*27 subjects the immunodominant epitope was against HLA B*27 Gag p24 epitope KRWIILGL, not A2 Gag epitopes.

HXB2 Location p24 (19–27)
Author Location p24 (151–159)
Epitope `TLNAWVKVV`
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Keywords HAART, ART
References Rinaldo *et al.* 2000

- Administration of triple-drug antiretroviral therapy (IDV, 3TC and ZDV) sometimes showed a transient increase and other times failed to increase CTL responses in patients with advanced HIV disease, but there is a stable population of tetramer stained HIV-specific CD8+ CD45RO+ cells that can persist after therapy and long periods of virus being below the level of detection.

HXB2 Location p24 (19–27)
Author Location Gag (151–159)
Epitope `TLNAWVKVV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

HXB2 Location p24 (19–27)
Author Location (LAI)
Epitope `TLNAWVKVV`
Epitope name T9V
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other
Species (MHC) human, transgenic mouse (A*02.01)
Country France
Assay type proliferation, CD4 T-cell Elispot - IFNγ, Chromium-release assay, Other
Keywords computational epitope prediction, Th1
References Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQNANPDCKTILKALGPA, KTILKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTILKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQNANPDCKTILKALGPA, NKIVRMYSPTSILDIRQGPK.
- Epitope T9V was one of 2 CTL reporter epitopes in recombinant mouse invariant chain constructs used for readout in a penatmer staining assay.

HXB2 Location p24 (19–27)
Author Location p24 (19–27)
Epitope `TLNAWVKVI`
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above epitope TLNAWVKVI, was predicted to be restricted by A*0201, A*0202, A*0203, A*0204, A*0206.

HXB2 Location p24 (19–27)
Author Location p24 (19–27)

Epitope TLNAWVKLV
Epitope name 8L
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords binding affinity, immunodominance, dendritic cells, variant cross-recognition or cross-neutralization, HIV-2
References Schaubert *et al.* 2007

- CTL responses to the rarely recognized, subdominant HLA-A2-restricted Gag p24 epitope TLNAWKVV (TV9) were studied since its functional sensitivity and viral suppression is relatively high compared to other, dominant HLA-A2-restricted HIV-1 epitopes. Subdominant CTL responses to TV9 were not related to immunogenicity, availability of cognate TCR repertoires or HLA-epitope binding avidity.
- This epitope, 8L (TLNAWVKLV), is the HIV-2 Gag homolog of HIV-1 TV9(TLNAWVKVV). Relative binding of 8L was comparable to that of TV9 in T2 stabilization assays. TV9-specific CTL cultures cross-recognized 8L.

HXB2 Location p24 (19–27)
Author Location p24 (19–27)
Epitope TLNAWVKVV
Epitope name TV9
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Chromium-release assay, HLA binding
Keywords binding affinity, immunodominance, dendritic cells
References Schaubert *et al.* 2007

- CTL responses to the rarely recognized, subdominant HLA-A2-restricted Gag p24 epitope TLNAWKVV (TV9) were studied since its functional sensitivity and viral suppression is relatively high compared to other, dominant HLA-A2-restricted HIV-1 epitopes. Subdominant CTL responses to TV9 were not related to immunogenicity, availability of cognate TCR repertoires or HLA-epitope binding avidity.
- Well-defined HLA-A2 restricted epitope TV9, TLNAWVKVV, though infrequently targeted in natural HIV infection is conserved across clades and has one known variant, 9I (TLNAWVKVi). Most people are capable of mounting responses to TV9 with large numbers of CTL.
- TV9 affinity for HLA-A*0201 is similar to the relative HLA-A2-binding of Gag epitope SL9, SLYNTVATL. TV9-specific CTLs, however, bound tetramers with a broad range of intensities, indicating structurally diverse clonotypes with heterogeneous avidity to TV9.
- TV9, (TLNAWVKVV), is also a part of oligopeptide PRTLNAWVKVVEEKAP where CTL reaction to TV9 was confirmed in one of 2 HLA-A2+, HLA-B*1503-samples (since this peptide contains an HLA-B*1503-restricted epitope as well).

HXB2 Location p24 (19–27)
Author Location p24 (19–27)
Epitope TLNAWVKVI
Epitope name 9I
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords binding affinity, immunodominance, dendritic cells
References Schaubert *et al.* 2007

- CTL responses to the rarely recognized, subdominant HLA-A2-restricted Gag p24 epitope TLNAWKVV (TV9) were studied since its functional sensitivity and viral suppression is relatively high compared to other, dominant HLA-A2-restricted HIV-1 epitopes. Subdominant CTL responses to TV9 were not related to immunogenicity, availability of cognate TCR repertoires or HLA-epitope binding avidity.
- This epitope, 9I, is the only known variant of HIV-1 TV9(TLNAWVKVV). Relative binding of 9I was comparable to that of TV9 in T2 stabilization assays. TV9-specific CTL cultures cross-recognized 9I.

HXB2 Location p24 (19–27)
Author Location p24 (151–159)
Epitope TLNAWVKVV
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Parker *et al.* 1992; Parker *et al.* 1994

- Study of sequence motifs preferred for peptide binding to class I HLA-A2.

HXB2 Location p24 (19–27)
Author Location p24 (19–27)
Epitope TLNAWVKVV
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (19–27)
Author Location p24 (150–159)
Epitope TLNAWVKVI
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A2)
Keywords subtype comparisons, HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- Variants TLNAWVKV(I/V) are A/B clade specific.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location p24 (19–27)
Author Location p24 (A02, A30, B4402, B15)
Epitope TLNAWVKVV
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A2)

CTL CD8+

Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords HIV exposed persistently seronegative (HEPS), characterizing CD8+ T cells
References Missale *et al.* 2004

- HIV-specific T-cell response was tested in patients exposed to blood from a patient with highly replicating HIV; these patients were nosocomially infected with HBV, but uninfected with HIV. HIV-specific T-cell responses were directed to structural and non-structural HIV proteins in 2 patients, suggesting that the virus replicated in these patients sufficiently to prime a cell-mediated immune response that protected them from HIV infection.
- This patient responded to 4/8 HIV epitopes tested in an IFNgamma EliSpot assay or tetramer assay. Responses were detected to this peptide 8 and 28 weeks after exposure with EliSpot, but not by tetramer binding.

HXB2 Location p24 (19–27)
Author Location p24 (19–27 HXB2)
Epitope `TLNAWVKVI`
Epitope name 24D
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* multiple epitope immunogen *HIV component:* p17/p24 Gag, Pol *Adjuvant:* IL-12
Species (MHC) transgenic mouse (A2)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-specific epitope characteristics, vaccine antigen design
References Bolesta *et al.* 2005

- Immunization of transgenic mice with a codon-optimized hGagp17p24-Polp51 DNA plasmid, consisting of clusters of highly conserved CTL epitopes presented by multiple MHC class I alleles, induced 2- to 5-fold higher CD8+ T-cell responses than the corresponding full-length proteins. The modified proteins had the ribosomal frameshift deleted, as well as the potentially immunosuppressive p15, and protease and integrase. This correlated with higher protection against challenge with Gag and Pol expressing recombinant vaccinia virus. Mice immunized with the hGagp17p24-Polp51 also showed an elevated level of type 1 cytokine production as well as an increased titer of p24- and RT-specific IgG2 antibody responses.
- This was 1 of 4 A2 gag/pol epitopes tested. Transgenic mice immunized with the deleted construct induced more potent EliSpot reactions to this epitope than those immunized with full length Gag/Pol.

HXB2 Location p24 (19–27)
Author Location Gag
Epitope `TLNAWVKVI`
Subtype A, C, D
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-A02-restricted epitope TLNAWVKVI is from subtype A and subtype C libraries, and is reactive in 2 subtype D-carrying subjects. This epitope is part of 2 reacting peptides, VTSPRTLNAWVKVIE and TLNAWVKVIEEKAFS.

HXB2 Location p24 (19–27)
Author Location p24 (19–27)
Epitope `TLNAWVKVV`
Epitope name TV9
Subtype B
Immunogen vaccine, in vitro stimulation or selection
Vector/Type: peptide *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords variant cross-recognition or cross-neutralization
References Blondelle *et al.* 2008

- To identify immunogenically optimized peptide epitopes for use in vaccines, two strategies were used. The first studied rare mutant epitopes that were effective in generating a cross-reactive immune response against a range of mutants. The second method was to use a synthetic combinatorial library of peptides and screen for highly effective responses against one epitope (TV9, TLNAWVKVV) and its mutants. Candidate epitopes were tested in HLA-A2 transgenic mice as well as ex vivo human lymphocytes.
- Natural TV9 mutants tested in transgenic HLA-A*02 mice showed the following responses - the common mutant V9I, TLNAWVKVi was less immunogenic and had low cross-reactivity. TLNAWVKaV (most cross-reactive) and TLNAWVKai were highly immunogenic and cross-reactive to the consensus. Other rare mutants were TfNAWVKVV, TLNAWVKVl, TLNArVKVV, TLNAWiKVi, TsNAWVKVi and TLNAWVKcV.
- Synthetic library mimics chosen were TvNAWnKdV, TLNAWwyaV, TLNAWnKaV, TLNAWnyaV (most immunogenic), TLNAWwydV, TvNAWnyaV, TvNAWwyaV, TvsAvwydV, TLNAWnydV, TLsAWnyaV, TLNAWwKaV, TLsAvwKaV, TLsAWwyaV, TLsAWnydV, TvNAWwKdV and TLNAvwKaV.

HXB2 Location p24 (19–27)
Author Location p24 (subtype B)
Epitope `TLNAWVKVV`
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A*0202, A2)
Keywords subtype comparisons
References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among A, B and D clade viruses.

HXB2 Location p24 (21–30)
Author Location Gag (153–162 WEAU)
Epitope NAWVKIEEK
Epitope name Gag NK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*2902, B*0801, B*4403
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, immunodominance, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.
- There was a weak response to this epitope during acute and early infection, and the epitope sequence did not vary during the first year of the infection.

HXB2 Location p24 (21–31)
Author Location Gag (129–139)
Epitope NAWVKVVEEKA
Epitope name Gag 8.4
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade *HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu
Species (MHC) macaque
Assay type T-cell Elispot, Intracellular cytokine staining
Keywords subtype comparisons, memory cells
References Amara *et al.* 2005

- A clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02_AG consensus Gag in macaques. The activity was better conserved for CD8 than CD4 T cells.
- All 5 CD8 and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation. The similar reported human epitope in this case is NAWVKVVEEKAFSPEVIPMF, HLA restriction:A2, B21, B57.
- The B clade immune response to NAWVKVVEEKA gives a diminished response to the CRF02 variant NAWVKViEEKA, but does cross-react. The M group clades are about evenly split between the 2 variants.

HXB2 Location p24 (21–40)
Author Location Gag (153–172)
Epitope NAWVKVVEEKAFSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Brodie *et al.* 1999

- The ability of CTL effector cells was studied by expanding autologous HIV-1 Gag-specific CTL *in vitro*, and adoptively transferring them.
- The transferred CTLs migrated to the lymph nodes and transiently reduced circulating productively infected CD4+ T cells, showing that CTL move to appropriate target sites and mediate anti-viral effects.

HXB2 Location p24 (21–40)
Author Location p24 (153–172)
Epitope NAWVKVVEEKAFSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Brodie *et al.* 2000

- Study tracks and quantifies *in vivo* migration of neo-marked CD8+ HIV-specific CTL.
- Adoptively transferred gene-marked HIV-specific CTL homed to specific lymph node sites, colocalizing within the parafollicular regions of the lymph node adjacent to cells expressing HIV tat-fusion transcripts, indicative of viral replication.
- The CTL clones expressed CCR5 and localized among HIV-1 infected cells expressing MIP-1? and MIP-1?, CC-chemokines produced at sites of viral replication, suggesting a possible homing mechanism.
- This study provides a methodology for tracking and studying antigen specific CTL *in vivo*.

HXB2 Location p24 (21–40)
Author Location Gag
Epitope NAWVKVVEEKAFSPEVIPMF
Epitope name NF20
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

CTL CD8+

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- NF20, NAWVKVVEEKAFSPEVIPMF, is a known HLA-B57-restricted epitope used as a positive control for eliciting CTL IFN-gamma response.

HXB2 Location p24 (21–40)
Author Location p24 (153–172 SF2)
Epitope `NAWVKVVEEKAFSPEVIPMF`
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A2, -B21.

HXB2 Location p24 (21–40)
Author Location p24 (153–172 SF2)
Epitope `NAWVKVVEEKAFSPEVIPMF`
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *HIV component:* CD4BS, Gag, gp120, V3
Species (MHC) macaque
References Wagner *et al.* 1998b

- A VLP is a non-infectious virus-like particle self-assembled from HIV Pr55 gag – macaques were immunized with VLPs bound to either gp120 or V3+CD4 linear domains Gag and Env specific CTL were stimulated in each case, and Ab response to gag and gp120 was elicited, but the gp120 neutralizing response occurred only with whole gp120, not V3+CD4 – despite the CTL and Ab response, immunized macaques were infected by intervenous challenge with SHIV chimeric challenge stock Wagner *et al.* [1998b]
- CTL specific for this epitope could be found both before and after SHIV challenge.

HXB2 Location p24 (21–42)
Author Location p24 (153–174 BH10)
Epitope `NAWVKVVEEKAFSPEVIPMFSA`
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Johnson *et al.* 1991

- Gag CTL response studied in three individuals.

HXB2 Location p24 (22–36)
Author Location Gag
Epitope `AWVKVVEEKGFNPEV`
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide AWVKVVEEKGFNPEV from subtype CRF01_AE.

HXB2 Location p24 (24–32)
Author Location (C consensus)
Epitope `VKVIEEKAF`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p24 (24–32)
Author Location (C consensus)
Epitope `VKVIEEKAF`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- VKVIEEKAF is an optimal epitope.

HXB2 Location p24 (24–32)
Author Location

Epitope VKVIEEKAF
Immunogen
Species (MHC) human (B*1503)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B*1503 epitope.

HXB2 Location p24 (24–32)
Author Location p24
Epitope VKVVEEKAF
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, rate of progression, immunodominance
References Frahm *et al.* 2006

- CTL responses restricted by HLA-B*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects inspite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominanat CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.
- VKVVEEKAF of clade B is a potential HLA-B*1503-restricted epitope, with epitope VKViEEKAF found in clade C.

HXB2 Location p24 (24–32)
Author Location Gag
Epitope VKVIEEKAF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Chopera *et al.* 2008

- Transmission of HIV-1-escape variants from individuals with protective HLA-B*57/-B*5801 alleles to those without these alleles was studied to determine if infection with such replication-deficient mutants offered any advantage to the new host. Dependency between slower rate of disease progression in the newly infected subject and protective genotype of the infecting individual was suggested.
- HLA-B*1503-restricted epitope VKVIEEKAF, within peptide PRTLNAWVKVIEEKAF was able to elicit CTL response in a wild type virus-carrying subject.

HXB2 Location p24 (24–32)
Author Location p24 (17–32)
Epitope VKVVEEKAF
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human (B*1503)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords binding affinity, immunodominance, dendritic cells
References Schaubert *et al.* 2007

- CTL responses to the rarely recognized, subdominant HLA-A2-restricted Gag p24 epitope TLNAWKVV (TV9) were studied since its functional sensitivity and viral suppression is relatively high compared to other, dominant HLA-A2-restricted HIV-1 epitopes. Subdominant CTL responses to TV9 were not related to immunogenicity, availability of cognate TCR repertoires or HLA-epitope binding avidity.
- 14 of 24 HLA-A2+ subjects recognizing oligopeptide PRTLNAWVKVVEEKAP, most likely directed their response against the HLA-B*1503-restricted VKVVEEKAF epitope found within this oligopeptide.

HXB2 Location p24 (24–32)
Author Location p24
Epitope VKVIEEKAF
Epitope name VF9(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B15)
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords non-susceptible form
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- The tested peptide sequence, PRTNAWVKVVEEKAF, contains a variant, VKVvEEKAF to the previously described HLA-B15 epitope VKVIEEKAF. None of the 21 HLA-B15 carriers responded to the variant VKVvEEKAF.

HXB2 Location p24 (25–39)
Author Location
Epitope KVVEEKAFSPEVIPM
Immunogen HIV-1 infection
Species (MHC) human (B44)
Donor MHC A2, A32, B44, B7
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.

CTL CD8+

- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 40 (NIH ARRP Cat# 7911), KVVEEKAFSPEVIPM, which contains an epitope in different patients that is HLA-B44 restricted elicited the following CTL responses: (1) 19+ years in a living non-progressor and (2) 22+ years in a former non-progressor who succumbed to loss of viremic control.

HXB2 Location p24 (26–40)
Author Location Gag
Epitope VIEEKAFSPEVIPMF
Subtype A, CRF02_AG, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide VIEEKAFSPEVIPMF from subtypes A and CRF02_AG; and to peptide VvEEKgFnPE-VIPMF from subtype CRF01_AE.

HXB2 Location p24 (27–36)
Author Location p24 (27–36)
Epitope IEEKAFSPEV
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope IEEKAFSPEV showed >60% conservation with subtype D. ELISpot response to this epitope's binding HLA-B*4006 was 40 SFUs/million cells.

HXB2 Location p24 (27–37)
Author Location (C consensus)
Epitope IEEKAFSPEVI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4501)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- IEEKAFSPEVI is an optimal epitope.

HXB2 Location p24 (28–36)
Author Location p24
Epitope EEKAFSPEV
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (B*4415)
Keywords HIV exposed persistently seronegative (HEPS)
References Bird *et al.* 2002

- 5/233, (4 HIV-1 positive, 1 HEPS) (2.1%) Kenyan female sex workers carried the novel HLA allele B*4415.
- Residues forming the B pocket of HLA B*4415 were identical to HLA B*4001, B*4402 and B*4403. These alleles preferred E, an acidic residue, at the P2 position.
- The amino acid residues forming the F pocket of allele B*4415 were not correlated with other known HLA molecules, but analogy suggests a binding preference for small, neutral amino acids.
- Based on the binding motif x[DE]xxxxxx[VILA], 19 potential B*4415 epitopes were identified, and 1/19 was reactive in an Elispot, EEKAFSPEV.

HXB2 Location p24 (28–36)
Author Location p24 (28–36)
Epitope EEKAFSPEV
Immunogen
Species (MHC) human (B*4415)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location p24 (28–36)
Author Location (C consensus)

Epitope EEKAFSPEV
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4501)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p24 (28–36)
Author Location Gag
Epitope EEKAFSPEV
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human (B*4501)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-B*4501-restricted epitope EEKAFSPEV is from a subtype B library, and is reactive as part of peptide VKVVEEKAFSPEVIP in a subtype D-carrying subject.

HXB2 Location p24 (28–36)
Author Location p24
Epitope EEKAFSPEV
Epitope name EV9(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B44)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B44-restricted epitope EEKAFSPEV elicited an immune response in Chinese HIV-1 positive subjects as part of peptide WVKVVEEKAFSPEVIPMF.
- 1 of the 6 HLA-B44 carriers responded to EEKAFSPEV-containing peptide with a magnitude of CTL response of 110 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p24 (28–47)
Author Location p24 (160–179)
Epitope EEKAFSPEVIPMFSALSEGA
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Musey *et al.* 1997

- Cervical and peripheral blood derived CTL clones from an HIV-infected woman recognized this epitope.

HXB2 Location p24 (29–36)
Author Location p24 (28–36)
Epitope EKAFSPEV
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa. 2
- 6 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope EKAFSPEV showed conservation across all clades with its conservation being 100% against subtypes B and Indian C. It was predicted to be HLA-Cw*0602-restricted.

HXB2 Location p24 (29–39)
Author Location Gag (161–171)
Epitope EKAFSPEVIPM
Epitope name Gag 8.5
Immunogen vaccine

Vector/Type: *Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade *HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu
Species (MHC) macaque
Assay type T-cell Elispot, Intracellular cytokine staining
Keywords subtype comparisons, variant cross-recognition or cross-neutralization, memory cells
References Amara *et al.* 2005

- A clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02_AG consensus Gag in macaques. The activity was better conserved for CD8 than CD4 T cells.
- All 5 CD8 and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation. The similar reported human epitope in this case is EEKAFSPEVIPMFSALSEGA, HLA restriction: B27
- This epitope is conserved in all HIV-1 clades except CRF01, and is identical in B and CRF02.

HXB2 Location p24 (29–48)
Author Location Gag (161–180 C consensus)
Epitope `EKAFSPEVPMFTALSEGAT`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location p24 (30–37)
Author Location p24 (30–37)
Epitope `KAFSPEVI`
Epitope name K18
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country United Kingdom, Kenya
Assay type CD8 T-cell Elispot - IFNγ
Keywords TCR usage, structure, characterizing CD8+ T cells
References Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B*57-peptide complexes were studied.
- In addition, immunodominance of the previously mapped B*57 epitopes during chronic infection was assessed. KGFNPEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

HXB2 Location p24 (30–37)
Author Location p24 (162–169)
Epitope `KAFSPEVI`
Epitope name KAF8
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country Kenya
References Peters *et al.* 2008a

- Gag sequences from 468 HIV-1 positive sex workers from the Kenyan Pumwani cohort were analyzed to bioinformatically identify positively selected residues that could be related to antigen processing. Mutation effects on disease progression were followed by mean CD4 counts. This method is also one way of identifying potential CTL epitopes and classifying them.
- A Gag positive selection map was generated and sites were classified as beneficial or harmful to HIV. They were correlated to antigen processing (proteasomal cleavage), antigen presentation (TAP transport efficiency) and T-cell receptor binding.
- p17 and p24's structural constraints limited their diversity, while p7-p1-p6 showed a higher average entropy.
- HLA-B*5703 correlating mutant A163G, KgFSPEVI, of KAF8 is associated with an increased CD4 count. Since the mutant epitope is still presented efficiently, it continues to correlate with slow disease progression.

HXB2 Location p24 (30–37)
Author Location p24 (162–170 LAI)
Epitope `KAFSPEVI`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5703)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*5703 epitope.

HXB2 Location p24 (30–37)
Author Location p24 (30–37)
Epitope `KAFSPEVI`
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Goulder *et al.* 2000c

- Two strong clonal CTL responses were generated in donor 026-BMC (HLA A3/-, B42/B57, Cw7/17) against different optimal versions of this epitope, one 8 amino acids long, one 11.
- Improved stabilization of the B57-peptide complex was demonstrated by the 11 mer which fits the B57 binding motif, relative to the 8 mer, which does not.
- B57 tolerates marked difference in optimal peptide length – and B57 is associated with non-progressive infection.

HXB2 Location p24 (30–37)
Author Location
Epitope `KAFSPEVI`
Epitope name Gag-KI8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Sabbaj *et al.* 2003

- Among HIV+ individuals tested who carried HLA B57, 0/5 (0%) recognized this epitope.

HXB2 Location p24 (30–38)
Author Location Gag
Epitope RAFSPEVIP
Subtype A, B, C
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-B57-restricted epitope RAFSPEVIP is from subtype A and B libraries, and is reactive as part of peptide ERAFSPEVIPMFSAL in a subtype C-carrying subject.

HXB2 Location p24 (30–40)
Author Location p24
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Keywords HAART, ART
References Spiegel *et al.* 1999

- Study examines the effect of highly active antiretroviral therapy (HAART) on HIV-1 plasma viral load, CTLp and CTLe frequencies in 8 infected children.
- CTLp (precursors) were measured by stimulating in culture and assaying using 51Cr release, against vaccina expressed IIIB Env, Gag, Pol, Nef, and CTLe were measured by ELISPOT.
- CTL against B*57-KAFSPEVIPMF was a de novo response observed in one of the children when viral load increased as a result of stopping therapy.
- HIV-1 specific CTL responses initially increased in children with complete viral suppression, but then decreased, suggesting viral replication is needed to maintain CTL responses.

HXB2 Location p24 (30–40)
Author Location Gag
Epitope KAFSPEVIPMF
Epitope name KF11
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords subtype comparisons, escape, viral fitness and reversion, optimal epitope
References Leslie *et al.* 2005

- An escape mutation, A2G (KgFSPEVIPMF), is suggested to be a result of selection pressure from the HLA-B*57 allele, and can be transmitted and stable in the absence of HLA-B*57. Evidence indicated that the mechanism of escape was an increased off-rate.

HXB2 Location p24 (30–40)
Author Location Gag
Epitope KAFSPEVIPMF
Epitope name KF11
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- A163S mutation in this epitope can potentially act as a CTL escape mutation.

HXB2 Location p24 (30–40)
Author Location p24 (30–40)
Epitope KAFSPEVIPMF
Epitope name KF11
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CTL suppression of replication
Keywords class I down-regulation by Nef
References Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Late protein Gag epitope KAFSPEVIPMF-recognizing CTLs were less affected by Nef.

HXB2 Location p24 (30–40)
Author Location
Epitope KAFSPEVIPMF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Addo *et al.* 2007

- Maturation phenotypes of CTLs were compared between HIV-1 Controller and Progressor subjects. Controllers were found to recognize a median of 18 epitopes compared to 15 by Progressors. While Controllers certainly had higher frequencies of terminally differentiated effector CTLs (CD45RA+/CCR7-), Progressors had higher mean frequencies of CD45RA-/CCR7- effector memory, CD45RA-/CCR7+ central memory (statistically significant) and CD45RA+/CCR7+ naive CTLs. No correlation was seen

CTL CD8+

between CTL effector phenotype and either HLA-type or epitope.
- B*57-restricted epitope KAFSPEVIPMF does not correlate with any particular CTL maturation phenotype. No study subjects generated terminally differentiated CTLs against this epitope.

HXB2 Location p24 (30–40)
Author Location
Epitope KAFSPEVIPMF
Epitope name KF11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Donor MHC A*310102, A*6603, B*440302, B*570301, Cw*040101, Cw*07
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords escape, viral fitness and reversion, drug resistance
References Bailey *et al.* 2007
- In this study the entire HIV-1 genome was analyzed before and after virologic escape for the first time and escape mutations were temporarily associated with an increased viremia in an otherwise B*57-elite controller of viral load. It is suggested that HLA-B*57-restricted CTL mutations were the major cause of escape because other multiple drug resistance mutations in Pol and RT (M184V and T215Y) did not result in a marked increase in viral replication capacity in vitro.
- CTLs detecting this Gag epitope, KAFSPEVIPMF, were detectable and levels remained unchanged over 20 months. No mutations developed in the KF11 epitope.

HXB2 Location p24 (30–40)
Author Location p24 (162–172)
Epitope KAFSPEVIPMF
Epitope name KF11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords rate of progression, acute/early infection, memory cells
References Sabbaj *et al.* 2007
- CD127 hi memory CTLs were correlated with different patient groups - subjects with chronic HIV-1 infection or controllers or those treated early with ART. For patients with chronic infection, CD127 hi CTL levels decrease greatly. Early ART treatment alone maintained these long-lived memory T cells.
- In response to epitope KF11, KAFSPEVIPMF, IFN-gamma was produced by CD127 lo cells by both controllers and chronic patients. IL-2 and TNF-alpha were produced by both CD127 hi and lo cells in controllers. HLA-restriction was to -B*57.

HXB2 Location p24 (30–40)
Author Location Gag (162–172)
Epitope KAFSPEVIPMF
Epitope name KF11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008
- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Supp-presssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- In this epitope, the ES had A163S substitution (KsFSPEVIPMF), which is very rare in B clade isolates, and the Progressor had A163N substitution (KnFSPEVIPMF). A163S substitution did not significantly affect viral replication, as shown using the pseudotype virus.

HXB2 Location p24 (30–40)
Author Location p24 (162–172)
Epitope KAFSPEVIPMF
Epitope name KAF11
Subtype A1
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country Kenya
References Peters *et al.* 2008a
- Gag sequences from 468 HIV-1 positive sex workers from the Kenyan Pumwani cohort were analyzed to bioinformatically identify positively selected residues that could be related to antigen processing. Mutation effects on disease progression were followed by mean CD4 counts. This method is also one way of identifying potential CTL epitopes and classifying them.
- A Gag positive selection map was generated and sites were classified as beneficial or harmful to HIV. They were correlated to antigen processing (proteasomal cleavage), antigen presentation (TAP transport efficiency) and T-cell receptor binding.
- p17 and p24's structural constraints limited their diversity, while p7-p1-p6 showed a higher average entropy.
- HLA-B*5703 correlating mutant A163G of KAF11, KgFSPEVIPMF, is associated with an increased CD4 count. Since the mutant epitope is still presented efficiently, it continues to correlate with slow disease progression.

HXB2 Location p24 (30–40)
Author Location Gag (16–172)
Epitope KAFSPEVIPMF
Epitope name KF11
Subtype B, C
Immunogen HIV-1 infection

Species (MHC) human (B*57)
Country Canada, South Africa
Keywords escape
References Carlson *et al.* 2008

- A statistical model, the phylogenetic dependency network (PDN), was developed to differentiate the confounding effects of codon variation, linkage disequilibrium of HLA alleles and HIV phylogeny from HLA-associated evolution including HIV selection by HLA-pressure and codon evolution.
- This approach was applied to 2 cohorts of 1144 Gag sequences from HIV-infected individuals, generating associations between HIV codons themselves and codons with HLA alleles. Results generated predicted escapes that confirmed that escape kinetics and compensating mutations are consistent across clades. General patterns of covariation and CTL adaptation were determined. Some clade-based differences were identified.
- HLA-B*57-restricted KAFSPEVIPMF escape, A163G i.e. KgFSPEVIPMF is predicted by escape substitutions in other epitopes, viz. T242N in TW10, I147M in IW9 and lack of escape at 310 in QW9.

HXB2 Location p24 (30–40)
Author Location p24 (162–172)
Epitope `KAFSPEVIPMF`
Epitope name KF11
Subtype ACD
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- Escape (and reversion) rates for B*57-restricted epitopes were highest for Gag-TW10 (TSTLQEQIGW) > RT-IW9 (IVLPEKDSW) > Nef-YY9 (YTPGPGIRY) > Nef-HW9 (HTQGYFPDW) > Gag-IW9 (ISPRTLNAW) > Gag-KF11 (KAFSPEVIPMF) .
- HLA-B*57-associated substitution within optimally defined epitope KAFSPEVIPMF is at position A2, KaFSPEVIPMF. Despite >40% frequency of recognition in acute infection, KF11 exhibited no HLA-driven sequence evolution.

HXB2 Location p24 (30–40)
Author Location Gag (162–172)
Epitope `KAFSPEVIPMF`
Epitope name KF11
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*57, B*5801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
References Chopera *et al.* 2008

- Transmission of HIV-1-escape variants from individuals with protective HLA-B*57/-B*5801 alleles to those without these alleles was studied to determine if infection with such replication-deficient mutants offered any advantage to the new host. Dependency between slower rate of disease progression in the newly infected subject and protective genotype of the infecting individual was suggested.
- Epitope KF11, KAFSPEVIPMF, was found with the A163X mutation in 3 sequences. Other variations found in KF11 were (E)KAFSPEVIPMF(i), (E)KgFSPEVIPMF(T) and (E)KsFSPEVIPMF(T).

HXB2 Location p24 (30–40)
Author Location p24 (162–172 LAI)
Epitope `KAFSPEVIPMF`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords rate of progression
References Goulder *et al.* 1996b

- This peptide was recognized by CTL from five slow progressors.
- Peptide defined on the basis of B*5801 binding motif, yet not cross-restricted except at high concentrations.
- This epitope is highly conserved.

HXB2 Location p24 (30–40)
Author Location p24 (162–172 LAI)
Epitope `KAFSPEVIPMF`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*5701 epitope.

HXB2 Location p24 (30–40)
Author Location
Epitope `KAFSPEVIPMF`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords rate of progression, immunodominance
References Migueles & Connors 2001

- HLA B*5701 was found in a very high frequency in HIV-1 infected non-progressors, 11/13 (85%) versus 19/200 (9.5%) of progressors. Non-progressors tended to have an immune response that was highly focused on four p24 epitopes that were presented by B*5701, ISPRTLNAW, KAFSPEVIPMF, TSTLQEQIGW, and QASQEVKNW.
- Attempts to make all for HLA B*5701-epitope tetramers were made, but only the HLA B*5701-KAFSPEVIPMF tetramer folded properly. The percentage of CD8+ T cells staining with this HLA B*57 gag tetramer and the fraction of CD69+IFN-+

CTL CD8+

cells responding to autologous B cells pulsed with KAFSPEVIPMF was highly correlated (r = 0.84; P = 0.005). The percent of CD8+ T cells that stain with the A*2 gag SLYNTVATL tetramer was low (0-0.31%) in a A2+ B57+ LTNP, emphasizing the focus of the immune response on the B*5701 epitopes.

HXB2 Location p24 (30–40)
Author Location
Epitope KAFSPEVIPMF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords rate of progression, immunodominance
References Migueles & Connors 2001

- CTL activity was monitored in 27 individuals, including 10 LTNP with an over-expression of HLA B*5701 – these individuals have viral loads below the threshold of infection without therapy, and their immune response tends to be focused on peptides that contain B*5701 epitopes ISPRTLNAW, KAFSPEVIPMF, TSTLQEQIGW, and QASQEVKNW.
- CTL responses are broader in B*5701+ individuals with progressive viremia than those that control viremia.
- The HLA-A*0201 SLYNTVATL epitope response was not as strong in individuals that carried both A2 and B57.

HXB2 Location p24 (30–40)
Author Location Gag (162–172)
Epitope KAFSPEVIPMF
Epitope name KAF11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Assay type Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Migueles *et al.* 2003

- cDNA Gag sequences from a set of 17 HLA-B*5701+ progressors and 10 LTNPs were obtained, and the variation in four p24 B*5701 epitopes examined. Sequence variants were more common ($p < 0.01$) in the epitopes in the progressors (median 3, range 1-7) than LTNPs (median 2, range 0-4).
- In general, use of the autologous protein in a target cell did not diminish the overall CD8+ T-cell responses.
- This epitope tends to be quantitatively immunodominant in B57+ people, including in some of the individuals in this study. It was extremely well conserved in the sequences obtained here, despite strong immune pressure, suggesting fitness constraints.

HXB2 Location p24 (30–40)
Author Location p24
Epitope KAFSPEVIPMF
Immunogen peptide-HLA interaction
Species (MHC) human (B*5701)
Assay type Tetramer binding
Keywords binding affinity
References Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, KAFSPEVIPMF (MHC Class I restriction, serotype Bw4Ile80) complexed with MHC B*5701 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C. However, the complex B*57-KAFSPEVIPMF does bind inhibitory KIR3DL1 subtype KIR3DL1*005.

HXB2 Location p24 (30–40)
Author Location p24
Epitope KGFNPEVIPMF
Immunogen peptide-HLA interaction
Species (MHC) human (B*5701)
Assay type Tetramer binding
Keywords binding affinity
References Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, KGFNPEVIPMF (MHC Class I restriction, serotype Bw4Ile80) complexed with MHC B*5701 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C.

HXB2 Location p24 (30–40)
Author Location p24 (30–40)
Epitope KAFSPEVIPMF
Epitope name KAF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords rate of progression, TCR usage, variant cross-recognition or cross-neutralization
References Turnbull *et al.* 2006

- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.

- This epitope, B57-KAF that is strongly associated with delayed progression to AIDS and its natural as well as alanine-substituted variants are efficiently cross-recognized. At lower peptide concentrations, efficiency of variant cross-recognition was reduced, even while interepitopic differences in variant cross-recognition efficiency were maintained. CTLs responding to this epitope expressed the same predominant TCR Vbeta family, but individuals whose CTLs predominantly used TCR Vbeta 17 had less efficient variant cross-reactivity.

HXB2 Location p24 (30–40)
Author Location p24 (30–40)
Epitope `KAFSPEVIPMF`
Epitope name KAFS
Subtype A, B
Immunogen HIV-1 infection
Species (MHC) human (B*5701, B*5703)
Keywords subtype comparisons, rate of progression
References Gillespie *et al.* 2002

- CTL responses of eight HIV+ slow progressors from Nairobi Kenya or Oxford, UK who were B*5701 or B*5703 were studied, as B*57 is associated with slow progression.
- This epitope is located between the structurally conserved alpha-helix 1 and alpha-helix 2 (H1-H2) region of the p24 capsid protein, and tends to elicit strong reactions in B*57 individuals.
- Broad heterogeneous cross-clade reactivity to 6 clade variants of the KAFS peptide sequence were observed in one B*5701 and 5 B*5703 HLA-restricted patients, measured by IFN-γ production Elispot assays as well as tetramer binding. The clade variants were: KAFSPEVIPMF (clades A and B), kGfNpevipmf (clades A/AC); kaLspevipmf (clade A); kafspevipVf (clade A); kafNpeIipmf (group O); kafspeIipmf (A/C); kafsQevipmf (A/C); and kaLspevipmf KNFSPEVIPMF A/G). Not all variants were well recognized in all patients, for example kafsQevipmf was not able to induce IFN gamma production in 3/6 tested, and had a diminished capacity to sensitize target cells for lysis.

HXB2 Location p24 (30–40)
Author Location p24 (30–40)
Epitope `KAFSPEVIPMF`
Epitope name KF11
Immunogen HIV-1 infection
Species (MHC) human (B*5701, B*5703)
Country United Kingdom, Kenya
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining
Keywords immunodominance, TCR usage, structure, characterizing CD8+ T cells
References Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B*57-peptide complexes were studied.
- In addition, immunodominancy of the previously mapped B*57 epitopes during chronic infection was assessed. KGFNPEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.
- KAFSPEVIPMF and variant KgFnPEVIPMF induce distinct functional responses in KAFSPEVIPMF and KgFnPEVIPMF specific T cells, while the structures of B*57-peptide complexes are similar.
- HLA-restriction for KAFSPEVIPMF was -B*5701 and for KgFnPEVIPMF was -B*5703.

HXB2 Location p24 (30–40)
Author Location Gag
Epitope `KAFSPEVIPMF`
Immunogen HIV-1 infection
Species (MHC) human (B*5701, B*5703)
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons, cross-presentation by different HLA, variant cross-recognition or cross-neutralization
References Currier *et al.* 2006

- The pattern of immunodominance and epitope clustering within Gag and Nef proteins in subtype A infected individuals was similar to that seen in subtype B and C infections. An immunodominant HLA-C restricted epitope, YVDRFFKTL (YL9 from Gag protein) was observed and restricted to Cw0304.
- The sequences EKAFSPEVIPMFSAL and EKgFnPEVIPMFSAL are associated with HLA-B*5701/03 and contain the epitope KAFSPEVIPMF (KF11). Variable cross-reactivity was seen between subjects with respect to the 2 sequence variants.

HXB2 Location p24 (30–40)
Author Location Gag
Epitope `KAFSPEVIPMF`
Epitope name KF11
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*5701, B*5703)
Country United Kingdom, India, United States, South Africa
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons, escape, TCR usage, immune evasion
References Yu *et al.* 2007a

- To study the contributions of HLA alleles and TCRs to the prevention of viral escape, HLAs B*5701 and B*5703 that differ at only 2 residues were followed with epitope KF11 and variants. B*5701-KF11 allowed fewer viral mutations along with a narrow TCR repertoire while B*5703-KF11 had a greater repertoire of TCR but also greater numbers of escape mutations. Therefore extensive TCR diversity is not a prerequisite to the prevention of viral mutations. More heterogeneous TCR-beta chains were also seen in the HLA-B*5703-KF11 situation and greater numbers of KF11 variants arose especially in clade C-infected subjects.

CTL CD8+

- For both Clades B and C HIV-1, this epitope KAFSPEVIPMF (wt) i.e. KF11 spawned variants KgFSPEVIPMF (A2G), KnFSPEVIPMF (A2N), KsFSPEVIPMF (A2S), KsFnPEVIPMF (A2S-S4N) and KsFSPEiIPMF (A2S-V7I). In addition, Clade C also allowed variants KgFnPEVIPMF (A2G-S4(N/K)) and KgFkPEVIPMF (A2G-S4(N/K). Overall, HLA-B*5703 subjects showed more of these sequence variants than HLA-B*5701 possessing subjects did.

HXB2 Location p24 (30–40)
Author Location Gag
Epitope `KAFSPEVIPMF`
Epitope name KF11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701, B*5703)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords TCR usage
References Simons *et al.* 2008

- To assess the role of TCR beta chain usage that is epitope-specific, 9 subjects with HLA-B*5701 or -B*5703-restricted, KF11-specific CTLs were studied. It was found that 8 subjects selectively recruited the TRBV7 chain even though it did not seem to confer any advantage.
- With a large range of epitope-specific TCR clonotypes in use in the subjects, there was still no structural or functional advantage to TRBV7, except perhaps in its functional avidity for a KF11 variant, K162R, rAFSPEVIPMF.

HXB2 Location p24 (30–40)
Author Location p24 (162–172 LAI)
Epitope `KAFSPEVIPMF`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5703)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*5703 epitope.

HXB2 Location p24 (30–40)
Author Location
Epitope `KAFSPEVIPMF`
Epitope name Gag-KF11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5703)
Donor MHC A*3402, A*7401, B*0801, B*5703, Cw*0302, Cw*0701
Keywords HAART, ART
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Subject 00RCH59 was African American, on HAART, viral load 170, CD4 count 477.
- Among HIV+ individuals who carried HLA-B57, 6/6 (100%) recognized this epitope.

HXB2 Location p24 (30–40)
Author Location p24 (162–172)
Epitope `KAFSPEVIPMF`
Epitope name KF11
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5703)
Country Ethiopia
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, escape, variant cross-recognition or cross-neutralization
References Currier *et al.* 2005

- HLA-B57 is associated with slow progression. Epitope sequence variation and CD8 T-cell responses were analyzed in HLA-B*5703-positive individuals from Ethiopia. KF11 epitope and its variants were found to be immunodominant in these subjects. Two HLA-B*5702 subjects did not respond to the KF11 epitope or its variants.
- 5 variants of the epitope were observed: KAFSPEVIPMF, KnFSPEVIPMF, rAFSPEVIPMF, KgFnPEVIPMF, and KAFSPEVIPMl. Depending on the subject, different versions of these variants were more or less susceptible to their CD8+ T cells, i.e., one person's escape form was another person's susceptible form.

HXB2 Location p24 (30–40)
Author Location (C consensus)
Epitope `KAFSPEVIPMF`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5703)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the A2 and S4 residues of KAFSPEVIPMF are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location p24 (30–40)
Author Location p24
Epitope `KAFSPEVIPMF`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5703)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism

References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- KAFSPEVIPMF is a previously described HLA-B*5703-restricted epitope (part of Gag reacting peptides NAWVKVIEEKaFSPEVIPMFT and WVKVIEEKAFsPEVIPMFTAL) that contains a B*5703-associated sequence polymorphism at residue A and S (KaFSPEVIPMF/KAFsPEVIPMF).

HXB2 Location p24 (30–40)
Author Location Gag
Epitope KAFSPEVIPMF
Epitope name KF11
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5701, B*5703)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, HLA associated polymorphism
References Frater *et al.* 2007

- To study whether CTL responses restricted by "good" HLA I molecules exert stronger immune selection than other HLA I molecules, 54 and 70 optimal epitopes within HIV-1 Gag, Pol and Nef genes for Caucasian and African cohorts were tested in patients over a mean of 14 months. "Good", advantageous HLA allele-restricted epitopes were much more polymorphic than epitopes restricted by other, non-advantageous HLA in patients, suggesting that benefits associated with HLA Class I alleles of elite controllers of disease progression are epitope-specific. Such "driver" epitopes with high polymorphism had high frequency of immune response, allowing them to be ranked for recognition and polymorphism.
- Patients with higher proportions of mutated epitopes also had lower plasma viral loads, and mean epitope variability correlated negatively with relative hazard of disease progression.
- This Gag epitope KF11 is highly variant in the African cohort when restricted by B*5703, but is conserved in the Caucasian B*5701-positive cohort.

HXB2 Location p24 (30–40)
Author Location p24 (30–40)
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Goulder *et al.* 2000c

- Two strong clonal CTL responses were generated in donor 026-BMC (HLA A3/-, B42/B57, Cw7/17) against different optimal versions of this epitope, one 8 amino acids long, one 11.
- Improved stabilization of the B57-peptide complex was demonstrated by the 11mer which fits the B57 binding motif, relative to the 8 mer, which does not.
- B57 tolerates marked difference in optimal peptide length – and B57 is associated with non-progressive infection.

HXB2 Location p24 (30–40)
Author Location p24 (162–172)
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the A2+ individuals was HLA A*0201, A1, B57 and responded to four B57 epitopes and two others.

HXB2 Location p24 (30–40)
Author Location p24 (SF2)
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a HIV+ Caucasian living in Boston – this epitope is not among the most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

HXB2 Location p24 (30–40)
Author Location Gag (SF2)
Epitope KAFSPEVIPMF
Epitope name KF11
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Goulder *et al.* 2001a

- Three CTL responses in patient PI004, to epitopes TSTLQEQIGW, ISPRTLNAW, and KAFSPEVIPMF, were evident early after infection; CTL responses to SLYNTVATL, QASQEVKNW, EIYKRWII, and FLKEKGGL were detectable at 5 months post-infection and beyond.

HXB2 Location p24 (30–40)
Author Location p24 (162–172)
Epitope KAFSPEVIPMF
Epitope name KAF
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords HAART, ART, acute/early infection
References Oxenius *et al.* 2000

CTL CD8+

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- None of the 8 study subjects recognized this epitope but none were HLA B57+.

HXB2 Location p24 (30–40)
Author Location p24
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Kostense *et al.* 2001

- HLA tetramers to six epitopes were used to study HLA-A2, B8 and B57 CTL in 54 patients – HIV-specific tetramer positive cells were inversely correlated with viral load in patients with high CD4, but in patients with CD4 T-cells below 400 high tetramer frequencies were found despite high viral load.
- Most patients have high levels of HIV-specific T-cell expansions, but many of these cells aren't functional.
- In 15 of the patients, the proportion of IFN gamma producing tetramer cells correlated with AIDS-free survival.

HXB2 Location p24 (30–40)
Author Location p24 (162–172 SF2)
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with preseroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B57+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/0 group 2, and 2/2 group 3.

HXB2 Location p24 (30–40)
Author Location p24 (163–174)
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Appay *et al.* 2000

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α.

HXB2 Location p24 (30–40)
Author Location
Epitope KAFSPEVIPMF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B57, 1/5 (20%) recognized this epitope.

HXB2 Location p24 (30–40)
Author Location p24
Epitope KAFSPEVIPMF
Epitope name KAF
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords HAART, ART, supervised treatment interruptions (STI)
References Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFN? Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

HXB2 Location p24 (30–40)
Author Location p24 (30–40)
Epitope KAFSPEVIPMF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A*0201, A3, B44, B57, Cw5, Cw6
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.

- All HIV-1 proteins except Vpu were recognized, and responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- Alleles A3, B35, B57, and B62 were more frequently recognized than alleles A1, A2, A30, and A44 e.g., during primary infection. 2/10 patients, 1372 and 1397, recognized A2-restricted epitopes. The common A2-restricted epitopes Gag SL9 and Pol IV9 were not recognized in peptide tetramer-binding assays.

HXB2 Location p24 (30–40)
Author Location p24
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type Intracellular cytokine staining
Keywords immunodominance, genital and mucosal immunity
References Kaul *et al.* 2003

- Predefined immunodominant peptide responses were used to compare CD8+ T-cell responses in the blood and cervix of 16 HIV+ Kenyan sex workers. Cervical responses were detected in 8/10 women from whom adequate samples could be obtained. The frequency of the CD8+ T-cell response in the genital tract was comparable to the blood, with a trend toward being slightly higher.
- The immunodominant response was to this epitope in the PBMC of 10/16 patients (Kaul *et al.* 2001, AIDS, 107:1303).

HXB2 Location p24 (30–40)
Author Location p24 (163–174)
Epitope KAFSPEVIPMF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A*0201, A3, B57, Cw*06, Cw*07; A*01, A*0201, B*08, B*57, Cw6, Cw7
Country United States
Assay type Cytokine production, Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization
Keywords TCR usage
References Betts *et al.* 2004

- Both cytokine production and degranulation in HIV-1 specific and CMV specific CD8+ T -cells occurs at high peptide concentrations together with TCR downregulation. Only degranulation is observed at lower peptide concentrations with no observed TCR downregulation. Thus the nature of CTL response depends not on the specific T cell clonotype or antigen, but on the concentration of Ag presented on APCs.

HXB2 Location p24 (30–40)
Author Location p24
Epitope KAFSPEVIPMF
Epitope name TW10
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords epitope processing, escape
References Draenert *et al.* 2004b

- This study characterizes the N-terminal flanking position of the epitope ISPRTLNAW, and mutations in this position are thought to impact processing. The B57 epitope KAFSPEVIPMF was used as a positive control in this study.

HXB2 Location p24 (30–40)
Author Location Gag (155–172 B con)
Epitope KAFSPEVIPMF
Epitope name KF11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Draenert *et al.* 2004c

- CD8+ T-cell responses that persisted in individuals with advanced disease were studied; most of the optimal epitopes defined were recognized with intermediate to high avidity. On average 13 (range, 2-39) epitopic regions were targeted in an average of 6 proteins (range, 1-8). HAART resulted in decrease in antigen and reduction in gamma IFN EliSpot responses, suggesting active responses to autologous virus. The lack of mutations within most viral epitopes suggest that persistent CTL through late disease do not exert strong immune selection pressure, yet the Elispot assays show robust responses, suggesting to the authors that gamma IFN-based screening methods may not reveal functional CD8+ T-cell impairment in patients with AIDS.
- 2 subjects recognized this epitope, 1 with high functional avidity, 1 with intermediate. Autologous sequence revealed no substitutions in this epitope compared to the B consensus.

HXB2 Location p24 (30–40)
Author Location Gag
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords HIV exposed persistently seronegative (HEPS)
References Koning *et al.* 2004

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A*11, A*31 and Cw*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
- 1/2 HLA B57+ infection-resistant men, compared to 0/1 pre-seroconversion men who went on to become infected, reacted to this epitope.

HXB2 Location p24 (30–40)
Author Location p24 (30–40)
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI)
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 7/7 patients recognized this epitope.

HXB2 Location p24 (30–40)
Author Location (162–172 B consensus)
Epitope KAFSPEVIPMF
Epitope name KF11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords immunodominance, characterizing CD8+ T cells
References Allen *et al.* 2004

- This study characterizes an escape mutation in a C-terminal flanking residue of the HLA-A3 gag p17 KK9 epitope that inhibits processing, and is embedded in the overlapping HLA-A3 RK9 epitope.
- The immune response was tracked in subject AC-38. The acute immunodominant response was to the B57 TW10 epitope; this response declined following viral escape (tsNlqeqigw) by day 64. The p17 KK9 and RK9 became immunodominant, but then declined as the escape mutation arose. FK11 is 1 of 3 other strong responses that persisted, along with 1 sub-dominant response.

HXB2 Location p24 (30–40)
Author Location (C consensus)
Epitope KAFSPEVIPMF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p24 (30–40)
Author Location p24
Epitope KAFSPEVIPMF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country United Kingdom
Assay type Tetramer binding, T-cell Elispot, Intracellular cytokine staining
Keywords rate of progression, acute/early infection, characterizing CD8+ T cells, immune dysfunction
References Papagno *et al.* 2004

- Acute HIV-1 infection induces massive activation of HIV-specific and non-HIV-specific CD8+ T-cells resulting in differentiation of these cells. High differentiation of CD8+ T-cells is correlated with disease progression. Differentiation is a natural process but it can be driven by elevated immune activation, such as in HIV infection.

HXB2 Location p24 (30–40)
Author Location Gag
Epitope KAFSPEVIPMF
Epitope name KF11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was quite conserved in people carrying B57, but two substitutions were found in 11 B57+ individuals tested: kNfspevipmf and kafspeIipmf.

HXB2 Location p24 (30–40)
Author Location Gag (162–172)
Epitope KAFSPEVIPMF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

CTL CD8+

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location p24 (30–40)
Author Location Gag (162–172 BRU)
Epitope KAFSPEVIPMF
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 1/9 CRF02_AG-infected Ivorians, and 1/9 B-infected French subjects.

HXB2 Location p24 (30–40)
Author Location Gag
Epitope KAFSPEVIPMF
Epitope name KAF
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords binding affinity, rate of progression, escape, characterizing CD8+ T cells
References Jansen *et al.* 2005

- HLA-B57 has been associated with long term non-progression in HIV+ people. The number and responsiveness of CD8 T-cells directed to different Gag peptides presented by HLA-A2, -B8 and B57 were compared. T cells specific for the HLA-B57 epitope KAFSPEVIPMF responded to a higher extent and more readily to antigenic stimulation than those specific for the A2 epitope SLYNTVATL and the B8 epitope EIYKRWII.
- Tetramer decay experiments indicate that the HLA-B57 peptide has a higher half-life than the A2 and B8 peptides. The authors point out that CD8+ T cells with high binding affinity may require less help.
- Variant forms of the HLA-B57 epitope KAFSPEVIPMF were found in the 3/5 HLA B57+ individuals sequenced, but the variants were always a minor form.

HXB2 Location p24 (30–40)
Author Location p24
Epitope KAFSPEVIPMF
Epitope name B57-KF11(p24)
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (30–40)
Author Location p24 (30–40)
Epitope KAFSPEVIPMF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, subtype comparisons, acute/early infection
References Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (ANC) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- This epitope, KAFSPEVIPMF, is invariant across CON A, B, C and M-Group sequences, as well as clade B COT and ANC sequences. HLA-B57 restriction was inferred based on subject possessing appropriate HLA class I allele and prior publication

HXB2 Location p24 (30–40)
Author Location
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (B57)

CTL CD8+

Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location p24 (30–40)
Author Location
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope KAFSPEVIPMF elicited a magnitude of response of 740 SFC with a functional avidity of 0.005nM and binding affinity of 21.

HXB2 Location p24 (30–40)
Author Location Gag
Epitope KAFSPEVIPMF
Epitope name KF11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Australia, Canada, United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, immune evasion, optimal epitope
References Streeck *et al.* 2007a

- To characterize HIV-1 proteome areas that are targeted in early, effective CTL responses, two cohorts were studied. Responses in early infection were against fewer epitopes and of lower magnitude than during chronic infection. While no region of the proteome was favored, Nef was the predominant target based on length of proteins.
- When based on the expression of protective versus nonprotective HLA I alleles, it was found that HLA-B27 and -57 possessing slow progressors to disease directed the majority of their responses to Gag in early infection, as opposed to those with HLA-B*3501 or B*3502, i.e. rapid progressors to AIDS, who had negligible responses to Gag. As compared with HLA-B57-/B27- subjects and HLA-B35 subjects, HLA-B57+/27+ subjects responded most to the p24 component of Gag. By using overlapping peptides within Gag p24, two were picked as being consistently targeted, and both contained previously described epitopes TSTLQEQIGW and KRWIILGLNK.
- IVLPEKDSW, i.e. epitope IW9 of RT protein was targeted in 62% of B57+ non-progressors to disease.

HXB2 Location p24 (30–40)
Author Location
Epitope KAFSPEVIPMF
Epitope name KF11 ?
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country United States, South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords memory cells
References Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

HXB2 Location p24 (30–40)
Author Location
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining
Keywords responses in children, rate of progression
References Chakraborty *et al.* 2005

- A study of long-term surviving children in Kenya revealed CD8 T-cell responses in all progression groups. The most striking atttribute of long term surviving children was strong CD4 T-cell responses, which may be significant in delaying disease progression.
- Response detected in 1 typically progressing child.

HXB2 Location p24 (30–40)
Author Location Gag
Epitope KAFSPEVIPMF
Epitope name KF11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

CTL CD8+

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- KF11, KAFSPEVIPMF, is a known HLA-B57-restricted epitope used as a positive control for eliciting CTL IFN-gamma response.

HXB2 Location p24 (30–40)
Author Location p24 (162–172 SF2, HXBc2/Bal R5)
Epitope KAFSPEVIPMF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A1, A2, B40, B57, Cw3, Cw6
Country United States
Assay type Cytokine production, Flow cytometric T-cell cytokine assay, Degranulation, CD107a and b cell surface mobilization
Keywords supervised treatment interruptions (STI), immunodominance, characterizing CD8+ T cells, drug resistance
References Daucher *et al.* 2008

- A detailed analysis of 6 chronically infected patients' CTL responses to autologous virus was performed after ART and SIT (structured interruption of therapy). Qualitative responses including degranulation and production of IFN-gamma, MIP-1beta, TNF-alpha, IL-2, but not memory CD27, CD45RO and CD57 T cells correlated with extended low plasma viremia. Frequency and breadth of CTL response as well as immune escape did not influence virological outcome.
- One patient exhibited drug resistance mutations K170R (to NNRTI efavirenz) and D76N, K70R (to NRTIs).
- Autologous epitopes were preferentially recognized over optimal, consensus sequences.
- Patients with favorable virological outcomes demonstrated CTL recognition within multiple, conserved regions of Gag and Nef.
- Patients with poor virological outcomes recognized optimal epitopes with much lower frequencies, though this was not significant.
- HLA-B57-restricted epitope, KAFSPEVIPMF, elicited a response in 1 patient and is found in Gag immunodominant region EKAFSPEVIPMFSAL.

HXB2 Location p24 (30–40)
Author Location
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords responses in children, mother-to-infant transmission, escape, characterizing CD8+ T cells
References Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.
- KAFSPEVIPMF was frequently recognized in children and in adults.

HXB2 Location p24 (30–40)
Author Location p24 (153–164)
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B57, B58)
Keywords HIV exposed persistently seronegative (HEPS), immunodominance
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B57/B58 women, 4/6 HEPS and 12/17 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in 2 of the 4/6 HEPS cases and in 7 of the 12/17 HIV-1 infected women.

HXB2 Location p24 (30–40)
Author Location p24 (30–40)
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human (B57, B58)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2002

- Neisseria gonorrhea cervititis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.

CTL CD8+

- Ghonorrhea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

HXB2 Location p24 (30–40)
Author Location p24
Epitope KAFSPEVIPMF
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B57, B63)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, cross-presentation by different HLA, optimal epitope
References Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This epitope was recognized by 60% of B63-positive subjects and 33% of B57/58-positive subjects.

HXB2 Location p24 (30–40)
Author Location p24 (30–40)
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human (B58)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (30–40)
Author Location p24
Epitope KAFSPEVIPMF
Subtype B, G
Immunogen HIV-1 infection
Species (MHC) human (B58)
Donor MHC A2, A36, B45, B58, Cw3, Cw6
Country Nigeria
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype G Gag. The autologous epitope sequence in this person matched the known epitope.

HXB2 Location p24 (30–40)
Author Location Gag
Epitope KAFSPEVIPMF
Subtype A, B
Immunogen HIV-1 infection
Species (MHC) human (B58)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-B58-restricted epitope KAFSPEVIPMF is from subtype A and B libraries, and is reactive as part of peptide EKAFSPEVIPMFSAL in a subtype B-carrying subject.

HXB2 Location p24 (30–40)
Author Location
Epitope KAFSPEVIPMF
Immunogen
Species (MHC) human (B63)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B63 epitope.

HXB2 Location p24 (30–40)
Author Location p24
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized by 1/22 HEPS sex worker controls, ML1250.

HXB2 Location p24 (30–40)
Author Location
Epitope KAFSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human

Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords binding affinity, acute/early infection
References Lichterfeld *et al.* 2007b

- Differences in early versus chronic AIDS include a decline in CTL number accompanied by a reducing viremia. Comparative analysis of such CTLs in this study show that early infection is characterized by a different clonotypic composition and higher functional avidity of CTLs followed by their selective depletion during transition to chronic disease. The total magnitude of CTL cytokine production is lower in early infection. Intraindividual, early CTLs' functional avidity for the same epitope decreases concomitantly with a reduction in clonotypic TCR repertoire especially of strongly activated and CD127lo, CD38+, Ki-67hi CTLs while progressing to chronic infection states.
- None of the target epitopes, including this epitope KAFSPEVIPMF seen in 1 patient, underwent sequence changes.

HXB2 Location p24 (31–41)
Author Location Gag (171–181)
Epitope `AFSPEVIPMFT`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p24 (31–44)
Author Location p24 (31–44 HXB2)
Epitope `AFSPEVIPMFSALS`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided, it appears to be HXB2.
- Responses to this peptide were detected in 22% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location p24 (31–47)
Author Location Gag
Epitope `AFSPEVIPMFSALSEGA`
Epitope name GAG-23
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, sqVSQNYPIVQNLQGQMV differs from the consensus C sequence kVSQNYPIVQNLQGQMV at 2 amino acid positions, i.e. by 11.1%.

HXB2 Location p24 (31–47)
Author Location Gag
Epitope `AFSPEVIPMFSALSEGA`
Epitope name GAG-23
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance

CTL CD8+

References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, AFSPEVIPMFsALSEGA differs from the consensus C sequence AFSPEVIPMFtALSEGA at 1 amino acid position, i.e. by 5.9%.

HXB2 Location p24 (31–47)
Author Location p24
Epitope `AFSPEVIPMFSALSEGA`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, AFSPEVIPMFSALSEGA, had an overall frequency of recognition of 15.3% - 16.9% AA, 11.5% C, 18.2% H, 9.5% WI. This peptide is included in a 49 aa Gag-p24 highly reactive region to be used for vaccine design. It is also part of 'Region III', PRTLNAWVKVVEEKAFSPEVIPMFSALSEGA, a 31 aa region recognized by >90% of subjects across ethnic groups.

HXB2 Location p24 (31–50)
Author Location p24 (163–182)
Epitope `AFSPEVIPMFSALSEGATPQ`
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

HXB2 Location p24 (31–50)
Author Location p24 (163–182 SF2)
Epitope `AFSPEVIPMFSALSEGATPQ`
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A2, B21.

HXB2 Location p24 (31–50)
Author Location p24 (163–182 SF2)
Epitope `AFSPEVIPMFSALSEGATPQ`
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

HXB2 Location p24 (31–50)
Author Location p24 (SF2)
Epitope `AFSPEVIPMFSALSEGATPQ`
Immunogen HIV-1 infection
Species (MHC) human
References Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.
- The response to the peptide was CD4 dependent, but the HLA presenting molecule and optimal epitope were not determined.

HXB2 Location p24 (32–40)
Author Location Gag (164–172)

Epitope FSPEVIPMF
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A28, A3, B53, B57
Assay type Chromium-release assay
Keywords TCR usage, genital and mucosal immunity
References Musey *et al.* 2003

- CTL clones from blood, semen, cervix and rectum samples from 12 individuals were compared. CTL clones derived from blood and mucosal samples had similar high lysis efficiency, primarily perforin dependent, and TCRβ VDJ region sequencing revealed cases of expansion of the same clone in different compartments.
- CD8+ T cell clones directed at this epitope were derived from blood and semen.
- The TCRβ VDJ rearrangement of a CTL clone from the blood was Vβ21S3DJ1.2, and a clone from the semen used Vβ7S1DJ2.3.

HXB2 Location p24 (32–40)
Author Location
Epitope FSPEVIPMF
Immunogen
Species (MHC) human (B57)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B57 epitope.

HXB2 Location p24 (32–40)
Author Location p24
Epitope FSPEVIPMF
Epitope name FF9
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B57, B58, B63)
Donor MHC A*74, A*8001, B*18, B*57, Cw*02, Cw*07
Assay type CD8 T-cell Elispot - IFNγ
Keywords cross-presentation by different HLA, optimal epitope
References Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This is a putative HLA-B63/57/58 epitope containing the B58 supertype binding motif. Significantly more often recognized by B63+ and B57/58+ subjects than by negative subjects. Optimal epitope defined.

HXB2 Location p24 (33–40)
Author Location p24 (33–40)
Epitope SPEVIPMF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope SPEVIPMF showed >70% conservation across all clades and was predicted to b HLA-B*35-restricted.

HXB2 Location p24 (33–47)
Author Location
Epitope SPEVIPMFASLSEGA
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, A24, B15, B40
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 42 (NIH ARRP Cat# 7913), SPEVIPMFASLSEGA, which contains an HLA-A2 restricted epitope, elicited a CTL response in a living non-progressor.

HXB2 Location p24 (33–47)
Author Location Gag (165–179)
Epitope SPEVIPMFSALSEGA
Immunogen vaccine

CTL CD8+

Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized both by mice co-immunized with Gag and Tat, and by mice immunized with Gag alone.

HXB2 Location p24 (34–49)
Author Location p24
Epitope PEVIPMFSALSEGATP
Epitope name PP16
Immunogen in vitro stimulation or selection
Species (MHC)
Assay type Other
Keywords assay standardization/improvement, characterizing CD8+ T cells
References Stone *et al.* 2005

- A new microarray technique was developed to screen small samples of T cells for specific peptide-MHC binding and functional responses. Each array element acts as an artificial antigen-presenting cell, consisting of immobilized recombinant MHC-peptide complex, costimulatory molecules, and cytokine-capture antibodies. The elements specifically elicit T-cell responses such as adhesion, secretion of cytokines, and modulation of surface markers.

HXB2 Location p24 (35–43)
Author Location p24 (167–175 LAI)
Epitope EVIPMFSAL
Subtype B
Immunogen
Species (MHC) human (A*2601)
Keywords subtype comparisons
References Goulder *et al.* 1996a

- Identified as optimal epitope within Gag sequence AFSPEVIPMFSALSEGATPQ.
- Relatively conserved epitope within B clade and in other clades.
- Suspected binding motif for HLA-A26 includes T or V anchor at position 2, negative charge at position 1.
- C. Brander notes that this is an A*2601 epitope in the 1999 database.

HXB2 Location p24 (35–43)
Author Location p24 (167–175 LAI)
Epitope EVIPMFSAL
Subtype B
Immunogen
Species (MHC) human (A*2601)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an A*2601.

HXB2 Location p24 (35–43)
Author Location Gag (169–177)
Epitope EVIPMFSAL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2601)
Country Japan
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay, Other, HLA binding
Keywords subtype comparisons, immunodominance, optimal epitope
References Satoh *et al.* 2005

- Reverse immunogenetics was used to identify HIV-1 epitopes presented by HLA-A*2601. 110 peptides were predicted to bind to HLA-A*2601. 24 of these were demonstrated to bind through a HLA-A*2601 stabilization assay. Four of these, including this one, were shown to be epitopes endogenously presented by this allele, that can induce peptide-specific CD8 T-cells. HLA-A*2601 is common in Asia.
- Immunodominant epitope recognized in 5/7 HIV-infected individuals with HLA-A*2601. This epitope is highly conserved in clade B and E (CRF01).

HXB2 Location p24 (35–43)
Author Location (C consensus)
Epitope EVIPMFTAL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2601)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- EVIPMFTAL is an optimal epitope.

HXB2 Location p24 (35–43)
Author Location Gag
Epitope EVIPMFTAL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2601)
Country South Africa

Assay type CD8 T-cell Elispot - IFNγ
References Chopera *et al.* 2008

- Transmission of HIV-1-escape variants from individuals with protective HLA-B*57/-B*5801 alleles to those without these alleles was studied to determine if infection with such replication-deficient mutants offered any advantage to the new host. Dependency between slower rate of disease progression in the newly infected subject and protective genotype of the infecting individual was suggested.
- HLA-A*2601-restricted epitope EVIPMFTAL, within peptide AFSPEVIPMFTALSEGA was able to elicit CTL response in a T242N/A146X viral-mutation-carrying subject.

HXB2 Location p24 (35–43)
Author Location Gag (169–177 SF2)
Epitope `EVIPMFSAL`
Subtype A, B, C, CRF01_AE, D
Immunogen HIV-1 infection
Species (MHC) human (A*2601, A*2603)
Country Japan
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay, HLA binding
Keywords binding affinity, subtype comparisons, rate of progression, immunodominance, escape, cross-presentation by different HLA, variant cross-recognition or cross-neutralization
References Kawashima *et al.* 2005

- A*26 is associated with slow progression to disease and is common in Asian populations (about 20%). 31/110 HIV peptides that carried the A*2603 motif ([VTILP] at P2, [ML] at the C-terminus) bound to HLA-A*2603. Only 2 of these were epitopes and could induce specific CD8 T-cell responses in PBMC from HLA-A*2603 positive subjects.
- This epitope induced specific CD8+ T cells in chronically infected individuals with either A*2603 or A*2601. It is an immunodominant epitope.
- 3 common B clade variants were synthesized. EVIPMFaAL and EVIPMFtAL bound to A*2603 with equal affinity as the consensus form, EVIPMFSAL, but could not be recognized by an EVIPMFSAL-specific T-cell clone so may mediate TCR escape. The other common variant, kVIPMFSAL, did not bind to A*2603.
- EVIPMFSAL is the most common form in clades A, B, D, and E (CRF01), but EVIPMFtAL is the most common form in clade C.

HXB2 Location p24 (35–43)
Author Location Gag (169–177 SF2)
Epitope `EVIPMFSAL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2601, A*2602, A*2603)
Country Japan
Assay type Intracellular cytokine staining, HLA binding
Keywords binding affinity, immunodominance
References Kawashima *et al.* 2008

- Of 110 possible peptide epitopes from Gag, Pol, Nef and Env, 32 were found to be HLA-A*2602 binding, using a reverse genetic approach. These are listed in Table 1.
- Only one epitope, EVIPMFSAL, elicited a CTL immune response in 8/11 HLA-A*2601-, 2/6 HLA-A*2602-, 7/8 HLA-A*2603-carrying patients indicating that EVIPMFSAL is a submominant epitope in the HLA-A*2602 donors.
- EVIPMFSAL overlaps with B*57-restricted KF11 (KAFSPEVIPMF). It binds HLAs A*2601, A*2602 and A*2603.

HXB2 Location p24 (35–43)
Author Location p24 (167–175)
Epitope `EVIPMFSAL`
Immunogen HIV-1 infection
Species (MHC) human (A26)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the A2+ individuals that didn't respond to SLYNTVATL reacted with seven other epitopes including this epitope.

HXB2 Location p24 (35–43)
Author Location Gag
Epitope `EVIPMFSAL`
Epitope name EL9
Immunogen HIV-1 infection
Species (MHC) human (A26)
Donor MHC A26, B27
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, rate of progression, immunodominance, escape
References Feeney *et al.* 2004

- Viral load in a perinatally infected child remained low until emergence of an escape variant (kTwiilglnk) in the immunodominant CTL epitope KRWIILGLNK when the child was 7.4 years old. The emergence of this escape mutation was followed by an increase in viremia and an increase in the number of targeted CTL epitopes, measured again when the child was 9.2 years old. The EL9 response was not observed until after the escape mutation occurred in the immunodominant epitope, and was detected in the 9.2 year sample for the first time.

HXB2 Location p24 (35–43)
Author Location p24
Epitope `EVIPMFSAL`
Epitope name A26-EL9(p24)
Immunogen HIV-1 infection
Species (MHC) human (A26)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.

- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (35–43)
Author Location
Epitope EVIPMFSAL
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (A26)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location p24 (35–43)
Author Location p24
Epitope EVIPMFSAL
Epitope name EL9(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A26)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A26-restricted epitope EVIPMFSAL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide AFSPEVIPMFSALSEGA.
- 5 of the 8 HLA-A26 carriers responded to EVIPMFSAL-containing peptide with average magnitude of CTL response of 646 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p24 (35–43)
Author Location p24 (167–175 SF2, HXBc2/Bal R5)
Epitope EVIPMFSAL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw3)
Donor MHC A1, A2, B40, B57, Cw3, Cw6
Country United States
Assay type Cytokine production, Flow cytometric T-cell cytokine assay, Degranulation, CD107a and b cell surface mobilization
Keywords supervised treatment interruptions (STI), immunodominance, characterizing CD8+ T cells, drug resistance
References Daucher *et al.* 2008

- A detailed analysis of 6 chronically infected patients' CTL responses to autologous virus was performed after ART and SIT (structured interruption of therapy). Qualitative responses including degranulation and production of IFN-gamma, MIP-1beta, TNF-alpha, IL-2, but not memory CD27, CD45RO and CD57 T cells correlated with extended low plasma viremia. Frequency and breadth of CTL response as well as immune escape did not influence virological outcome.
- One patient exhibited drug resistance mutations K170R (to NNRTI efavirenz) and D76N, K70R (to NRTIs).
- Data confirmed that autologous epitopes were preferentially recognized over optimal, consensus sequences.
- Patients with favorable virological outcomes demonstrated CTL recognition within multiple, conserved regions of Gag and Nef.
- Patients with poor virological outcomes recognized optimal epitopes with much lower frequencies, though this was not significant.
- HLA-Cw3-restricted epitope, EVIPMFSAL, elicited a response in 1 patient and is found in Gag immunodominant region EKAFSPEVIPMFSAL.

HXB2 Location p24 (35–49)
Author Location p24 (35–48 HXB2)
Epitope EVIPMFSALSEGATP
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.

- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- Responses to this peptide were detected in 16% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location p24 (36–43)
Author Location Gag
Epitope `VIPMFSAL`
Epitope name VL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*01)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords binding affinity, immunodominance
References Cao *et al.* 2008

- For the first time, viral immune evasion is reported via an insertion mutation, in an ART-naive patient. A 3 aa repeat, SPT inserted within p6<sup>Pol<sup> epitope NL8 is reported. This insertion is associated often with ART drug resistance to NRTI drugs. Thus immune pressure and drug resistance may cause HIV-1 to select the same variation.
- A concomitant insertion mutation APP, is seen in p6<sup>Gag<sup>, permitting viral budding.
- Epitope VIPMFSAL elicited an early, dominant response in subject PIC1362. Epitope VL8 bound its MHC I less strongly than NL8, NSPTRREL, did its MHC I molecule.

HXB2 Location p24 (36–43)
Author Location p24 (168–175 LAI)
Epitope `VIPMFSAL`
Subtype B
Immunogen
Species (MHC) human (Cw*0102)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a C*0102(Cw1) epitope.

HXB2 Location p24 (36–43)
Author Location p24 (36–43 HXB2)
Epitope `VIPMFSAL`
Epitope name VL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*0102)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.

HXB2 Location p24 (36–43)
Author Location p24 (168–175 LAI)
Epitope `VIPMFSAL`
Subtype B
Immunogen
Species (MHC) human (Cw*0102, Cw1)
References Goulder *et al.* 1997b

HXB2 Location p24 (36–43)
Author Location p24
Epitope `VIPMFSAL`
Epitope name VL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw1)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords superinfection
References Streeck *et al.* 2008b

- Loss of viral replication control by an elite controller after superinfection was found to coincide with rapid recombination events in 2, ∼50 residue regions of Gag and Env that include immunodominant epitopes KK10 (KRWIILGLNK) and CL9 (CAPAGFAIL). Viral escape was seen at both epitopes and consequent CTL responses against the epitope-variants.
- CTL responses to previously described HLA-Cw1-restricted VIPMFSAL, were seen post-superinfection and -recombination.

HXB2 Location p24 (36–43)
Author Location Gag
Epitope `VIPMFSAL`
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human (Cw1)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-Cw1-restricted epitope VIPMFSAL is from a subtype D librariy, and is reactive as part of peptide PEVIPMFSALSEGAT in a subtype B-carrying subject.

HXB2 Location p24 (36–43)
Author Location p24 (168–175)
Epitope VIPMFSAL
Immunogen HIV-1 infection
Species (MHC) human (Cw1, Cw2)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the A2+ individuals that didn't respond to SLYNTVATL reacted with seven other epitopes including this epitope.

HXB2 Location p24 (37–46)
Author Location Gag
Epitope IPMFSALSEG
Epitope name Gag1166
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Epitope IPMFSALSEG elicits IFN-gamma ELISpot responses in 3/7 subjects; and bound HLA-B7 with low and high affinities in soluble and cell-based assays respectively. Previously published HLA restrictions of this epitope include A2, B21, B61, B60 associations (LANL database), DRB1*0101, DRB1*0401, DRB1*0404, DRB1*0405 (Immune Epitope Database).

HXB2 Location p24 (37–51)
Author Location
Epitope IPMFSALSEGATPQD
Immunogen HIV-1 infection
Species (MHC) human (A2, B44)
Donor MHC A2, A32, B44, B7; A2, A24, B15, B40
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 43 (NIH ARRP Cat# 7914), IPMFSALSEGATPQD, which contains epitopes restricted by HLA-B44 and -A2 in different patients elicited the following CTL responses: (1)>100 sfc/million PBMC for 19+ years in a living non-progressor (2) <1000 sfc/million PBMC for 22+ years in another living non-progressor.

HXB2 Location p24 (37–52)
Author Location Gag (169–184 LAI)
Epitope IPMFSALSEGATPQDL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B12)
References Buseyne *et al.* 1993a

- Vertical transmission of HIV ranges from 13% to 39%
- Primary assays showed that cytotoxic activity against at least one HIV protein was detected in 70% of infected children.
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
- Patient EM17 (CDC P2A+C+D2) had a CTL response to two epitopes in Gag.

HXB2 Location p24 (37–52)
Author Location p24 (169–184 LAI)
Epitope IPMFSALSEGATPQDL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B44)
References Buseyne *et al.* 1993b

- Clustering of Gag p24 CTL epitopes recognized in 29 HIV-infected people.

HXB2 Location p24 (37–52)
Author Location p24 (37–52)
Epitope IPMFSALSEGATPDQL
Immunogen HIV-1 infection
Species (MHC) human (B44)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (38–48)
Author Location Gag (178–188)
Epitope PMFTALSEGAT
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p24 (38–55)
Author Location Gag
Epitope PMFSALSEGATPQDLNTM
Epitope name GAG-24
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, PMFsALSEGATPQDLNTM differs from the consensus C sequence PMFtALSEGATPQDLNTM at 1 amino acid position, i.e. by 5.6%.

HXB2 Location p24 (38–55)
Author Location p24
Epitope PMFSALSEGATPQDLNTM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, PMFSALSEGATPQDLNTM, had an overall frequency of recognition of 16% - 20.3% AA, 15.4% C, 13.6% H, 4.8% WI. This peptide is included in a 49 aa Gag-p24 highly reactive region to be used for vaccine design. It is also part of 'Region III', PRTLNAWVKVVEEKAFSPEVIPMFSALSEGA, a 31 aa region recognized by >90% of subjects across ethnic groups.

HXB2 Location p24 (38–55)
Author Location Gag
Epitope PMFSALSEGATPQDLNTM
Subtype A, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide PMFSALSEGATPQDLNTM from subtypes A and CRF01_AE.

HXB2 Location p24 (39–47)
Author Location Gag (171–179 SF2)

Epitope MFSALSEGA
Epitope name MFS
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF2 *HIV component:* Gag, Tat *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse (H-2^d)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes
References Cellini *et al.* 2008

- In order to increase the known number of epitopes in Gag protein so that they can be assayed for reactivity in vaccine studies, BALB/c mice were inoculated with Gag or Gag+Tat. OLPs were used to elicit T-cell immune responses from mouse splenocytes, tested for by cytotoxicity or ELISpot assays. 5 novel predicted optimal CTL epitopes, 2 novel predicted CD4 epitopes and 2 immune response eliciting peptides were found.
- Predicted epitope MFSALSEGA was found in reactive Peptide 42, SPEVIPMFSALSEGA.

HXB2 Location p24 (39–53)
Author Location Gag
Epitope MFSALSEGATPHDLN
Subtype A, D
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*02, A*11, B*07, B*35, Cw*04, Cw*07, DPA1*0103, DPB1*0201, DPB1*0401, DQB1*06, DRB1*13, DRB1*15, DRB3
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- Epitope-containing reacting peptide MFSALSEGATPHDLN, seen in a subtype-D carrying subject was derived from a subtype A library and was not previously associated with host class I alleles A*02/*11; B*07/*35, Cw*04/*07.

HXB2 Location p24 (39–58)
Author Location Gag (171–190)
Epitope MFTALSEGTPQDLNTMLNT
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 8 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location p24 (41–55)
Author Location
Epitope SALSEGATPQDLNTM
Immunogen HIV-1 infection
Species (MHC) human (B44)
Donor MHC A2, A32, B44, B7
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 44 (NIH ARRP Cat# 7915), SALSEGATPQDLNTM, which contains an epitope restricted by HLA-B*44 elicited a CTL response for 19+ years in a living non-progressor.

HXB2 Location p24 (41–56)
Author Location Gag (175–190)
Epitope QALSEGCTPYDINQML
Subtype HIV-2
Immunogen HIV-2 infection
Species (MHC) human
Country Guinea-Bissau
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords rate of progression, optimal epitope, HIV-2
References Leligdowicz *et al.* 2007

- To find the factors involved in attenuated disease course and long term non-progression, HIV-2 and immune control were studied. HIV-2 viral load was used as a predictor of patient survival. HIV-2 viral load correlated inversely with magnitude of IFN-gamma response, relative dominance of Gag-specific peptides' responses over other proteins' responses, and the breadth of different peptide-specific immune responses. The most frequently recognized peptides were in Gag protein, followed by Env and Pol, while Nef and accessory proteins (Vif, Vpx, Vpr, Tat and Rev) rarely elicited responses. The 6 most recognized peptides were clustered in a highly conserved region of Gag.

CTL CD8+

- This peptide, QALSEGCTPYDINQML, was recognized by 13 out of 65 subjects. It is found in the 149 amino-acid long HIV-2 proteome region of Gag 175-323.

HXB2 Location p24 (41–60)
Author Location p24 (179–188 subtype A)
Epitope SALSEGATPQDLNMMLNIVG
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Keywords subtype comparisons
References Dorrell *et al.* 1999

- CTL responses in three individuals with non-clade B infections were studied, 2 with subtype A infections, 1 with subtype C – their infections all originated in East Africa.
- This CTL epitope is presented by B*8101 in one of the patients with an A subtype infection – B*8101 is a newly discovered HLA allele found in Africans, and the epitope has yet to be mapped precisely.
- This epitope is distinct in subtype A relative to subtypes B, C, and D which share the dominant sequence: SALSEGATPQDLNTMLNTVG.

HXB2 Location p24 (41–60)
Author Location p24 (173–192 SF2)
Epitope SALSEGATPQDLNTMLNTVG
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- Three of these 12 had CTL response to this peptide.
- The responding subjects were HLA-A3, A32, B7, B14; and HLA-A2, A3, B14, B44.

HXB2 Location p24 (41–60)
Author Location p24 (173–192 SF2)
Epitope SALSEGATPQDLNTMLNTVG
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

HXB2 Location p24 (41–60)
Author Location p24 (SF2)
Epitope SALSEGATPQDLNTMLNTVG
Immunogen HIV-1 infection
Species (MHC) human
References Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined.

HXB2 Location p24 (41–60)
Author Location p24 (41–60 B1 and B2)
Epitope SALSEGATPQDLNTMLNTVG
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A3, A32, B62, B8, Cw3
Country Netherlands
Assay type Other
Keywords subtype comparisons, computational epitope prediction, superinfection
References Kozaczynska *et al.* 2007

- The influence of superinfection upon changes in HIV-1 strains was studied in a triple infected subject. While continuous expression of all three strains was observed, the LTR promoters of subtype AE had highest activity of all 3 strains, and subtype B2 had the lowest. Env-V3 sequences were present in higher numbers in strains B2 and CRF01_AE. Recombination was seen between viruses B1/B2 in gag and vpr genes.
- This epitope, SALSEGATPQDLNTMLNTVG, of unknown HLA restriction, is strongly reactive in ethnic Africans and deviates to SALSEGATPQDLNmMLNiVG in subtype CRF01_AE but shows no changes over time. Convergent evolution of this epitope to tALSEGATPQDLNTMLNTVG (S to T) was seen in subtypes B1 and B2 in 92% and 96% viruses after 4 and 3 years respectively. It overlaps with a CD4+ T-cell epitope.

HXB2 Location p24 (41–62)
Author Location p24 (173–194 BH10)
Epitope SALSEGATPQDLNTMLNTVGGH
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Johnson *et al.* 1991

- Gag CTL response studied in three individuals.

HXB2 Location p24 (42–52)
Author Location Gag (343–353)
Epitope ALSEGATPQDL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p24 (42–55)
Author Location Gag
Epitope ALSEGATPQDLNMM
Subtype A, CRF02_AG, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire

CTL CD8+

Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 2 subjects responded to peptide ALSEGATPQDLNMM from all 3 subtypes studied.

HXB2 Location p24 (43–52)
Author Location Gag (175–184 WEAU)
Epitope LSEGATPQDL
Epitope name Gag LL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*4403)
Donor MHC A*2902, B*0801, B*4403
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, immunodominance, escape, kinetics, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.
- There was a weak response to this epitope during acute and early infection, and the epitope sequence did not vary during the first year of the infection.

HXB2 Location p24 (43–52)
Author Location p24 (subtype A)
Epitope LSEGATPQDL
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (B42, B44)
Keywords subtype comparisons
References Cao *et al.* 2000

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, Pol, RT or Nef from HIV-1 clades A, B, and D.
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype.
- This optimal epitope sequence, recognized by CTL derived from a Ugandan with an A subtype infection (patient SP 511), is cross-reactive with subtypes A, B and D peptides.

HXB2 Location p24 (44–52)
Author Location p24 (176–184)
Epitope SEGATPQDL
Immunogen
Species (MHC) human (B*4001)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*4001, B60 epitope.

HXB2 Location p24 (44–52)
Author Location p24
Epitope SEGATPQDL
Epitope name B40-SL9(p24)
Immunogen HIV-1 infection
Species (MHC) human (B40)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (44–52)
Author Location
Epitope SEGATPQDL
Immunogen HIV-1 infection
Species (MHC) human (B40)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

CTL CD8+

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B40), an additional HLA (B44) was statistically predicted to be associated with this epitope.

HXB2 Location p24 (44–52)
Author Location p24
Epitope SEGATPQDL
Epitope name SL9(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B40)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B40-restricted epitope SEGATPQDL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide PMFSALSEGATPQDLNTM.
- 4 of the 20 HLA-B40 carriers responded to SEGATPQDL-containing peptide with average magnitude of CTL response of 590 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p24 (44–52)
Author Location Gag (178–186 BRU)
Epitope SEGATPQDL
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (B44)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 1/9 CRF02_AG-infected Ivorians, and 1/9 B-infected French subjects.

HXB2 Location p24 (44–52)
Author Location p24 (SF2)
Epitope SEGATPQDL
Immunogen HIV-1 infection
Species (MHC) human (B60)
References Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes.
- B60 is present in 10-20% of the Caucasoid and very common in Asian populations.

HXB2 Location p24 (44–52)
Author Location p24
Epitope SEGATPQDL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (B60)
Donor MHC A2, A24, B38, B60, Cw12, Cw2
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, supervised treatment interruptions (STI), acute/early infection, early treatment
References Montefiori *et al.* 2003

- HIV-1 + patient AC10 underwent early HAART treatment, which was discontinued 1.5 years later. At this timepoint potent NAb responses against autologous virus were detected. Treatment interruption initially induced weak CD8+ responses directed against 5 epitopes. By days 873d and 923d the CTL response had broadened to target 22 epitopes; of these six were fully characterized. Eventually the virus escaped the NAb response, but escape was not accompanied by a rise in viral load, and the authors suggest the virus was contained by the CTL response.

HXB2 Location p24 (44–52)
Author Location p24 (44–52 NL43)
Epitope SEGATPQDL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B60)
Assay type Chromium-release assay, CTL suppression of replication
Keywords escape
References Yang *et al.* 2003a

- Virus was cultured in the presence of CTL lines specific for 5 different epitopes (SLYNTVATL, ILKEPVHGV, IEIKDTKEAL, SEGATPQDL, and KEKGGLEGL) to study the emergence of escape mutations. Escape varied between clones for the same epitope, and between different epitopes. Gag and RT epitope escape, if it occurred at all, tended to be monoclonal and within the epitope, indicating strong fitness constraints, while the Nef epitope escape was rapid, polyconal, and sometimes the result of upstream frameshifts.
- One CTL clone, 161Jx12, recognized this epitope, and apparently no resistance mutations were selected by this clone, although the data was not shown in the paper.

HXB2 Location p24 (44–52)
Author Location p24 (176–184)
Epitope SEGATPQDL
Epitope name Gag/p24-SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B60)

Assay type Chromium-release assay
Keywords binding affinity, TCR usage, characterizing CD8+ T cells
References Yang *et al.* 2003b

- Killing efficiency of CTLs and their ability to suppress viral replication is shown to depend more on epitope specificity than to antigenic avidity. Different clones recognizing the same epitope had similar killing efficiency despite their variation in avidity. Nef specific CTL clones tended to be most inhibitory, followed by Gag, then by RT specific clones, regardless of avidity.
- 1/14 CTL T-cell clones tested were specific for Gag/p24-SL9. Under conditions of excess peptide (100ug/ml), there was no difference in their lytic potential; all possessed similar effector capacity. Avidity was measured as the sensitizing dose of peptide required for 50% of maximal killing (SD50), which varied from 20 pg/ml to 100 ng/ml, over four orders of magnitude for all 14 epitopes. The SD50 value for Gag/p24-SL9 was 30 pg/ml, it was among the peptides with the highest avidity.

HXB2 Location p24 (44–52)
Author Location p24 (HXB2)
Epitope SEGATPQDL
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (B60)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords epitope processing, vaccine antigen design, characterizing CD8+ T cells
References SenGupta *et al.* 2004

- Multiple HLA calss I-restricted and class II-restricted T-cell epitopes were shown to be processed and presented from an exogenously added HIV-1 gag-p24 peptide complexed to a heat shock protein. T-cell recognition of the complex was shown to be inhibited by brefeldin A indicating an endoplasmic reticulum-dependent pathway.

HXB2 Location p24 (44–52)
Author Location p24 (44–52)
Epitope SEGATPQDL
Immunogen HIV-1 infection
Species (MHC) human (B60, B61)
Keywords immunodominance
References Day *et al.* 2001

- No immunodominant responses were detected to five B61-restricted epitopes tested.
- All five B60-restricted epitopes were reactive in another subject, the strongest CTL response directed against the B60-epitope p24 SEGATPQDL, and the B60-restricted responses together contributed over one-third of the total CTL response.

HXB2 Location p24 (45–56)
Author Location Gag
Epitope EGATPQDLNMML
Subtype A, CRF02_AG, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide EGATPQDLNMML from all three subtypes.

HXB2 Location p24 (45–59)
Author Location Gag (178–192)
Epitope EGATPQDLNTMLNTV
Epitope name EV15
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- One subject responded to peptide EV15, a non-B*57-restricted peptide.

HXB2 Location p24 (45–59)
Author Location
Epitope EGATPQDLNTMLNTV
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A2, A32, B44, B7
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.

CTL CD8+

- Peptide 45 (NIH ARRP Cat# 7916), EGATPQDLNTMLNTV, which contains an epitope that is restricted by HLA-B7, elicited a CTL response of <100 sfc/million PBMC for 19+ years in a living non-progressor.

HXB2 Location p24 (46–59)
Author Location p24 (SF2)
Epitope `GATPQDLNTMLNTV`
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a HIV+ African American living in Boston with HLA A*3002/68 B14/*5802 Cw6/8 – this epitope fell within the most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

HXB2 Location p24 (46–59)
Author Location Gag
Epitope `GATPQDLNMMLNIV`
Subtype A, CRF02_AG, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide GATPQDLNMMLNIV from all 3 subtypes studied.

HXB2 Location p24 (46–62)
Author Location p24
Epitope `GATPQDLNTMLNTVGGH`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, GATPQDLNTMLNTVGGH, had an overall frequency of recognition of 20% - 18.6% AA, 11.5% C, 18.2% H, 4.8% WI. This peptide is included in a 49 aa Gag-p24 highly reactive region to be used for vaccine design. It is also part of 'Region III', PRTLNAWVKVVEEKAFSPEVIPMFSALSEGA, a 31 aa region recognized by >90% of subjects across ethnic groups.

HXB2 Location p24 (47–55)
Author Location p24 (47–55)
Epitope `ATPQDLNTM`
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (47–56)
Author Location p24 (subtype A)
Epitope `ATPQDLNMML`
Subtype A
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B53)
References Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses.
- Low risk individuals did not have such CD8+ cells.

- CD8+ T-cell epitopes: DTVLEDINL (3 individuals), SLYNTVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

HXB2 Location p24 (47–58)
Author Location Gag
Epitope `ATPQDLNTMLNT`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5802)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Chopera *et al.* 2008

- Transmission of HIV-1-escape variants from individuals with protective HLA-B*57/-B*5801 alleles to those without these alleles was studied to determine if infection with such replication-deficient mutants offered any advantage to the new host. Dependency between slower rate of disease progression in the newly infected subject and protective genotype of the infecting individual was suggested.
- HLA-B*5802-restricted epitope ATPQDLNTMLNT, within peptide GATPQDLNTMLNTVGGHQAAMQMLK was able to elicit CTL response in a wild type virus-carrying subject.

HXB2 Location p24 (47–58)
Author Location Gag (181–192)
Epitope `CTPYDINQMLNC`
Subtype HIV-2
Immunogen HIV-2 infection
Species (MHC) human (B58)
Country Gambia
Keywords HIV-2
References Bertoletti 1998

- HIV-2 epitope defined from an infection in Gambia, Bertoletti, pers. comm.

HXB2 Location p24 (47–58)
Author Location p24
Epitope `ATPQDLNTMLNT`
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human (B58)
Donor MHC A23, A24, B35, B58, Cw4, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence in this person matched the known epitope.

HXB2 Location p24 (48–55)
Author Location p24
Epitope `TPQDLNTM`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- TPQDLNTM is a previously described HLA-B*8101-restricted epitope (part of Gag reacting peptide EVIPMFTALSeGATPQDLNTM) that contains a B*8101-associated reversion at residues E, T or Q (TPQDLNtM/TPqDLNTM).

HXB2 Location p24 (48–55)
Author Location p24 (48–55)
Epitope `TPQDLNTM`
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 7 patients recognized this epitope.

HXB2 Location p24 (48–56)
Author Location p24 (180–188 IIIB)
Epitope `TPQDLNTML`
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*0702 epitope.

HXB2 Location p24 (48–56)
Author Location p24

CTL CD8+

Epitope TPQDLNTML
Immunogen peptide-HLA interaction
Species (MHC) human (B*0702)
Assay type Tetramer binding
Keywords binding affinity
References Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, TPQDLNTML (MHC Class I restriction, serotype Bw6) complexed with MHC B*0702 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C.

HXB2 Location p24 (48–56)
Author Location Gag
Epitope TPQDLNTML
Epitope name TL9
Subtype A, C, D
Immunogen HIV-1 infection
Species (MHC) human (B*0702, B*4201, B*8101)
Country Tanzania
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords rate of progression, immunodominance
References Geldmacher *et al.* 2007b

- The objectives of this study were to find antiviral epitopic determinants of Gag HIV-specific CTL response and to find 'host HLA-CTL response' correlations. By studying 56 ART-naive subjects including low viral load (LVL) responders, the authors show that subjects expressing the "protective" HLA-B*0702, -B*5801, and -B*8101 have broader Gag epitope recognition which may be abrogated if co-expressed with HLA-B alleles associated with rapid AIDS progression. Also, a negative linear relation was seen between Gag epitope numbers and plasma viral load while a positive relationship was seen with CD4 T-cell count. Finally, LVL subjects recognized specific Gag regions at the N- and C-termini of the protein more often than peptides in the middle of the protein.
- The epitope TPQDLNTML elicits a strong CTL-response and was targeted with high magnitude by 41% of the subjects. TL9 is highly conserved in subtype C and shows no evidence of viral escape by point mutations. This immunodominant response did not have a role in viral control, as subjects with B*8101 who do target TL9 have high viral loads. TL9 is presented by HLA Class I alleles B*0702, B*4201 and B*8101.

HXB2 Location p24 (48–56)
Author Location
Epitope TPQDLNTML
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0702, B*4201, B*8101)
Donor MHC A*3001, A*3303, B*5301, B*8101, Cw*0401
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- Known epitope TPQDLNTML, is HLA-B*4201, -B*8101 and -B*0702 restricted. Response to a peptide containing this epitope was detected in an early controller 12 weeks post-infection.

HXB2 Location p24 (48–56)
Author Location (C consensus)
Epitope TPQDLNTML
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*3910)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the L9 residue of TPQDLNTML are associated with the presence of the HLA presenting molecule in the host.
- TPQDLNTML is cross-presented by B*8101 and B*3901.

HXB2 Location p24 (48–56)
Author Location
Epitope TPQDLNTML
Immunogen
Species (MHC) human (B*3910)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B*3910 epitope.

HXB2 Location p24 (48–56)
Author Location p24 (48–56)
Epitope TPQDLNTML
Immunogen peptide-HLA interaction
Species (MHC) human (B*3910)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords optimal epitope
References Honeyborne *et al.* 2006

CTL CD8+

- Novel epitopes are defined for four HLA-alleles common in South African Zulu/Xhosa populations: B*3910, B*4201, B*8101 and Cw*1801, by motif inference. HLA-A*2902 was found to overlap those of A1 and A24 supertypes.
- TPQDLNTML was the optimal epitope for HLA-B*3910 with variants TPQDLNTM, PQDLNTML, TPQDLNTMLn, aTPQDLNTML having been tested.

HXB2 Location p24 (48–56)
Author Location p24 (180–188)
Epitope TPQDLNTML
Epitope name TL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*42, Cw*08)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*42 and Cw*08-associated substitution within optimally defined epitope TPQDLNTML is at position Q3, TPqDLNTML and at position T7, TPQDLNtML respectively.

HXB2 Location p24 (48–56)
Author Location p24 (179–187 LAI)
Epitope TPQDLNTML
Subtype B
Immunogen
Species (MHC) human (B*4201)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*4201 epitope.

HXB2 Location p24 (48–56)
Author Location (C consensus)
Epitope TPQDLNTML
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- TPQDLNTML is an optimal epitope.

HXB2 Location p24 (48–56)
Author Location p24
Epitope TPQDLNTML
Epitope name TL9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization
Keywords rate of progression
References Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naive patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer B*4201 TL9 was used to test 38 patients and gave a median ex vivo tetramer frequency of 2.23.

HXB2 Location p24 (48–56)
Author Location p24
Epitope TPQDLNTML
Epitope name TL9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization
Keywords rate of progression
References Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naive patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer B*4201 TL9 was used to test 38 patients and gave a median ex vivo tetramer frequency of 2.23.

HXB2 Location p24 (48–56)
Author Location
Epitope TPQDLNTML
Epitope name TL9
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type proliferation, Tetramer binding, Intracellular cytokine staining
References Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

HXB2 Location p24 (48–56)
Author Location Gag (96ZM651.8)
Epitope TPQDLNTML
Epitope name G180-TL9
Immunogen
Species (MHC) human (B*4201, B*8101)
Keywords subtype comparisons, immunodominance
References Novitsky *et al.* 2001

- This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort.
- 19/46 (41.3%) had CTL responses to one or more peptides within the first immunodominant region of Gag (peptides TLNAWVKVIEEKAFSPEVIP, EKAFSPEVIPMFTALSEGAT, and MFTALSEGATPQDLNTMLNT), with magnitudes of response with ELISPOT results median and range 495 (103 to 1,447) SFC/10^6 PBMC
- 7/11 HLA-A*4201+ subjects (64%) responded to peptide MFTALSEGATPQDLNTMLNT.
- TPQDLNTML is a A*4201 epitope within TLNAWVKVIEEKAFSPEVIP.

HXB2 Location p24 (48–56)
Author Location p24
Epitope TPQDLNTML
Epitope name TL-9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201, B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords subtype comparisons, epitope processing, immunodominance, cross-presentation by different HLA
References Masemola *et al.* 2004b

- Highly targeted regions in Gag for CD8+ T-cells were defined for individuals with C clade infections in South Africa. 9 specific epitopes within the most reactive regions were characterized. Some epitopes were shown to be promiscuous, presented by multiple class I restricting alleles.
- TPQDLNTML was presented by B*4201 and B*8101. B*44 is more common among Caucasians than Zulus (allele frequency 0.149 versus 0.107), while A*29 is more common in Zulus (0.045 versus 0.125). This epitope had previously identified in B clade infections.

HXB2 Location p24 (48–56)
Author Location Gag
Epitope TPQDLNMML
Immunogen HIV-1 infection
Species (MHC) human (B*4202)
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons, cross-presentation by different HLA, variant cross-recognition or cross-neutralization
References Currier *et al.* 2006

- The pattern of immunodominance and epitope clustering within Gag and Nef proteins in subtype A infected individuals was similar to that seen in subtype B and C infections. An immunodominant HLA-C restricted epitope, YVDRFFKTL (YL9 from Gag protein) was observed and restricted to Cw0304.
- The sequences egaTPQDLNMMLniv and egaTPQDLNtMLntv are associated with HLA-B*4202 and contain the epitope TPQDLNMML (TL9). Subtype specificity was seen as the variant epitope TPQDLNtML was rarely cross-reacted with.

HXB2 Location p24 (48–56)
Author Location Gag (173–181 HIV-2)
Epitope TPYDINQML
Subtype HIV-2
Immunogen HIV-2 infection
Species (MHC) human (B*5301)
Keywords optimal epitope, HIV-2
References Llano *et al.* 2009

- C. Brander notes this is a HIV-2 B*5301 epitope.

HXB2 Location p24 (48–56)
Author Location p24
Epitope TPQDLNMML
Immunogen peptide-HLA interaction
Species (MHC) human (B*5301)
Assay type Tetramer binding
Keywords binding affinity
References Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, TPQDLNMML (MHC Class I restriction, serotype Bw4Ile80) complexed with MHC B*5301 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C.

HXB2 Location p24 (48–56)
Author Location Gag (182–190 HIV-2 ROD)
Epitope TPYDINQML
Epitope name TPY
Subtype HIV-2
Immunogen HIV-2 infection
Species (MHC) human (B*5801)
Donor MHC A*0101, A*2402, B*07, B*5801
Country India
Keywords escape, HIV-2
References Kageyama *et al.* 2008

- This longitudinal case study in 1 patient found 3 amino acid substitutions - V286I in Gag and K303T, N337K/R in Env with an increase in HIV-2 load. Sites encompassing these 3 substitutions are candidates for HIV-2 epitopes.

CTL CD8+

- Epitope TPYDINQML of Gag 182-190 (relative to strain SMM239), restricted by HLA-B*5801, showed no changes in this patient.

HXB2 Location p24 (48–56)
Author Location Gag
Epitope TPQDLNTML
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*81)
Keywords HLA associated polymorphism
References Rousseau *et al.* 2008

- 3 phylogenetic correction methods—MLL (maximum likelihood character state analysis followed by likelihood ratio test), MLF (maximum likelihood character state analysis followed by Fisher test), and parsimony character state analysis were used to identify points in the HIV-1 subtype C proteome that conferred susceptibility or resistance to CTLs. Associations of HLA-epitope combinations that were inferred to be susceptible or resistant were organized into immunological sets. While all proteins were interrogated, Gag, Pol, Env and Nef were focused upon. Amino acid changes were evaluated for association with plasma viral load.
- Proteome maps may be seen at `http://www.hiv.lanl.gov/content/immunology/hlatem/study5/index.html` with information showing single or multiple sites involving escape and reversion.
- HLA- B and -C alleles associated more with aa changes than HLA-A, suggesting that the former two are more important in driving viral evolution.
- The ratio of susceptible to resistant residues in HIV proteins was in descending order, Vpr>Gag>Rev>Pol>Nef>Vif>Tat>Env>Vpu, showing that epitopes from the earlier proteins are more conserved owing to viral fitness cost upon mutation.
- This previously described Gag p24 HLA B*81-restricted epitope, TPQDLNTML was susceptible at L5. Variants TPQDmNTML, TPQDyNTML, TPQDsNTML were resistant to CTL response, but associated with lower viral loads. This epitope is 1 of 7 that suggest a fitness cost to immune escape.

HXB2 Location p24 (48–56)
Author Location p24 (180–188 LAI)
Epitope TPQDLNTML
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*8101 epitope.

HXB2 Location p24 (48–56)
Author Location (C consensus)
Epitope TPQDLNTML
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the T7 residue of TPQDLNTML are associated with the presence of the HLA presenting molecule in the host.
- TPQDLNTML is cross-presented by B*8101 and B*3901.

HXB2 Location p24 (48–56)
Author Location p24
Epitope TPQDLNTML
Epitope name TL9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Country South Africa
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization
Keywords rate of progression
References Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naive patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer B*8101 TL9 was used to test 15 patients and gave a median ex vivo tetramer frequency of 1.00.

HXB2 Location p24 (48–56)
Author Location p24
Epitope TPQDLNTML
Epitope name TL9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Country South Africa
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization
Keywords rate of progression
References Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naive patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer B*8101 TL9 was used to test 15 patients and gave a median ex vivo tetramer frequency of 1.00.

HXB2 Location p24 (48–56)
Author Location Gag
Epitope TPQDLNTML
Epitope name TL9
Subtype C

Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, HLA associated polymorphism
References Frater *et al.* 2007

- To study whether CTL responses restricted by "good" HLA I molecules exert stronger immune selection than other HLA I molecules, 54 and 70 optimal epitopes within HIV-1 Gag, Pol and Nef genes for Caucasian and African cohorts were tested in patients over a mean of 14 months. "Good", advantageous HLA allele-restricted epitopes were much more polymorphic than epitopes restricted by other, non-advantageous HLA in patients, suggesting that benefits associated with HLA Class I alleles of elite controllers of disease progression are epitope-specific. Such "driver" epitopes with high polymorphism had high frequency of immune response, allowing them to be ranked for recognition and polymorphism.
- Patients with higher proportions of mutated epitopes also had lower plasma viral loads, and mean epitope variability correlated negatively with relative hazard of disease progression.
- Variants TPsDLNTML and TPQDLNsML at positions 3 and 7 were the predominant polymorphisms found.

HXB2 Location p24 (48–56)
Author Location
Epitope `TPQDLNTML`
Epitope name TL9
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Country South Africa
Assay type proliferation, Tetramer binding, Intracellular cytokine staining
References Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

HXB2 Location p24 (48–56)
Author Location Gag
Epitope `TPQDLNTML`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
References Chopera *et al.* 2008

- Transmission of HIV-1-escape variants from individuals with protective HLA-B*57/-B*5801 alleles to those without these alleles was studied to determine if infection with such replication-deficient mutants offered any advantage to the new host. Dependency between slower rate of disease progression in the newly infected subject and protective genotype of the infecting individual was suggested.
- HLA-B*8101-restricted epitope TPQDLNTML, within peptide GATPQDLNTMLNTVGGH was able to elicit CTL response in a T242N/A146X viral-mutation-carrying subject.

HXB2 Location p24 (48–56)
Author Location p24
Epitope `TPQDLNTML`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- TPQDLNTML is a previously described HLA-B*8101-restricted epitope (part of Gag reacting peptides FTALSEGATPqDLNTMLNTVG and SEGATPQDLNtMLNTVGGHQA) that contains B*8101-associated reversions at residues Q and T (TPqDLNTML/TPQDLNtML).

HXB2 Location p24 (48–56)
Author Location
Epitope `TPQDLNTML`
Epitope name Gag-TL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5301, B*8101, B7)
Donor MHC A*3402, A*7401, B*5301, B*8101, Cw*0401, Cw*0802
Keywords HAART, ART
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Subjects 00RCH86 and 03RCH59 both recognized this epitope, both restricted by HLA B*8101.
- Subject 00RCH86 was African American, not on HAART, viral load 51000, CD4 count 520.
- Subject 03RCH59 was African American, male, on HAART, viral load 22000, CD4 count 769.
- Among HIV+ individuals who carried HLA B07, 2/9 (22%) recognized this epitope.
- Among HIV+ individuals who carried HLA B*5301, 3/15 (20%) recognized this epitope.
- Among HIV+ individuals who carried HLA B81, 4/6 (67%) recognized this epitope.

HXB2 Location p24 (48–56)
Author Location
Epitope `TPQDLNTML`
Immunogen HIV-1 infection
Species (MHC) human (B07)

CTL CD8+

Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope TPQDLNTML elicited a magnitude of response of 659 SFC with a functional avidity of 0.75nM and binding affinity of 4597nM.

HXB2 Location p24 (48–56)
Author Location
Epitope TPQDLNTML
Immunogen HIV-1 infection
Species (MHC) human (B07, B42, B53, B81)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- Based on a prediction of the minimum number of HLA alleles needed to cover the HLA representation in all responders to this epitope, a minimum set of 6 alleles was found: 4 alleles previously known to be associated (B07, B42, B53, B81) and 3 additional alleles (A02, A24, B14).

HXB2 Location p24 (48–56)
Author Location Gag (180–188)
Epitope TPQDLNTML
Subtype A, C, D
Immunogen HIV-1 infection
Species (MHC) human (B07, B42, B81)
Country Tanzania
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, immunodominance
References Geldmacher *et al.* 2007a

- 56 ART-naive subjects were studied to assess whether T-cell responses to Gag and Nef are biased towards infecting subtype recognition, in a setting of epidemic consisting of subtypes A,C and D and their recombinant forms. The infecting subtype was determined by multi-region hybridization assay. Overlapping 15-mer isolate-based Gag and Nef peptide sets representative of local subtypes were used. The best recognized epitope variant in terms of magnitude and breadth corresponded to infecting subtype, in this case usually type-C. Hot spots of CTL recognition in Gag were in p24, p17 and p15; hotspots against Nef were in its central, conserved region.
- Epitope variants TPQDLNtML and TPQDLNmML were studied as peptide sequences EGATPQDLNtMLNTV (subtypes C and D) and EGATPQDLNmMLNIV (subtype A), with >40% responders altogether. Subtypes C and D sequence was recognized best. Associated HLAs frequently expressed within the studied cohort are listed in the study as B07, B42 and B81.

HXB2 Location p24 (48–56)
Author Location Gag
Epitope TPQDLNTMLNT
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B14)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-B14-restricted epitope TPQDLNTMLNT is from subtype B and C libraries, and is reactive as part of peptide SEGATPQDLNTMLNT in a subtype B-carrying subject.

HXB2 Location p24 (48–56)
Author Location (C consensus)
Epitope TPQDLNTML
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201, B*8101, B39, Cw*0802)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords cross-presentation by different HLA, characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p24 (48–56)
Author Location p24

CTL CD8+

Epitope TPQDLNTML
Epitope name TL9(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B39, B7)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide sequence contains the exact sequence of a previously described HLA-B7- and -B39-restricted epitope, TPQDLNTML, none of the 9 HLA-B7 carriers responded to it (author communication and Fig.1). No information regarding HLA-B39 reactivity is provided.

HXB2 Location p24 (48–56)
Author Location p24 (C consensus)
Epitope TPQDLNTML
Immunogen HIV-1 infection
Species (MHC) human (B42)
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- B42 and B81 are very similar, and both can present this epitope to B42-positive effector cells – this epitope is almost certainly optimal for B81 as well – B42 and or B81 are expressed in 40-45% of Zulu and Xhosa infected individuals in South Africa, and in 14/18 B42 or B81+ individuals, the dominant gag response was to TPQDLNTML.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects.

HXB2 Location p24 (48–56)
Author Location Gag
Epitope TPQDLNTML
Immunogen HIV-1 infection
Species (MHC) human (B42)
References Goulder *et al.* 2000b

- Tetramer assays were compared with three functional assays in 42 people with chronic HIV infection: ELISPOT, intracellular cytokine staining, and precursor frequency (limiting dilution assay [LDA]).
- HIV-specific tetramer staining CTLs appeared to be active, and inert CTL were not found to play a significant role in chronic pediatric or adult HIV infection.

HXB2 Location p24 (48–56)
Author Location
Epitope TPQDLNTML
Epitope name TL9 ?
Immunogen HIV-1 infection
Species (MHC) human (B42)
Country United States, South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords memory cells
References Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

HXB2 Location p24 (48–56)
Author Location p24
Epitope TPQDLNQML
Immunogen
Species (MHC) human (B53)
References Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective.
- HIV-2 sequence: TPYDINQML, no cross-reactivity, Gotch *et al.* [1993]

HXB2 Location p24 (48–56)
Author Location Gag (173–181)
Epitope TPYDINQML
Subtype HIV-2
Immunogen HIV-2 infection
Species (MHC) human (B53)
Country Gambia
Keywords HIV-2
References Gotch *et al.* 1993

- HIV-2 Gag-specific responses were studied in 9 Gambian HIV-2 patients. High levels of HIV-2 Gag-specific CTL were found in all B53+ patients.
- Two HIV-2-positive B53+ patients reacted to this epitope, but failed to react to the HIV-1 equivalent peptide. One HIV-1-positive B53+ patient failed to react to this HIV-2 epitope. Thus, this epitope is unlikely to provide HIV1/HIV2 cross-protection.

HXB2 Location p24 (48–56)
Author Location Gag (180–188 subtype A)

Epitope TPQDLNMML
Subtype A
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human (B53)
Keywords subtype comparisons
References Dorrell *et al.* 2001

- In vitro restimulation of CTL specific for dominant epitopes from infected individuals is possible using recombinant modified vaccinia virus Ankara (MVA) carrying A or D subtype HIV-1 Gag proteins.

HXB2 Location p24 (48–56)
Author Location p24 (180–188 subtype A consensus)
Epitope TPQDLNMML
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (B53)
Keywords subtype comparisons, immunodominance, TCR usage
References Dorrell *et al.* 2001

- In clade A infected Gambians, three HLA-B53 epitopes were defined in Gag p24 using ELISPOT, tetramer, and cytotoxicity assays.
- This optimal epitope was identified within the 20 mer reactive peptide that carried it by homology with a B53 epitope from HIV-2, a B subtype B7 peptide that corresponds to it, as B53 is part of the B7 superfamily, and by the proline in the anchor at position 2.
- TPQDLNMML was recognized in 6/7 HLA-B53 subjects and was immunodominant in most subjects.
- TPQDLNMML was A subtype-specific with no cross-recognition of the subtype B, C, and D variant, TPQDLNTML, although the B/C/D variant bound more efficiently to B53 – position 7 show great positional variation in crystal structures of two HLA-B53 complexes, suggesting variation here might significantly alter the position of the peptide in the binding groove and thus affect TCR interactions.
- Only one subject might have had a cross-reactive response with the HIV-2 and Mamu-A*01 variant CTPYDINQML, and this subject might have been dual infected with HIV-2.

HXB2 Location p24 (48–56)
Author Location p24
Epitope TPQDLNMML
Immunogen HIV-1 infection
Species (MHC) human (B53)
Assay type Intracellular cytokine staining
Keywords immunodominance, genital and mucosal immunity
References Kaul *et al.* 2003

- Predefined immunodominant peptide responses were used to compare CD8+ T cells responses in the blood and cervix of 16 HIV+ Kenyan sex workers. Cervical responses were detected in 8/10 women from whom adequate samples could be obtained. The frequency of the CD8+ T cell response in the genital tract was comparable to the blood, with a trend toward being slightly higher.
- The immunodominant response was to this epitope in the PBMC of 2/16 patients (Kaul *et al.* 2001, AIDS, 107:1303).

HXB2 Location p24 (48–56)
Author Location Gag (180–188)
Epitope TPQDLNMML
Epitope name TPQ
Immunogen HIV-1 infection
Species (MHC) human (B53)
Country Gambia
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells, HIV-2
References Gillespie *et al.* 2005

- CD8 T-cell responses were evaluated and compared in HIV-1 and HIV-2 infected individuals living in the Gambia. A significantly greater magnitude and breadth of Gag-specific responses were found in HIV-1 infected individuals, possibly because of low or undetectable viral loads in HIV-2 infected individuals. This finding suggests that responses in HIV-2 infection reflect antigen load in plasma, as is the case in HIV-1 infection. No correlation was found between immune control of HIV-2 and the frequency of perforin-expressing virus-specific CD8 T-cells.
- 5/7 HIV-1-infected B53-positive subjects recognized TPQDLNMML, the HIV-1 version of this epitope. 3/3 HIV-2-infected B53-positive subjects responded to TPYDINQML, the HIV-2 version of the epitope.

HXB2 Location p24 (48–56)
Author Location Gag (180–188)
Epitope TPYDINQML
Epitope name TPY
Subtype HIV-2
Immunogen HIV-2 infection
Species (MHC) human (B53)
Country Gambia
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells, HIV-2
References Gillespie *et al.* 2005

- CD8 T-cell responses were evaluated and compared in HIV-1 and HIV-2 infected individuals living in the Gambia. A significantly greater magnitude and breadth of Gag-specific responses were found in HIV-1 infected individuals, possibly because of low or undetectable viral loads in HIV-2 infected individuals. This finding suggests that responses in HIV-2 infection reflect antigen load in plasma, as is the case in HIV-1 infection. No correlation was found between immune control of HIV-2 and the frequency of perforin-expressing virus-specific CD8 T-cells.
- 5/7 HIV-1-infected B53-positive subjects recognized TPQDLNMML, the HIV-1 version of this epitope. 3/3 HIV-2-infected B53-positive subjects responded to TPYDINQML, the HIV-2 version of the epitope.

HXB2 Location p24 (48–56)
Author Location Gag
Epitope TPYDINQML
Subtype A, CRF02_AG
Immunogen HIV-2 infection, HIV-1 or HIV-2 infection
Species (MHC) human (B53)
Country Gambia

Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, variant cross-recognition or cross-neutralization, HIV-2
References Ondondo *et al.* 2008

- To comprehensively compare Gag-specific cellular immunity against HIV-1 versus HIV-2, 20 subjects each infected with HIV-1 or -2, and with similar CD4+ counts were tested for CTL response to Gag peptide pools. No significant difference was seen in magnitude/breadth of CTL response, immunodominance and frequency of targeted Gag peptides, and cross-recognition.
- HIV-2 epitope TPYDINQML is cross-reactive with its HIV-1 variants, TPQDLNTML and TPQDLNMML when tested as a part of longer peptides. B53 restriction of this epitope is previously published.

HXB2 Location p24 (48–56)
Author Location Gag
Epitope TPQDLNTML
Subtype B, C
Immunogen HIV-1 infection, HIV-1 or HIV-2 infection
Species (MHC) human (B53)
Country Gambia
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, HIV-2
References Ondondo *et al.* 2008

- To comprehensively compare Gag-specific cellular immunity against HIV-1 versus HIV-2, 20 subjects each infected with HIV-1 or -2, and with similar CD4+ counts were tested for CTL response to Gag peptide pools. No significant difference was seen in magnitude/breadth of CTL response, immunodominance and frequency of targeted Gag peptides, and cross-recognition.
- HIV-1 epitope TPQDLNTML is cross-reactive with its HIV-2 variant, TPYDINQML when tested as a part of a longer, reactive peptide. B53 restriction of this epitope is previously published.

HXB2 Location p24 (48–56)
Author Location Gag
Epitope TPQDLNMML
Subtype A, CRF02_AG
Immunogen HIV-1 infection, HIV-1 or HIV-2 infection
Species (MHC) human (B53)
Country Gambia
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, variant cross-recognition or cross-neutralization, HIV-2
References Ondondo *et al.* 2008

- To comprehensively compare Gag-specific cellular immunity against HIV-1 versus HIV-2, 20 subjects each infected with HIV-1 or -2, and with similar CD4+ counts were tested for CTL response to Gag peptide pools. No significant difference was seen in magnitude/breadth of CTL response, immunodominance and frequency of targeted Gag peptides, and cross-recognition.
- HIV-1 epitope TPQDLNMML is cross-reactive with its HIV-2 variant TPYDINQML when tested as part of a longer reactive peptide. B53 restriction of this epitope is previously published.

HXB2 Location p24 (48–56)
Author Location Gag
Epitope TPYDINQML
Immunogen HIV-2 infection, HIV-1 or HIV-2 infection
Species (MHC) human (B53)
Country Belgium, Senegal
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords subtype comparisons, HIV-2
References Jennes *et al.* 2008

- To compare HIV-1 and HIV-2 CTL responses to Gag as far as homologous levels of response and cross-reactivity, 12 consecutive Gag OLP pools were used with cells from 17 HIV-1 and 17 HIV-2 patients in enhanced IFN-gamma ELISpot assays. Gag-specific homologous CTL responses were significantly higher in HIV-2 patients, but cross-reactivity in HIV-1-infected patients was broader and stronger.
- Cross-reactivity correlated with sequence similarity in HIV-2 patients, but not HIV-1 patients. CD4+ T-cell counts of HIV-2-infected patients correlated directly with homologous responses and inversely with cross-reactive responses; this was not true of HIV-1-infected subjects.
- The authors favor a model in which high HIV-2-specific CTL responses control its replication, containing immune evasion and thus limiting the possibility of cross-reaction to HIV-1 homologous epitopes.
- HIV-2 Gag epitope TPYDINQML is not cross-recognized with its homologous HIV-1 epitope, TPQDLNMML.

HXB2 Location p24 (48–56)
Author Location p24 (180–188 IIIB)
Epitope TPQDLNTML
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords responses in children, mother-to-infant transmission, escape
References Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- No variants of this epitope were found in a non-transmitting mother that had a CTL response to this epitope.

HXB2 Location p24 (48–56)
Author Location p24 (180–188)
Epitope TPQDLNTML
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords immunodominance
References Jin *et al.* 2000b

- This is the optimal epitope for the immunodominant response defined using a conventional approach in an HLA B7+ long-term non-progressor.
- Three additional sub-dominant HLA B7 epitopes were defined using EpiMatrix, a non-anchor based strategy for defining potential epitopes, which highlighted 2078 possible epitopes in the autologous HIV-1 derived from the study subject – this was followed by B7 anchor residue prediction which narrowed the

CTL CD8+

set to 55 peptides, three of which could serve as functional CTL epitopes.

HXB2 Location p24 (48–56)
Author Location p24 (SF2)
Epitope TPQDLNTML
Epitope name TL9
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Goulder *et al.* 2001a

- Recognized by patient 9354 during chronic infection, used as a positive control in a study of the SLYNTVATL epitope.

HXB2 Location p24 (48–56)
Author Location p24 (48–56)
Epitope TPQDLNTML
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes.
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

HXB2 Location p24 (48–56)
Author Location p24 (48–56)
Epitope TPQDLNTML
Epitope name B7-TL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 1/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 1/4 individuals had detectable responses to this epitope after STI.

HXB2 Location p24 (48–56)
Author Location p24
Epitope TPQDLNTML
Epitope name B7-TL9(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A32, B14, B7
Keywords HAART, ART, supervised treatment interruptions (STI)
References Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (`http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html`) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8+ T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient A displayed the greatest response to epitope B14-EL9(gp41), a strong response to B7-TL9(p24), and responses to B7-TM9(Nef) and A32-PW10(RT).

HXB2 Location p24 (48–56)
Author Location p24 (48–56)
Epitope TPQDLNTML
Epitope name B7-TL9 Gag
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), escape, early treatment, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response, but in this case the epitope did not vary.

HXB2 Location p24 (48–56)
Author Location (B consensus)
Epitope TPQDLNTML
Epitope name TL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A03, B07, Cw7
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope

HXB2 Location p24 (48–56)
Author Location p24 (HXB2)
Epitope TPQDLNTML
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (B42, B7, Cw8)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords epitope processing, vaccine antigen design, characterizing CD8+ T cells
References SenGupta *et al.* 2004

- Multiple HLA class I-restricted and class II-restricted T-cell epitopes were shown to be processed and presented from an exogenously added HIV-1 gag-p24 peptide complexed to a heat shock protein. T-cell recognition of the complex was shown to be inhibited by brefeldin A indicating an endoplasmic reticulum-dependent pathway.

HXB2 Location p24 (48–56)
Author Location (48–56)
Epitope TPQDLNTML
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B81)
Assay type Other
Keywords epitope processing, HLA associated polymorphism
References Boutwell & Essex 2007

- Publicly available HIV-1 subtype C sequences from South Africa and Botswana were analyzed, and 94 HLA-associated amino acid polymorphisms were found. Many polymorphisms were associated with multiple HLA allele classes. 12% associations were negative: association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles accounted for 50% of associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes.
- TPQDLNTML was a previously defined B81 presented epitope that encompassed associated polymorphisms, SeGA|TPQDLNtML, in the seventh position of as well in the third position before the known epitope.

HXB2 Location p24 (48–56)
Author Location
Epitope TPQDLNTML?
Epitope name TL9
Immunogen HIV-1 infection
Species (MHC) human (B81)
Country United States, South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords memory cells
References Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

HXB2 Location p24 (48–56)
Author Location p24 (180–188 LAI)
Epitope TPQDLNTML
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*0802)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a C*0802(Cw8) epitope.

HXB2 Location p24 (48–56)
Author Location (C consensus)
Epitope TPQDLNTML
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0802)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- TPQDLNTML is an optimal epitope.

HXB2 Location p24 (48–56)
Author Location Gag (180–188)
Epitope TPQDLNTML
Epitope name TL9
Subtype B

CTL CD8+

Immunogen HIV-1 infection
Species (MHC) human (Cw8)
Donor MHC A*02, A*68, B*14, B*52, Cw*08, Cw*12
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords escape, optimal epitope
References Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- The B consensus form of this epitope, TPQDLNTML, persisted throughout 6 years of chronic infection in 1 individual.

CTL CD8+

HXB2 Location p24 (48–56)
Author Location p24
Epitope `TPQDLNTML`
Epitope name Cw8-TL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw8)
Donor MHC A2, A68, B14, B44, Cw5, Cw8
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape, acute/early infection, antibody generation, co-receptor, immune evasion
References Streeck *et al.* 2007b

- A subject with acute and rapid disease progression to AIDS showed no neutralizing antibody activity and rapid decline in HIV-specific CTL response by 6 months post-infection. Virus from this rapid progressor was resistant to neutralization by plasma from a long-term progressor. Viral epitopes did not vary much. This suggests viral immune evasion in the absence of viral sequence variation.
- This epitope, TPQDLNTML, elicited a sub-dominant CTL response, not detectable after 6 months post-infection. TL9 and its flanking sequences EGATPQDLNTMLNTV did not show any escape mutations.

HXB2 Location p24 (48–56)
Author Location Gag
Epitope `TPQDLNTML`
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, epitope processing, characterizing CD8+ T cells
References Beattie *et al.* 2004

- This study compared CD8+ T-cell EliSpot reponses to 58 Gag peptides that were optimal epitopes, with responses to overlapping 15 mers that spanned Gag. When screening for HIV-1-specific CD8+ T-cell responses from 49 HIV+ people, overlapping 15-mer peptide pools revealed several novel responses that would have been missed using predefined CD8 epitopes. However, the 15-mer pools often missed low-level responses to predefined epitopes, especially when the epitope was located centrally in the 15-mer peptide, and the overall level of response to the 15 mers was generally lower(mean 1.4 five fold dilutions lower, range 0-3).
- The response to TPQDLNTML was used as an example of a titration curve. When comparing the peptide TPQDLNTML to the 15 mer EGATPQDLNTMLNTV, the 15 mer had a diminished response to the same amount of peptide.

HXB2 Location p24 (48–56)
Author Location Gag (180–188)
Epitope `TPQDLNTML`
Epitope name TL9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Other
Keywords supertype, escape, cross-presentation by different HLA, TCR usage, HLA associated polymorphism
References Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alelles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Functional avidity was correlated with selection pressure observed in HLA allele-epitope restriction.
- TL9 selection pressure was evidenced by studying changing epitope variants associated with HLAs of the B7 supertype.
- Higher level of polymorphism variation, escape mutations and TCR diversity was associated with the B*8101 allele.
- Statistically significant associations between numbers of HLA-B8101 and -B4201 expressing subjects and epitope TPQDLNTML were found.
- In 3 B-supertype alleles studied, B*4201, B*8101 and B*3910, the TL9 variant at the seventh position, TPQDLNsML, was most common. Several more variants are listed in the paper.

HXB2 Location p24 (48–56)
Author Location Pol
Epitope `TPQDLNTML`
Subtype B, C, A1
Immunogen HIV-1 infection

Species (MHC) human
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition.
- TPQDLNTML was predicted to be HLA supertype B7-restricted. It was recognized by at least 4 patients with restricting HLA supertype who were infected with several different HIV subtypes.

HXB2 Location p24 (48–57)
Author Location Gag
Epitope TPQDLNMMLN
Immunogen
Species (MHC) human (B7)
References De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFNγ production in an ELISPOT assay.
- TPQDLNMMLN was newly defined as an HLA-B7 epitope in this study, athough it was previously published as a B*8101 epitope.
- TPQDLNMMLN was shown to stimulate an ELISPOT response, but could not be shown to bind to HLA-B7.
- The variant TPQDLNTMLN was cross-reactive, had previously been identified as a HLA-B14 epitope, and could bind to HLA-B7.

HXB2 Location p24 (48–57)
Author Location Gag
Epitope TPQDLNMMLN
Epitope name 1309
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A03, A24, B07, B38, Cw07, Cw12/13
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for TPQDLNMMLN: 31%.

HXB2 Location p24 (48–57)
Author Location Gag
Epitope TPQDLNTMLN
Subtype B, C, D
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-B7-restricted epitope TPQDLNTMLN is from subtype B and C libraries, and is reactive as part of peptide SEGATPQDLNTMLNT in a subtype D-carrying subject.

HXB2 Location p24 (48–57)
Author Location Gag
Epitope TPQDLNTMLN
Epitope name 1308
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (B14, B7)
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for TPQDLNTMLN: 31%. This epitope was not confirmed in this study, but has been reported to be a B14 epitope.

HXB2 Location p24 (48–59)
Author Location p24
Epitope TPQDLNQMLNTV
Subtype B, G

CTL CD8+

Immunogen HIV-1 infection
Species (MHC) human (B58)
Donor MHC A2, A36, B45, B58, Cw3, Cw6
Country Nigeria
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype G Gag. The autologous epitope sequence in this person differed from the known epitope in one position, Q7T, TPQDLNtMLNTV

HXB2 Location p24 (48–62)
Author Location p24 (48–56)
Epitope TPQDLNMMLNIVGGH
Subtype A, D
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0201, A*2902, B*1402, B*1503; A*0101, A*7401, B*5801
Country Uganda
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References Barugahare *et al.* 2005

- T-cell immune responses were examined in HIV-1 infected Ugandans. Similar levels of cross-clade responses for Gag, Env and Nef were observed. Higher frequencies of responses in conserved regions were found for Gag within a single clade, while areas with higher viral sequence variation had fewer detectable responses. Differential interclade sequence homologies between the Gag regions did not affect the respective level of cross-clade recognition.
- This sequence contains a known B7 and B53 epitope, but the subjects recognizing it are B7- and B53-negative. It was conserved in the two people that recognized the peptide.

HXB2 Location p24 (49–57)
Author Location p24 (181–189 LAI)
Epitope PQDLNTMLN
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14, Cw8)
References Lubaki *et al.* 1997

- Eighty two HIV-1-specific CTL clones from 5 long-term non-progressors were isolated and analyzed for breadth of response.
- A sustained Gag, Env and Nef response was observed, and clones were restricted by multiple HLA epitopes, indicating a polyclonal response.
- Despite this being a well defined conserved epitope, none of the 11 gag-specific clones from a B-14 positive subject could recognize either it or p24 RAEQASQEV.
- Christian Brander notes that B14 and Cw8 are in linkage disequilibrium, and that this epitope may be Cw8.

HXB2 Location p24 (49–57)
Author Location p24 (49–57)
Epitope PQDLNTMLN
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw7)
Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords rate of progression, immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-Cw7-restricted autologous epitope PQDLNTMLN failed to generate CTL response. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location p24 (49–59)
Author Location Gag
Epitope PQDLNTMLNTV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.

- HLA-B14-restricted epitope PQDLNTMLNTV is from a subtype B peptide library, and is reactive as part of peptide PQDLNTMLNTVGGHQ in a subtype B-carrying subject.

HXB2 Location p24 (49–63)
Author Location
Epitope PQDLNTMLNTVGGHQ
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Dissection of Gag-specific responses showed that a broad CTL response was essential to elite control of disease. Immune escape at KRWIILGLNK was not a major cause of disease progression.
- Peptide 46 (NIH ARRP Cat# 7917), PQDLNTMLNTVGGHQ, contains an epitope that is restricted by HLA-A2 in different patients and elicited the following CTL response: (1) >50 sfc/million PBMC for 19+ years in a living non-progressor (2) 22+ years in another living non-progressor.

HXB2 Location p24 (51–59)
Author Location p24 (subtype A)
Epitope DLNMMLNIV
Subtype A
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B14)
References Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T-cell epitopes: DTVLEDINL (3 individuals), SLYNTVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

HXB2 Location p24 (51–59)
Author Location p24
Epitope DLNMMLNIV
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 1/22 HEPS sex worker controls, ML1792.

HXB2 Location p24 (51–59)
Author Location p24 (183–191 LAI)
Epitope DLNTMLNTV
Epitope name G5
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords HAART, ART
References Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNgamma production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

HXB2 Location p24 (51–59)
Author Location p24 (183–191)
Epitope DLNMMLNIV
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B14)
Keywords HIV exposed persistently seronegative (HEPS), immunodominance
References Kaul *et al.* 2001a

- Variants DLNMMLNIV/DLNTMLNVV are specific for clades A/B.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.

CTL CD8+

- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B14 women, 4/4 HEPS and 3/7 HIV-1 infected women recognized this epitope, likelihood ratio 4.8, p value 0.1, and HEPS women tended to respond to DLNMMLNIV/DLNTMLNVV, while infected women tended to respond to DRF(F/W)KTLRA.
- The dominant response to this HLA allele was to this epitope for all 4/4 HEPS cases and in only one of the 3/7 HIV-1 infected women.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.
- Four epitopes were considered to be "resistant epitopes", as they were preferentially reactive in HEPS women and so may confer resistance, and these were found in three different proteins: A2 ILK(D/E)PVHGV in RT, A*6802 DTVLEDINL in Protease, B14 DLN(M/T)LN(I/V)V in p24 and B18 FRDYVDRF(Y/F)K also in p24.

HXB2 Location p24 (51–59)
Author Location p24
Epitope `DLNMMLNIV`
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2002

- Neisseria gonorrhea cervititis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
- Ghonorrhea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

HXB2 Location p24 (51–59)
Author Location p24 (183–191 LAI)
Epitope `DLNTMLNTV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14, Cw8)
References Johnson *et al.* 1992; Nixon *et al.* 1988

- Recent evidence indicates this is a Cw8 epitope; B14 and Cw8 are in linkage disequilibrium and the HLA presenting molecule is hard to distinguish (P. Goulder, personal communication).

HXB2 Location p24 (51–59)
Author Location p24
Epitope `DLNTMLNTV`
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B14, Cw8)
Keywords subtype comparisons, HIV exposed persistently seronegative (HEPS)
References Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A subtype consensus is identical to the B clade epitope.
- The D subtype consensus is dLNmMLNiV.
- Recent evidence indicates this is a Cw8 epitope;B14 and Cw8 are in linkage disequilibrium and the HLA presenting molecule is hard to distinguish (P. Goulder, personal communication).

HXB2 Location p24 (51–59)
Author Location p24 (183–191 LAI)
Epitope `DLNTMLNTV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw8)
Keywords review
References McMichael & Walker 1994

- Review of HIV CTL epitopes – defined by B14 motif found within a larger peptide.
- Recent evidence indicates this is a Cw8 epitope;B14 and Cw8 are in linkage disequilibrium and the HLA presenting molecule is hard to distinguish (P. Goulder, personal communication).

HXB2 Location p24 (51–59)
Author Location p24 (subtype B)
Epitope `DLNTMLNTV`
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B*1402, Cw8)
Keywords subtype comparisons
References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among B and D clade viruses.
- The Clade A version of the epitope, DLNNMLNIV, was preferentially recognized by CTL.
- Recent evidence indicates this is a Cw8 epitope;B14 and Cw8 are in linkage disequilibrium and the HLA presenting molecule is hard to distinguish (P. Goulder, personal communication).

HXB2 Location p24 (51–59)
Author Location p24
Epitope `DLNTMLNTV`
Immunogen HIV-1 infection
Species (MHC) chimpanzee
References Santra *et al.* 1999

- 3/4 animals displayed HIV-1 Gag-specific CTL activity.

- Effector cells from two chimpanzees were able to recognize two epitopes also recognized by human HIV-1 Gag-specific CTL (SPRTLNAWV, HLA-B7, and DLNTMLNTV, HLA-B14).
- No chimpanzee CTL were detected to the following human HIV-1 specific Gag epitopes, although they were embedded within 20mer peptides that contained a reactive epitope: ISPRTLNAW, HLA-B57; KRWIILGLNK, HLA-B27; and DRFYKTLRA, HLA-B14.

HXB2 Location p24 (51–60)
Author Location Gag
Epitope `DLNTMLNTVG`
Epitope name 1238
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A2, B14)
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for DLNTMLNTVG: 65%. This epitope was not confirmed in this study, but was previously reported to be presented by B14.

HXB2 Location p24 (51–70)
Author Location p24 (183–202 SF2)
Epitope `DLNTMLNTVGGHQAAMQMLK`
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A26, A30, B38.

HXB2 Location p24 (51–82)
Author Location Gag (183–214 LAI)
Epitope `DLNTMLNTVGGHQAAMQMLKETINEEAAEWDR`
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide
Species (MHC) human
References Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long amino acid peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 2/10 reacted to this peptide.
- 9/12 tested mounted a CTL response to at least one of the six peptides; each of the six peptides elicited a CTL response in at least one individual.
- None of the 12 tested had an IgG response to this peptide.

HXB2 Location p24 (53–66)
Author Location Gag (188–201)
Epitope `NTMLNTVGGHQAAM`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p24 (57–71)
Author Location
Epitope `NTVGGHQAAMQMLKE`
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, A24, B15, B40
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 48 (NIH ARRP Cat# 7919), NTVGGHQAAMQMLKE, which contains an epitope restricted by HLA-A2, elicited CTL responses for 22+ years in a living non-progressor.

HXB2 Location p24 (60–70)
Author Location Gag (195–205)
Epitope `GGHQAAMQMLK`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human

Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p24 (61–69)
Author Location p24 (61–69)
Epitope GHQAAMQML
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location p24 (61–69)
Author Location (C consensus)
Epitope GHQAAMQML
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p24 (61–69)
Author Location (C consensus)
Epitope GHQAAMQML
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- GHQAAMQML is an optimal epitope.

HXB2 Location p24 (61–69)
Author Location p24 (193–201 LAI)
Epitope GHQAAMQML
Subtype B
Immunogen
Species (MHC) human (B*3901)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*3901 epitope.

HXB2 Location p24 (61–69)
Author Location p24
Epitope GHQAAMQML
Epitope name GL9(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B15, B39)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B15-restricted epitope GHQAAMQML elicited an immune response as part of peptide NTMLNTVGGHQAAMQMLK. This epitope is also restricted by HLA-B39 and elicited responses as part of the above peptide and peptide GHQAAMQMLKETINEEAA.
- 2 of the 21 HLA-B15 carriers responded to GHQAAMQML-containing peptide with average magnitude of CTL response of 105 SFC/million PBMC (author communication and Fig.1). No information regarding HLA-B39 reactivity is provided.

HXB2 Location p24 (61–69)
Author Location Gag (193–201 IIIB)
Epitope GHQAAMQML
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B38)
Assay type Chromium-release assay
References Kurane *et al.* 2003

- Three CD8+ CTL cell clones were derived from 2 HIV-1 positive asymptomatic patients, and their epitope specificities and HLA presenting proteins were defined.

HXB2 Location p24 (61–69)
Author Location p24 (193–201 LAI)
Epitope GHQAAMQML
Subtype B
Immunogen
Species (MHC) human (B39)
References Kurane & West 1998

- Optimal peptide defined by titration.

HXB2 Location p24 (61–69)
Author Location
Epitope GHQAAMQML
Immunogen HIV-1 infection
Species (MHC) human (B39)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B39), 2 additional HLAs (A03, B38) were statistically predicted to be associated with this epitope.

HXB2 Location p24 (61–71)
Author Location p24 (61–77)
Epitope GHQAAMQMLKE
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, GHQAAMQMLKE, was detected within overlapping peptide GGHQAAMQMLKETINEEA.

HXB2 Location p24 (61–71)
Author Location p24 (193–203 BRU)
Epitope GHQAAMQMLKE
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Claverie *et al.* 1988

- One of 4 epitopes first predicted, then shown to stimulate HLA-A2 restricted CTL line.

HXB2 Location p24 (61–71)
Author Location p24 (61–70)
Epitope GHQAAMQMLKE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 7/19 patients recognized this epitope.

HXB2 Location p24 (61–71)
Author Location Gag
Epitope GHQAAMEMLKD
Subtype A, B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-A2-restricted epitope GHQAAMEMLKD is from a subtype A peptide library, and is reactive as part of peptide GGHQAAMEMLKDTI in a subtype B-carrying subject.

HXB2 Location p24 (61–71)
Author Location Gag
Epitope GHQAAMQMLKD
Subtype C, D
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-A2-restricted epitope GHQAAMEMLKD is from a subtype C peptide library, and is reactive as part of peptide VGHQAAMEMLKDTI in a subtype D-carrying subject.

HXB2 Location p24 (61–75)
Author Location

CTL CD8+

Epitope GHQAAMQMLKETINE
Immunogen HIV-1 infection
Species (MHC) human (A2, B15)
Donor MHC A2, A24, B15, B40; A2, A31, B27, B44
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 49 (NIH ARRP Cat# 7920), GHQAAMQMLKETINE, which contains epitopes restricted by HLA-A2 and -B15 in different patients elicited the following CTL responses: (1) for 22+ years in a living non-progressor (2) for >22 years in a former non-progressor who succumbed to a loss of viremic control.

HXB2 Location p24 (61–75)
Author Location Gag (193–207)
Epitope GHQAAMQMLKETINE
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized both by mice co-immunized with Gag and Tat, and by mice immunized with Gag alone.

HXB2 Location p24 (61–78)
Author Location Gag
Epitope GHQAAMQMLKETINEEAA
Epitope name GAG-27
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, GHQAAMQMLKeTINEEAA differs from the consensus C sequence GHQAAMQMLKdTINEEAA at 1 amino acid position, i.e. by 5.6%.

HXB2 Location p24 (61–80)
Author Location p24 (193–212 SF2)
Epitope GHQAAMQMKETINEEAAEW
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A26, A30, B38.

HXB2 Location p24 (61–82)
Author Location p24 (193–214 BH10)
Epitope GHQAAMQMLKETINEEAAEWDR
Immunogen HIV-1 infection
Species (MHC) human (B52)
References Johnson *et al.* 1991

- Gag CTL response studied in three individuals.

HXB2 Location p24 (62–70)
Author Location Gag (Henan isolate)
Epitope HQAAMQMLK
Subtype B

Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p24 (62–70)
Author Location p24 (194–202 LAI)
Epitope `HQAAMQMLK`
Subtype B
Immunogen
Species (MHC) human (B52)
References Brander & Walker 1996

- P. Goulder, pers. comm.

HXB2 Location p24 (62–70)
Author Location p24
Epitope `HQAAMQMLK`
Epitope name HK9(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B52)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide sequence contains the exact sequence of a previously described HLA-B52 optimal epitope, HQAAMQMLK, none of the 5 HLA-B52 carriers responded to it (author communication and Fig.1).

HXB2 Location p24 (62–75)
Author Location Gag
Epitope `HQAAMQMLKETINE`
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide HQAAMQMLKETINE from subtype CRF01_AE.

HXB2 Location p24 (64–78)
Author Location Gag
Epitope `AAMQMLKDTINEEAA`
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*02, A*03, B*07, B*08, Cw*07, Cw*16, DPA1*0103, DPA1*0202, DPB1, DQB1*06, DRB1*1301, DRB1*1501, DRB3
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- Epitope-containing peptide AAMQMLKDTINEEAA, seen in a subtype-B carrying subject is derived from subtype B and C libraries and was not previously associated with host class I alleles A*02/*03; B*07/*08, Cw*07/*16.

HXB2 Location p24 (64–80)
Author Location p24 (63–80 HXB2)
Epitope `AAMQMLKETINEEAAEW`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%)

recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 22% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location p24 (65–72)
Author Location p24
Epitope AMQMLKET
Epitope name A9I
Immunogen vaccine
Vector/Type: DNA *HIV component:* Gag
Species (MHC) mouse (H-2^d)
Assay type Chromium-release assay
References Bojak *et al.* 2002b
- Codon-optimized gag gene DNA vaccines were compared to wild type by vaccination of BALB/c mice. Codon optimized DNA gave a Th1 polarized Th response, a strong antibody response that persisted from more than 20 weeks, and CTL responses, while wild-type DNA induced weak and inconsistent immune responses.

HXB2 Location p24 (65–72)
Author Location Gag (197–205 SF2)
Epitope AMQMLKET
Epitope name AMQ
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF2 *HIV component:* Gag, Tat *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse (H-2^d)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes
References Cellini *et al.* 2008
- In order to increase the known number of epitopes in Gag protein so that they can be assayed for reactivity in vaccine studies, BALB/c mice were inoculated with Gag or Gag+Tat. OLPs were used to elicit T-cell immune responses from mouse splenocytes, tested for by cytotoxicity or ELISpot assays. 5 novel predicted optimal CTL epitopes, 2 novel predicted CD4 epitopes and 2 immune response eliciting peptides were found.
- Previously known epitope AMQMLKET was found in reactive Peptides 49 and 50, GHQAAMQMLKETINEEAAE and AMQMLKETINEEAAE.

HXB2 Location p24 (65–73)
Author Location Gag (197–205 BRU)
Epitope AMQMLKETI
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005
- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 1/9 CRF02_AG-infected Ivorians, and 1/9 B-infected French subjects.

HXB2 Location p24 (65–73)
Author Location Gag (199–207 HXB2)
Epitope AMQMLKETI
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade HXB2 *HIV component:* Gag
Species (MHC) mouse (H-2^d)
References Qiu *et al.* 1999
- Different expression vectors were tested to increase Gag expression in cell lines and create suitable vectors for DNA vaccines.
- Stable Gag expression was achieved in murine p815 cells, using a Gag gene that had mutated silent base positions that disrupt inhibitory RNA sequences which promote RNA degradation.
- Silent mutations were more effective than introduction of the D retrovirus cis-acting posttranscriptional control element (CTE) for enhancing Gag expression.
- The gag vector with silent mutations given as a vaccine to BALB/c mice gave CTL responses in splenic mononuclear cells, using peptide pulsed cells as targets.

HXB2 Location p24 (65–73)
Author Location p24 (199–207 SF2)
Epitope AMQMLKETI
Epitope name p7g
Immunogen vaccine
Vector/Type: protein, vaccinia *Strain:* B clade SF2 *HIV component:* Gag, Gag-Pol *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse (H-2^d)
References Neidleman *et al.* 2000
- Intranasal immunization of CB6F1 (H2bxd) mice with soluble gag p55 with LT ADP-ribosyltransferase mutants (LTK63 and LTK73) from Escherichia coli as adjuvants was tested.
- Intranasal and intramucosal immunization of p55 gag protein with LTK63 or LTK72 adjuvant induced a CTL response comparable to intramuscular immunization responses.
- Oral co-administration of LTR72, with residual ADP-ribosyltransferase activity, induced systemic CTL responses, but LTK63 with no ADP-ribosyltransferase activity did not.

HXB2 Location p24 (65–73)
Author Location p24 (66–74)

Epitope AMQMLKETI
Immunogen vaccine
Vector/Type: DNA *HIV component:* Gag *Adjuvant:* vesicular stomatitis virus glycoprotein (VSV-G)
Species (MHC) mouse (H-2^{d})
References Marsac *et al.* 2002

- BALB/c mice were injected with plasmids expressing HIV-1 Gag with or without coinjection of a plasmid expressing vesicular stomatitis virus glycoprotein (VSV-G). The combination encodes VSV-G pseudotyped Gag particles that can be taken up by cells for presentation in either the class I or class II pathways, while exogenous Gag alone can only be taken into the class II pathway.
- Vaccination with DNA expressing VSV-G pseudotyped Gag particles rather than just Gag increase Gag-specific CTL responses generally as well as the specific H-2d restricted anti-AMQMLKETI response.

HXB2 Location p24 (65–73)
Author Location Gag
Epitope ANQMLKDTI
Subtype C
Immunogen vaccine
Vector/Type: DNA with CMV promotor *HIV component:* Gag, Protease
Species (MHC) mouse (H-2^{d})
Country India
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Cytolytic LDH release assay
Keywords subtype comparisons, vaccine-induced epitopes, Th1
References Chugh & Seth 2004

- A gag-protease gene construct from HIV-1 subtype C Indian strain has been shown to be successful in evoking immune responses to gag epitopes from both CD4+ and CD8+ T-cells in BALB/c mice. The immune response was of TH1 type. Recognition of seven Gag peptides carrying multiple epitopes indicates a broad-based immune response.
- A cross-clade response to the C clade epitope ANQMLKDTI was observed to the B clade version of this epitope, aNqmlkEti. 66% lysis was observed to the peptide carrying the C clade epitope, only 33% to the B clade variant.

HXB2 Location p24 (65–73)
Author Location Gag
Epitope AMQMLKETI
Subtype A, B
Immunogen vaccine
Vector/Type: DNA *Strain:* A clade, B clade *HIV component:* Env, Gag
Species (MHC) mouse (H-2^{d})
Country Finland
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Malm *et al.* 2007

- A novel mouse model was used to test the efficacy of 2 HIV DNA vaccines in protection against tumor challenge. Comparable immunogenicity between the single and multi-clade vaccines tested was seen in different mouse strains. CTL response to HIV-1-APCs was both in vivo and in vitro and this animal model not only evaluated vaccine immunogenicity but also confirmed the potency of GTU-multi-HIV vaccines.

HXB2 Location p24 (65–73)
Author Location p24 (199–207 SF2)
Epitope AMQMLKETI
Epitope name p7G
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF2 *HIV component:* Gag *Adjuvant:* DDA, DOTAP, CpG immunostimulatory sequence (ISS), MF59, PLG, urea
Species (MHC) mouse (H-2^{kd})
Keywords dendritic cells
References O'Hagan *et al.* 2002

- Intramuscular or intraperitoneal immunization of BALB/c or CB6F1 mice with urea-solubilized, emulsified, or PLG-microparticle associated p55 Gag was studied in conjunction with the adjuvant CpG. CpG did not enhance CTL immunity when combined with urea solubilized p55, but did when combined with emulsions and PLG-microparticle antigen.
- CpG shifted the Ab response towards a IgG2a, and CpG was shown to upregulate CD86 on mouse bone-marrow derived dendritic cells.

HXB2 Location p24 (65–73)
Author Location
Epitope AMQMLKDTI
Subtype C
Immunogen vaccine
Vector/Type: DNA, DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* C clade Du422, C clade Du151 *HIV component:* Gag, gp160 deletions, Nef, RT, Tat
Species (MHC) mouse (H-2^{kd})
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, Th1
References Shephard *et al.* 2008

- A DNA (SAAVI DNA-C) and MVA (SAAVI MVA-C) vaccines vaccines were tested in BALB/c mice. Combining the vaccines in a DNA prime and MVA boost regimen increased the cumulative peptide response compared to the DNA vaccine alone 10-fold.
- Th1 cytokine IFN-γ and TNF-α levels from HIV-specific CD8 and CD4 T cells increased 20- and 8- fold respectively, with a SAAVI MVA-C boost.
- Effector and effector memory RT- and Env-epsific memory CD8 T cell subsets were boosted after MVA immunizations.
- CD8 epitope AMQMLKDTI was used for detection of IFN-γ-secreting cells.

HXB2 Location p24 (65–73)

CTL CD8+

Author Location p24 (199–207 SF2)
Epitope AMQMLKETI
Subtype B
Immunogen vaccine
Vector/Type: DNA with CMV promotor *Strain:* B clade SF2 *HIV component:* Gag, gp120
Species (MHC) mouse (H-2D^d)
Assay type Chromium-release assay
Keywords epitope processing, vaccine-induced epitopes
References Doe *et al.* 1996

- Spleen cells from mice with distinct MHC types were infused into HIV vaccinated scid mice, to study the antigen presenting cells used by CTL induced in intramuscular injections. Bone marrow derived cells are used for presenation, but DNA infection is not required for priming, rather APCs can present proteins synthesized in other host cells.

HXB2 Location p24 (65–73)
Author Location p24 (199–207 SF2)
Epitope AMQMLKETI
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* Gag, Pol
Species (MHC) mouse (H-2K^d)
Keywords immunodominance
References Doe & Walker 1996

- Immunodominant murine CTL response to this peptide observed after immunization with vaccine VVgagpol.
- Optimal peptide was defined.

HXB2 Location p24 (65–73)
Author Location Gag (197–205)
Epitope AMQMLKETI
Immunogen vaccine
Vector/Type: Listeria monocytogenes *HIV component:* Gag
Species (MHC) mouse (H-2K^d)
References Rayevskaya & Frankel 2001

- BALB/c mice were immunized with a highly attenuated recombinant Listeria monocytogenes, Lmdaldat, that can grow only when supplemented with D-alanine, and that expresses HIV-1 HXB2 Gag.
- Parenteral immunization provided protection against systemic and mucosal challenges with a recombinant vaccinia virus expressing HIV-1 gag, and a long lasting memory CTL response against Gag in spleen, mesenteric lymph nodes, and Peyer's patches directed against the gag protein.
- Oral immunization gave protection only against mucosal virus challenge and was associated with a transient CTL response in the three lymphoid tissues examined.
- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted L. monocytogenes antigens are processed and presented by both class I and class II pathways.

HXB2 Location p24 (65–73)
Author Location Gag (197–205 SF2)
Epitope AMQMLKETI
Immunogen vaccine
Vector/Type: Listeria monocytogenes *Strain:* B clade HXB2 *HIV component:* Gag
Species (MHC) mouse (H-2K^d)
Keywords immunodominance
References Mata *et al.* 1998

- BALB/c mice were immunized with recombinant Listeria monocytogenes (Lm-Gag) expressing HIV-1 HXB2 Gag.
- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted L. monocytogenes antigens are processed and presented by both class I and class II pathways.
- This is the immunodominant CTL epitope in Gag in BALB/c mice.
- AMQMLKETI does not contain established Kd anchoring residue in position 2, tyrosine or phenylalanine, thus deviating from the typical Kd anchoring motif – the lack of the aromatic anchor residue is compensated for by interaction of the glutamine at P3 with pocket D of Kd.

HXB2 Location p24 (65–73)
Author Location Gag (HXB2)
Epitope AMQMLKETI
Subtype B
Immunogen vaccine
Vector/Type: vaccinia, vesicular stomatitis virus (VSV) *Strain:* B clade HXB2, B clade IIIB *HIV component:* Env, Gag
Species (MHC) mouse (H-2K^d)
Keywords immunodominance
References Haglund *et al.* 2002a

- Different HIV strains were used for different regions: Env IIIB, Gag HXB2.
- BALB/c mice were vaccinated with rec vesicular stomatitis virus (rVSV) expressing either HIV-1 Gag, Env, or both, and compared to using rec Env and Gag in vaccinia virus (rVVs). The primary response was determined by cell lysis, cytokine production and tetramer staining.
- Primary CTL responses to the immunodominant Gag (AMQMLKETI) epitope peaked in 7 days for GAG-rVSV, 3% of the cells were tetramer positive, and this response was 8-fold higher than for Gag-rVV.
- Vaccinating with GagEnv-rVSV carrying both Gag and Env allowed recognition of both HIV-1 proteins, but at reduced levels compared to either Gag-rVSV or Env-rVSV alone.
- Intranasal immunization with Env-rVSV yielded CTL responses that were strong but reduced compared to an intraperitoneal route.

HXB2 Location p24 (65–73)
Author Location Gag (HXB2)
Epitope AMQMLKETI
Subtype B
Immunogen vaccine
Vector/Type: vaccinia, vesicular stomatitis virus (VSV) *Strain:* B clade HXB2, B clade IIIB *HIV component:* Env, Gag
Species (MHC) mouse (H-2K^d)
Keywords immunodominance
References Haglund *et al.* 2002b

- Different HIV strains were used for different regions: Env IIIB, Gag HXB2.
- BALB/c mice were vaccinated with rec vesicular stomatitis virus (rVSV) expressing either HIV-1 Gag or Env, or both, and retention of memory responses and recall responses were studied by tetramer staining and IFN-gamma production.
- Seven months after vaccination with Env-rVSV, 6% of the CD8+ cells were tetramer positive for the immunodominant Env epitope; these cells had a memory phenotype, CD44-Hi positive.
- Env in rec vaccinia virus (Env-rVV) elicited a strong recall response, with up to 45% to the CD8+ T-cell population tetramer positive and activated (expressing CD62L-Lo), and capable of IFN-gamma production.
- A prime with Env-rVSV and heterologous boost of Env-rVV gave remarkably high levels of memory cells, with approximately 1/3 of the CD8+ splenocytes being Env specific memory cells 150 days after the boost.
- A Gag-rVSV or EnvGag-rVSV prime and with a heterologous Gag-rVV or EnvGag-rVV boost combination gave 40% tetramer positive CD8+ cells, but the fraction of IFN-gamma producing cells was only about 25%. Still the heterologous vector prime-boost combination showed a profound benefit.
- A HIV-1 protein rVSV prime, rVV boost was a more potent combination than a vector reversal of a rVV prime and rVSV boost.

HXB2 Location p24 (65–73)
Author Location Gag
Epitope AMQMLKETI
Subtype B
Immunogen vaccine
Vector/Type: Listeria monocytogenes *HIV component:* Gag
Species (MHC) mouse (H-2K^d)
Donor MHC H-2d
Assay type Tetramer binding, Intracellular cytokine staining
Keywords genital and mucosal immunity
References Peters *et al.* 2003

- Intravenous, rectal, and oral vaccination of recombinant L. monocytogenes expressing HIV-1 Gag antigen were compared for their ability to stimulate a mucosal CTL response; mucosal administration of this vaccine gave strong mucosal response that was readily boosted.
- This CTL epitope is the immunodominant epitope in Gag for BALB/c mice, and was used to characterize the vaccine responses.

HXB2 Location p24 (65–73)
Author Location Gag (197–205)
Epitope AMQMLKETI
Subtype B
Immunogen vaccine
Vector/Type: vaccinia, Listeria monocytogenes *HIV component:* Gag, Nef
Species (MHC) mouse (H-2K^d)
Donor MHC H-2d
Assay type Cytokine production, proliferation, Tetramer binding, Intracellular cytokine staining, Chromium-release assay
Keywords memory cells
References Rayevskaya *et al.* 2003

- Splenocytes derived from BALB/c mice immunized and boosted with Lmdd-gag were stimulated with gag-peptide specific antigen *in vitro*. In culture, CTL activity against this epitope reached a maximum at 9 days, then declined. Peptide restimulation gave a delayed (18 hours) but potent response, and growth was IL-2 or IL-15 dependent. Adoptive transfer of 5000 of the sorting purified cells could protect recipient BALB/c against vaccinia-gag challenge up to 3 months after transfer.

HXB2 Location p24 (65–73)
Author Location
Epitope AMQMLKETI
Epitope name A9I
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), polyepitope *HIV component:* Gag, p24 Gag, V3
Species (MHC) mouse (H-2K^d)
Assay type Cytokine production, Chromium-release assay
Keywords epitope processing, vaccine-specific epitope characteristics, immunodominance, vaccine antigen design
References Wild *et al.* 2004

- A codon optimized gag DNA vaccine was compared to a myristylation defective gag and p24 alone, both of which lack signals for secretion from transfected cells. Gag-derived immunogens that were secreted as VLPs and those that remained intracellular (p24) each produced strong CTL responses, and neither the size of antigen nor cellular trafficking and localization significantly influenced the strength of humoral and cellular immune activation. The formation and release of VLPs was not essential for eliciting strong CTL. BALB/c mice were given the DNA vaccine by i.m. administration of plasmid DNA for the prime and boost.
- Linking the region encoding the V3 immunodominant epitope to the gag gene did not diminish the response to the Gag p24 epitope A9I, but did enable a response to the V3 epitope.
- Minigenes were made incorporating just 1 epitope, minitopes, carrying 1 of 3 murine class I eptiopes linked to the Ad2-E3 protein-derived signal peptide to allow access of the epitope to the ER. Weak induction of cellular immune responses was observed, in contrast to the complex polyprotein.

HXB2 Location p24 (65–73)
Author Location Gag (197–205)
Epitope AMQMLKETI
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade HXB2 *HIV component:* Gag
Species (MHC) mouse (H-2K^d)
Country United States
Assay type proliferation, T-cell Elispot
Keywords vaccine antigen design

CTL CD8+

References Kwak *et al.* 2004

- A recombinant vaccinia virus with HIV-1 Gag replacing the cytoplasmic domain of the B5R protein was shown to induce better primary CD4 response than recombinant vaccinia virus expressing Gag from the TK-locus; CD8 responses were less specific. When immunized BALB/c mice were challenged with a recombinant Listeria that expresses HIV-Gag, lower colony counts of Listeria were found in the liver and spleen of mice immunized with virus expressing B5R-Gag fusion protein.

HXB2 Location p24 (65–73)
Author Location Gag
Epitope AMQMLKDTI
Epitope name G
Subtype A, B, C
Immunogen vaccine
Vector/Type: DNA with CMV promotor, modified vaccinia Ankara (MVA), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade, B clade, C clade Du422, Other *HIV component:* Gag, Nef, RT
Species (MHC) mouse (H-2K^{d})
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords subtype comparisons, vaccine-induced epitopes, variant cross-recognition or cross-neutralization, antagonism
References Larke *et al.* 2007

- Cross-clade vaccine recognition was studied using either single-, multi or several anatomically separated single-clade vaccines. Limited cross-clade response was seen with single-clade administrations. Multi-clade vaccines gave immune interference (antagonism and original antigenic sin), reducing CTL response. Simultaneously administered but anatomically separated vaccines from clades A, B, C decreased antagonism and increased immune responses.
- After immunization with Clades A or C vaccines, both containing Epitope G, AMQMLKDTI, T cells responded well to this index epitope, but poorly to Clade B variant AMQMLKeTI, and intermediately to variant AMQiLKDTI. Induction by Clade B vaccine, containing epitope AMQMLKETI, generated good responses to both Clade B and A variants, but not to variant AMQiLKDTI.

HXB2 Location p24 (65–73)
Author Location Gag (C-96BW04.09)
Epitope AMQMLKDTI
Epitope name A
Subtype C
Immunogen vaccine
Vector/Type: DNA, alphavirus replicon *Strain:* C clade C-96BW04.09, C clade C-96BW15C05 *HIV component:* Gag, Gag-Pol, Pol
Species (MHC) mouse (H-2d)
Assay type Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, vaccine antigen design
References Megede *et al.* 2006

- HIV clade C gag, pol and fusion gagpol vaccines were compared in mice. Breadth of T cell responses was improved in mice immunized with gagpol fusion genes, compared to single antigen constructs. 5 new murine CD8+ T cell epitopes were mapped.
- AMQMLKDTI has a previously identified B clade homolog AMQMLKeTI.

HXB2 Location p24 (65–73)
Author Location Gag (199–207)
Epitope AMQMLKETI
Epitope name p7g
Subtype B
Immunogen vaccine
Vector/Type: vaccinia, Sindbis *HIV component:* Gag
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ
Keywords genital and mucosal immunity
References Vajdy *et al.* 2001

- Nasal, vaginal, rectal and i.m. immunization was performed with Sindbis virus expressing HIV-1 Gag (SIN-Gag), followed by intravaginal or intrarectal challenge with vaccinia virus expressing either Gag (VV-Gag) or gp160 (VV-gp160) as a control.
- Intranasal and intramuscular immunization followed by intravaginal challenge induced HIV-1 Gag specific, IFN-γ producing CD8+ T-cells in the vaginal/uteral mucosal tissue, as well as in the draining iliac lymph nodes and in the spleen, but could not protect against a VV-Gag infection of the ovaries. Local vaginal or rectal immunization, despite lower CD8+ T-cell responses, did provide protection.

HXB2 Location p24 (65–73)
Author Location Gag (Du422)
Epitope AMQMLKDTI
Subtype C
Immunogen vaccine
Vector/Type: DNA *Strain:* C clade Du422 *HIV component:* Gag
Species (MHC) mouse
Donor MHC H-2d
Assay type Chromium-release assay
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References van Harmelen *et al.* 2003

- The pTHgagC DNA vaccine employed in this study expressed the gag gene derived from the South African isolate Du422, which was selected on the basis of being the natural strain most similar to the South African subtype C consensus sequence (aa distance of 1.8%).
- A E7D mutation was introduced into the epitope to match the gag subtype C sequence in the vaccine. Mice vaccinated with the gag DNA made strong CTL responses against AMQMLKDTI, boosting enhanced the response, and memory cells persisted for 15 weeks.

HXB2 Location p24 (65–73)
Author Location p24 (197–205)

Epitope AMQMLKETI?
Immunogen vaccine
Vector/Type: protein *HIV component:* Gag *Adjuvant:* Cholera toxin (CT)
Species (MHC) mouse
Donor MHC H-2d
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords TCR usage, genital and mucosal immunity
References Yoshizawa *et al.* 2003

- Intranasal immunization triggered CTL response in the nasal-associated lymphoid tissue (NALT), posterior cervical lymph nodes (pCLNs) and the spleen, but not in the mesenteric lymph nodes (MLNs). Rectal immunzation elicited CTL responses only in the MLNs. By immunizing mice nasally following rectal immunization, CTL responses were detected in NALT, pCLNs, spleen and MLNs. Epitope-specific CD8+ T-cells were primarily located in NALT after 6 days and in pCLNs after 2 months.
- The strongest specific lysis was induced by NALT-specific CTL clones. pCLNs derived memory CTL clones originated from NALT CTL clones, as determined by T-cell receptor Vβ usage.

HXB2 Location p24 (65–73)
Author Location Gag
Epitope AMQMLKETI
Subtype B
Immunogen vaccine
Vector/Type: modified vaccinia Ankara (MVA) *Strain:* B clade ADA *HIV component:* Env, Gag-Pol
Species (MHC) human
Assay type Other
Keywords vaccine antigen design
References Wyatt *et al.* 2008b

- An in-frame initiation codon upsteam of Env gene in rMVA increases Env protein 5-fold in inoculated mice. This results in enhanced immune responses to Env that do not affect responses to Gag.
- The immunodominant Gag peptide AMQMLKETI was used to elicit IFN-gamma production as a marker of CTL function against Gag.

HXB2 Location p24 (65–73)
Author Location Gag
Epitope AMQMLKDTI
Epitope name Gag A-I
Subtype BC
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost *Strain:* Other *HIV component:* Env, Gag, Nef, Pol, Tat
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine-specific epitope characteristics, vaccine antigen design
References Huang *et al.* 2008b

- 2 dual promoter candidate vaccines were constructed: ADVAX-I containing env and gag; ADVAX-II containing pol and nef-tat. The combined vaccine, ADVAX, showed equal immunogenicity in mice to single-gene plasmid vaccines, and elicited dose-dependent T-cell responses. Sequences were based on the Yunnanese subtype C/B' recombinant form of HIV-1.
- Both vaccine components induced dose-dependent IFN-gamma responses to epitope AMQMLKDTI, Gag A-I.
- IFN-gamma response was also elicited by 2 CD4 epitope-containing 20mers.

HXB2 Location p24 (65–79)
Author Location
Epitope AMQMLKETINEEAAE
Immunogen HIV-1 infection
Species (MHC) human (B40)
Donor MHC A2, A24, B15, B40
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 50 (NIH ARRP Cat# 7921), AMQMLKETINEEAAE, which contains an epitope restricted by HLA-B40, elicited CTL responses for 22+ years in a living non-progressor.

HXB2 Location p24 (65–79)
Author Location Gag (197–211)
Epitope AMQMLKETINEEAAE
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice

CTL CD8+

vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized both by mice co-immunized with Gag and Tat, and by mice immunized with Gag alone.

HXB2 Location p24 (66–79)
Author Location Gag
Epitope MQMLKDTINEEAAE
Subtype A, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008
- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 2 subjects responded to peptide MQMLKDTINEEAAE from subtype A and 1 of the 2 responded to peptide MQMLKeTINEEAAE of subtype CRF01_AE.

HXB2 Location p24 (69–83)
Author Location
Epitope LKETINEEAAEWDRV
Immunogen HIV-1 infection
Species (MHC) human (A25)
Donor MHC A25, A3, B18, B27
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008
- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 51 (NIH ARRP Cat# 7922), LKETINEEAAEWDRV, which contains an epitope that is HLA-A25 restricted in one patient, elicited a CTL response in that living non-progressor at <1000 sfc/million PBMC for up to 12.5 years and <50 sfc/million PBMC at 22 years.

HXB2 Location p24 (69–86)
Author Location (C consensus)
Epitope LKDTINEEAAEWDRLHPV
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*6801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location p24 (69–86)
Author Location Gag (201–218 LAI)
Epitope LKETINEEAAEWDRVPV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Buseyne *et al.* 1993a
- Vertical transmission of HIV ranges from 13% to 39%.
- Primary assays showed that cytotoxic activity against at least one HIV protein detected in 70% of infected children.
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
- Patient EM28 (CDC P2A) had a CTL response to four epitopes in Gag.

HXB2 Location p24 (69–86)
Author Location Gag
Epitope LKETINEEAAEWDRLHPV
Epitope name GAG-28
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007
- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.

- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, LKeTINEEAAEWDRLHPV differs from the consensus C sequence LKdTINEEAAEWDRLHPV at 1 amino acid position, i.e. by 5.6%.

HXB2 Location p24 (70–78)
Author Location p24 (70–78)
Epitope KETINEEAA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*40)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, KETINEEAA, was detected within overlapping peptideS GGHQAAMQMLKETINEEA, LKETINEEAAEWDRLHPV and AAEWDRLHPVHAGPIA.

HXB2 Location p24 (70–78)
Author Location
Epitope KETINEEAA
Epitope name Gag-KA9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*4002)
Donor MHC 01RCH46: A*0201, A*0217, B*0801, B*4002, Cw*0303, Cw*0701
Keywords HAART, ART
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- This epitope was newly defined in this study.
- Patient 01RCH46 was Hispanic, on HAART, and had a viral load of 21000 and CD4 count of 623 – she also recognized GELDRWEKI, p17(11-19), HLA B*4002, and TAFTIPSI, RT(128-135), HLA A*0217.
- Among HIV+ individuals who carried HLA B40, 3/5 (60%) recognized this epitope.

HXB2 Location p24 (70–78)
Author Location p24 (70–78)
Epitope KETINEEAA
Immunogen HIV-1 infection
Species (MHC) human (B*4002)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location p24 (70–78)
Author Location p24
Epitope KETINEEAA
Epitope name KA9(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B40)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B40-restricted epitope KETINEEAA elicited an immune response in Chinese HIV-1 positive subjects as part of peptides GHQAAMQMLKETINEEAA and LKETINEEAAEWDRLHPV.
- 5 of the 20 HLA-B40 carriers responded to KETINEEAA-containing peptide #27 with average magnitude of CTL response of 450 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p24 (70–83)
Author Location Gag
Epitope KDTINEEAAEWDRL
Subtype A, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

CTL CD8+

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma EliSpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. Fifteen test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide VGGPSHKARILAEAM from subtypes A and CRF01_AE.

HXB2 Location p24 (71–80)
Author Location
Epitope `ETINEEAAEW`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*25)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Addo *et al.* 2007

- Maturation phenotypes of CTLs were compared between HIV-1 Controller and Progressor subjects. Controllers were found to recognize a median of 18 epitopes compared to 15 by Progressors. While Controllers certainly had higher frequencies of terminally differentiated effector CTLs (CD45RA+/CCR7-), Progressors had higher mean frequencies of CD45RA-/CCR7- effector memory, CD45RA-/CCR7+ central memory (statistically significant) and CD45RA+/CCR7+ naive CTLs. No correlation was seen between CTL effector phenotype and either HLA-type or epitope.
- A*25-restricted epitope ETINEEAAEW does not correlate with any particular CTL maturation phenotype.

HXB2 Location p24 (71–80)
Author Location Gag
Epitope `ETINEEAAEW`
Epitope name EW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*25)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords immunodominance
References Cao *et al.* 2008

- For the first time, viral immune evasion is reported via an insertion mutation, in an ART-naive patient. A 3 aa repeat, SPT inserted within p6<sup>Pol<sup> epitope NL8 is reported. This insertion is associated often with ART drug resistance to NRTI drugs. Thus immune pressure and drug resistance may cause HIV-1 to select the same variation.
- A concomitant insertion mutation APP, is seen in p6<sup>Gag<sup>, permitting viral budding.
- Epitope ETINEEAAEW elicited an early, dominant response in subject PIC1362.

HXB2 Location p24 (71–80)
Author Location p24 (203–212)
Epitope `ETINEEAAEW`
Epitope name EW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*25)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-A*25-associated substitution within optimally defined epitope ETINEEAAEW is at positions E9, ETINEEAAeW. EW10 exhibited little HLA-driven sequence evolution despite being recognized relatively often.

HXB2 Location p24 (71–80)
Author Location p24 (203–212)
Epitope `ETINEEAAEW`
Immunogen HIV-1 infection
Species (MHC) human (A*2501)
Keywords subtype comparisons
References Klenerman *et al.* 1996

- The epitope was defined through direct stimulation of PBMC with 20-mer peptides.
- It is in a conserved region, ETINEEAAEW is found in most B, D, and E subtype isolates.
- DTINEEAAEW is found in A and some D subtype sequences.

HXB2 Location p24 (71–80)
Author Location p24 (203–212)
Epitope `ETINEEAAEW`
Immunogen HIV-1 infection
Species (MHC) human (A*2501)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*2501 epitope.

HXB2 Location p24 (71–80)
Author Location p24 (203–212)
Epitope `ETINEEAAEW`
Immunogen HIV-1 infection
Species (MHC) human (A*2501)
References van Baalen *et al.* 1996

- Conserved between B and D subtypes, variable in other clades; a consensus of clades A, C, F, G, and H and a peptide of HIV-2ROD over this region were not recognized by CTL recognizing the index peptide.

- C. Brander notes that this is an A*2501 epitope in the 1999 database.

HXB2 Location p24 (71–80)
Author Location p24 (71–80 HXB2)
Epitope ETINEEAAEW
Epitope name EW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2501)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- ETINdEAAEW CTL escape mutant elicited a reduced CTL response.

HXB2 Location p24 (71–80)
Author Location p24
Epitope ETINEEAAEW
Immunogen
Species (MHC) human (A25)
References Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective.
- HIV-2 sequence: EIINEEAAEW, no cross-reactivity van Baalen *et al.* [1996]

HXB2 Location p24 (71–80)
Author Location p24 (203–212 SF2)
Epitope ETINEEAAEW
Immunogen HIV-1 infection
Species (MHC) human (A25)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A25+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/2 group 2, and 1/3 group 3.

HXB2 Location p24 (71–80)
Author Location p24 (202–211)
Epitope ETINEEAAEW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A25)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords Th1, characterizing CD8+ T cells
References Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8+ cells are found, each one constituting 30-40% of the CD8+ cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- 1/3 patients responded to this peptide with GzB producing cells, and the other two responded with IFN-gamma producing cells.

HXB2 Location p24 (71–80)
Author Location
Epitope ETINEEAAEW
Immunogen HIV-1 infection
Species (MHC) human (A25)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope ETINEEAAEW elicited a magnitude of response of 380 SFC with a functional avidity of 0.005nM.

HXB2 Location p24 (71–80)
Author Location p24 (203–212 SF2, HXBc2/Bal R5)
Epitope ETINEEAAEW
Epitope name EW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A25)
Donor MHC A24, A25, B18, B7, Cw12, Cw7
Country United States

CTL CD8+

Assay type Cytokine production, Flow cytometric T-cell cytokine assay, Degranulation, CD107a and b cell surface mobilization
Keywords supervised treatment interruptions (STI), immunodominance, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells, drug resistance
References Daucher *et al.* 2008

- A detailed analysis of 6 chronically infected patients' CTL responses to autologous virus was performed after ART and SIT (structured interruption of therapy). Qualitative responses including degranulation and production of IFN-gamma, MIP-1beta, TNF-alpha, IL-2, but not memory CD27, CD45RO and CD57 T cells correlated with extended low plasma viremia. Frequency and breadth of CTL response as well as immune escape did not influence virological outcome.
- One patient exhibited drug resistance mutations K170R (to NNRTI efavirenz) and D76N, K70R (to NRTIs).
- Autologous epitopes were preferentially recognized over optimal, consensus sequences.
- Patients with favorable virological outcomes demonstrated CTL recognition within multiple, conserved regions of Gag and Nef.
- Patients with poor virological outcomes recognized optimal epitopes with much lower frequencies, though this was not significant.
- HLA-A25-restricted epitope, ETINEEAAEW, elicited a response in 1 patient with low viremia who also targeted Nef epitopes with high frequency. EW10 is found in Gag immunodominant region LKETINEEAAEWDRVHP. Patient autologous sequence was ETINdEAAEW.

HXB2 Location p24 (71–80)
Author Location
Epitope DTINEEAAEW
Epitope name Gag-DW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5301)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B*5301, 2/15 (13%) recognized this epitope.

HXB2 Location p24 (71–80)
Author Location
Epitope ETINEEAAEW
Epitope name Gag-EW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5301)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B*5301, 2/15 (13%) recognized this epitope.

HXB2 Location p24 (71–80)
Author Location p24 (203–212)
Epitope DTINEEAAEW
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B53)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B53 women, 0/2 HEPS and 7/9 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in 4 of the 7/9 responsive HIV-1 infected women.

HXB2 Location p24 (71–80)
Author Location p24 (203–212 subtype A consensus)
Epitope DTINEEAAEW
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (B53)
Keywords binding affinity, subtype comparisons, epitope processing
References Dorrell *et al.* 2001

- In clade A infected Gambians, three HLA-B53 epitopes were defined in Gag p24 using ELISPOT, tetramer, and cytotoxicity assays.
- Two of the new epitopes lacked the predicted P2 anchors, DTINEEAAEW and QATQEVKNM, and bound to B53 with high affinity, thus extending the anchor residue motif for B53 and the related B35.
- Two overlapping 20 mer peptides carry this complete epitope, but only one stimulates recognition, which could be due to different peptide processing.
- DTINEEAAEW was recognized in only 2/7 HLA-B53 subjects.
- DTINEEAAEW was not A subtype specific and there was cross-recognition although diminished, of the subtype B, C, and D variant, ETINEEAAEW.
- In one of the two subjects there was cross-recognition of the HIV-2 version of the epitope, EIINEEAADW.

HXB2 Location p24 (71–80)
Author Location p24
Epitope ETINEEAAEW
Subtype A, B, D
Immunogen HIV-1 infection
Species (MHC) human (B53, B58)
Donor MHC A36, A74, B53, B58, Cw4, Cw6; A23, A34, B44, B53, Cw4, Cw6; A23, A24, B35, B58, Cw4, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ

Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described B53 epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype A Gag. The autologous epitope sequence in this person differed from the known epitope by one amino acid, E1D, dTINEEAAEW. It was also recognized in a person carrying a subtype D gag, and in this case the autologous sequence matched the epitope. This was also predicted to possibly be a B58 cross-presented epitope in another subtype D Gag infected person based on peptide reactivity and a known B58 motif.

HXB2 Location p24 (71–80)
Author Location p24 (71–80)
Epitope `DTINEEAAEW`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope DTINEEAAEW is highly conserved across clades, >70% to clades A and C. It was predicted to have HLA-B*5801 restriction.

HXB2 Location p24 (71–80)
Author Location
Epitope `ETINEEAAEW`
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A*2501, A*3002; B*0702, B*1801
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location p24 (71–90)
Author Location p24 (203–222 SF2)
Epitope `ETINEEAAEWDRVHPVVHAGP`
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A2, B21.

HXB2 Location p24 (72–80)
Author Location Gag
Epitope `TINEEAAEW`
Epitope name TW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.

CTL CD8+

- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- TW9, TINEEAAEW, is a novel HLA-B57-restricted epitope that elicits a CTL IFN-gamma response in the same range as Los Alamos database peptides.

HXB2 Location p24 (73–87)
Author Location
Epitope `INEEAAEWDRVHPVH`
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 52 (NIH ARRP Cat# 7923), INEEAAEWDRVHPVH, which contains an epitope restricted by HLA-A2 in different patients elicited the following CTL responses: (1) >1000 sfc/million PBMC for 22+ years in a living non-progressor (2) ∼100 sfc/million PBMC for 22+ years in another living non-progressor (3) ∼1000 sfc/million PBMC for 22+ years in yet another living non-progressor (4) for >12 years in a former non-progressor who succumbed to non-AIDS death.

HXB2 Location p24 (75–83)
Author Location Gag (207–215)
Epitope `EEAAEWDRV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*40)
Donor MHC A*03, A*24, B*35, B*40
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, variant cross-recognition or cross-neutralization, superinfection
References Yang *et al.* 2005b

- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
- The response to the epitope EEAAEWDRV was found in the patient before superinfection and diminished afterwards; the initial infecting and superinfecting strain carried EEAAEWDRl.

HXB2 Location p24 (75–83)
Author Location Gag
Epitope `EEAAEWDRL`
Epitope name EL9-B40
Subtype B, F
Immunogen HIV-1 infection
Species (MHC) human (B40)
Country Argentina
Keywords dynamics, escape, HLA associated polymorphism
References Dilernia *et al.* 2008

- Dynamics of CTL escape mutations was studied theoretically by analyzing plasma samples from 302 subjects (collected over 20 years). HLA associated polymorphisms accumulated in a subtype-specific manner.
- Epitope EEAAEWDRL with anchor residues at E(E)AAEWDR(L) mutates to variant EEAAEWDRv. The consensus epitope EEAAEWDRl increases with time.

HXB2 Location p24 (77–87)
Author Location Gag (216–226)
Epitope `AAEWDRLHPVH`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p24 (77–91)
Author Location
Epitope `AAEWDRVHPVHAGPI`
Immunogen HIV-1 infection
Species (MHC) human (A2, B40, B44)
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 53 (NIH ARRP Cat# 7924), AAEWDRVHPVHAGPI, which contains epitopes restricted by HLA-A2, -B40 and -B44 in different patients elicited the following CTL responses: (1) >1000 sfc/million PBMC for 22+ years in a living non-progressor (2) 22+ years in another living non-progressor (3) >1000 sfc/million PBMC for 22+ years in yet another living non-progressor (4) 12+ years in a former non-progressor who succumbed to a non-AIDS death.

HXB2 Location p24 (77–91)
Author Location Gag (209–223 SF2)
Epitope AAEWDRLHPVHAGPI
Epitope name Peptide 53
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF2 *HIV component:* Gag, Tat *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse (H-2^d)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes
References Cellini *et al.* 2008

- In order to increase the known number of epitopes in Gag protein so that they can be assayed for reactivity in vaccine studies, BALB/c mice were inoculated with Gag or Gag+Tat. OLPs were used to elicit T-cell immune responses from mouse splenocytes, tested for by cytotoxicity or ELISpot assays. 5 novel predicted optimal CTL epitopes, 2 novel predicted CD4 epitopes and 2 immune response eliciting peptides were found.
- Reactive peptide AAEWDRLHPVHAGPI is now predicted to have a potential CTL epitope.

HXB2 Location p24 (77–91)
Author Location Gag (209–223)
Epitope AAEWDRLHPVHAGPI
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized both by mice co-immunized with Gag and Tat, and by mice immunized with Gag alone.

HXB2 Location p24 (77–92)
Author Location p24
Epitope AAEWDRLHPVHAGPIA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.

- This immunodominant, frequently targeted overlapping peptide, AAEWDRLHPVHAGPIA, had an overall frequency of recognition of 20% - 18.6% AA, 23.1% C, 25% H, 9.5% WI. This peptide is included in a 41 aa Gag-p17 highly reactive region to be used for vaccine design.

HXB2 Location p24 (78–86)
Author Location p24 (78–86)
Epitope AEWDRLHPV
Epitope name AEW
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, A68.1, B*07, B*3503, Cw*0401, Cw*0702, DQ2, DQ6, DR15, DR17, DR51, DR52
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ
Keywords rate of progression, escape
References Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses,and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relative efficiency of the variant eptiopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- This was one of 8 reactive epitopes found not to vary over time.

HXB2 Location p24 (78–86)
Author Location p24 (Henan isolate)
Epitope AEWDRLHPV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- AEWDRLHPV was among 5 mostly recognized epitopes (69%).

HXB2 Location p24 (78–86)
Author Location Gag (210–218)
Epitope AEWDRVHPV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*40)
Donor MHC A*03, A*24, B*35, B*40
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, variant cross-recognition or cross-neutralization, superinfection
References Yang *et al.* 2005b

- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
- The epitope AEWDRVHPV was recognized in the patient before superinfection and diminished afterwards. The initial and superinfecting strains had the variant AEWDRlHPV.

HXB2 Location p24 (78–86)
Author Location p24 (78–86)
Epitope AEWDRLHPV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*40)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, AEWDRLHPV, was detected within overlapping peptides LKETINEEAAEWDRLHPV and AAEWDRLHPVHAGPIA.

HXB2 Location p24 (78–86)
Author Location
Epitope AEWDRVHPV
Epitope name Gag-AV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*4002)
Donor MHC A*0201, A*3201, B*4002, B*5301, Cw*0202, Cw*0401
Keywords HAART, ART
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- This epitope was newly defined in this study.
- Patient 01RCH59 was Hispanic, not on HAART, and had a viral load of 5100 and CD4 count of 349 – she also recognized TERQANFL, p2p7p1p6(64-71), HLA-B*4002, and KEKGGLEGL, Nef(92-100), HLA-B*4002.
- Among HIV+ individuals who carried HLA B40, 4/5 (80%) recognized this epitope.

HXB2 Location p24 (78–86)
Author Location p24 (78–86)
Epitope AEWDRVHPV
Immunogen HIV-1 infection
Species (MHC) human (B*4002)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location p24 (78–86)
Author Location p24 (78–86)
Epitope AEWDRLHPV
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4006)
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope AEWDRLHPV showed >50% conservation across clades with >90% conservation to subtype D sequence. This epitope was restricted to HLA-B*4006 in one subject and to HLA-B*4006 or -Cw*0602 in another subject.

HXB2 Location p24 (78–86)
Author Location Gag
Epitope AEWDRLHPV
Epitope name AV9-B40
Subtype B, F
Immunogen HIV-1 infection
Species (MHC) human (B40)
Country Argentina
Keywords dynamics, HLA associated polymorphism
References Dilernia *et al.* 2008

- Dynamics of CTL escape mutations was studied theoretically by analyzing plasma samples from 302 subjects (collected over 20 years). HLA associated polymorphisms accumulated in a subtype-specific manner.
- Epitope AEWDRLHPV with anchor residues at A(E)WDRLHP(V) mutates to variant AEWDRLHPa. The consensus epitope AEWDRLHPl increases with time.

HXB2 Location p24 (78–86)
Author Location p24
Epitope AEWDRVHPV
Epitope name AV9(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B40)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B40-restricted epitope AEWDRVHPV elicited an immune response in Chinese HIV-1 positive subjects as part of peptide AAEWDRVHPVHAGPIA.
- 7 of the 20 HLA-B40 carriers responded to AEWDRVHPV-containing peptide with average magnitude of CTL response of 460 SFC/million PBMC.

HXB2 Location p24 (79–86)
Author Location Gag
Epitope EWDRVHPV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-A2-restricted epitope EWDRVHPV is from a subtype B peptide library, and is reactive as part of peptide EWDRVHPVHAGPIA in a subtype B-carrying subject.

HXB2 Location p24 (81–91)
Author Location Gag (213–223)
Epitope DRVHPVHAGPI

CTL CD8+

Epitope name Gag 11.4
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade *HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu
Species (MHC) macaque
Assay type T-cell Elispot, Intracellular cytokine staining
Keywords subtype comparisons, variant cross-recognition or cross-neutralization, memory cells
References Amara *et al.* 2005

- A clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02_AG consensus Gag in macaques. The activity was better conserved for CD8 than CD4 T cells.
- All 5 CD8 and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation. The similar reported human epitope in this case is VHPVHAGPIA, restricted by HLA B55.
- 3 of 5 CD8 epitopes and 2 of 8 CD4 epitopes were conserved across multiple HIV-1 clades. DRVHPVHAGPI is identical in HXB2 and the CRF02 consensus. It is relatively conserved across other clades, but usually has an L in the third position: DRlHPVHAGPI.

HXB2 Location p24 (81–95)
Author Location
Epitope `DRVHPVHAGPIAPGQ`
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A11, A2, B60, B7; A2, A32, B44, B7
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 54 (NIH ARRP Cat# 7925), DRVHPVHAGPIAPGQ, which contains epitopes restricted by HLA-B7 in different patients elicited the following CTL responses: (1) 19+ years in a living non-progressor (2) <50 sfc/million PBMC for 19+ years in another living non-progressor.

HXB2 Location p24 (81–100)
Author Location p24 (81–100)
Epitope `DRLHPVHAGPAAPGQMREPR`
Epitope name DRL
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A2, A68.1, B*07, B*3503, Cw*0401, Cw*0702, DQ2, DQ6, DR15, DR17, DR51, DR52
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, escape
References Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses,and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relative efficiency of the variant eptiopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- This epitope was not precisely defined, but was one of six epitopes found to be under positive selection for escape mutations and was completely replaced by escape variants between days 66 and 327 (drlhpvhagpIapgqmrepr).

HXB2 Location p24 (82–92)
Author Location Gag (217–227)
Epitope `RLHPVHAGPIA`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p24 (83–91)
Author Location Gag (215–223)
Epitope `LHPVHAGPI`
Subtype B
Immunogen HIV-1 infection, peptide-HLA interaction
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance
References Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome

in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, LHPVHAGPI, is similar to human protein PTPRE, sequence LnPVHAGPIV and human protein T cell leukemia Homeobox 1, sequence LHPgHAePIV.

HXB2 Location p24 (83–92)
Author Location p24 (215–223 IIIB)
Epitope `VHPVHAGPIA`
Immunogen HIV-1 infection
Species (MHC) human (B55)
References Sipsas *et al.* 1997
- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB.
- LHPVHAGPVA, a variant found in HIV-1 PH136, was also recognized.
- LHPVHAGPIA, a variant found in HIV-1 RF, was also recognized.
- LHPVHAGPIT, a variant found in HIV-1 MN, was also recognized.
- LHPAQAGPIA, a variant found in HIV-1 JH3, was recognized at high peptide concentrations.

HXB2 Location p24 (83–92)
Author Location Gag (215–224)
Epitope `VHPVHAGPIA`
Immunogen HIV-1 infection
Species (MHC) human (B55)
Donor MHC A11, A24, B55, B56
Country United Kingdom
Assay type Flow cytometric T-cell cytokine assay, Other
Keywords HAART, ART, immunodominance, TCR usage, memory cells
References Weekes *et al.* 2006
- The effect of HAART on the population size, phenotype and function of HIV- and HCMV-specific CTL clones was analyzed. It was determined that the clonal composition of gag and env HIV-specific CD8 T-cells did not change after HAART. Following HAART, the size of immunodominant HIV-specific CD8 T-cell clones was found to diminish even with the relative preservation of functional memory responses. Maintainance of such strong functional responses implied the preferential loss of HIV-specific cells that have reduced cloning efficiency in vitro. HCMV-specific CTL clones had different kinetics and phenotypes than HIV-specific CTL clones in the same subject.

HXB2 Location p24 (84–91)
Author Location p24
Epitope `HPVHAGPI`
Subtype D
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC A23, A24, B35, B58, Cw4, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Geels *et al.* 2005
- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

HXB2 Location p24 (84–91)
Author Location Gag
Epitope `HPVHAGPV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008
- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-B35-restricted epitope HPVHAGPV is from a subtype B peptide library, and is reactive as part of peptide HPVHAGPVAPGQMRE in a subtype B-carrying subject.

HXB2 Location p24 (84–92)
Author Location Gag (237–)
Epitope `HPVHAGPIA`
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (B*0702)
Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008
- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.

CTL CD8+

- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location p24 (84–92)
Author Location (C consensus)
Epitope `HPVHAGPIA`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*3910)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- HPVHAGPIA is an optimal epitope.

HXB2 Location p24 (84–92)
Author Location
Epitope `HPVHAGPIA`
Immunogen HIV-1 infection
Species (MHC) human (B07)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B07), an additional HLA (B55) was statistically predicted to be associated with this epitope.

HXB2 Location p24 (84–92)
Author Location (C consensus)
Epitope `HPVHAGPIA`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p24 (84–92)
Author Location (C consensus)
Epitope `HPVHAGPIA`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- HPVHAGPIA is an optimal epitope.

HXB2 Location p24 (84–92)
Author Location Gag
Epitope `HPVHAGPIA`
Subtype B, C, D
Immunogen HIV-1 infection
Species (MHC) human (B35, B7)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-B7-restricted epitope HPVHAGPIA is from a subtype B peptide library, and is reactive as part of peptide EWDRVHPVHAGPIAP in a subtype B-carrying subject. HLA-B35-restricted epitope HPVHAGPIA is from a subtype C peptide library, and is reactive as part of peptide HPVHAGPIAPGQMRE in a subtype D-carrying subject.

HXB2 Location p24 (84–92)
Author Location p24
Epitope `HPVHAGPIA`
Epitope name HA9(p24)
Subtype B
Immunogen HIV-1 infection

Species (MHC) human (B39, B7)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide sequence contains the exact sequence of a previously described HLA-B7 and -B39 optimal epitope, HPVHAGPIA, none of the 9 HLA-B7 carriers responded to it (author communication and Fig.1). No information regarding HLA-B39 reactivity is provided.

HXB2 Location p24 (84–92)
Author Location p24 (84–92)
Epitope HPVHAGPIA
Epitope name B7-HA9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 1/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection—10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 3/4 individuals had detectable responses to this epitope after STI.

HXB2 Location p24 (84–92)
Author Location p24 (84–92)
Epitope HPVHAGPIA
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location p24 (84–92)
Author Location p24 (84–92)
Epitope HPVHAGPVA
Epitope name B7-HA9 Gag
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), escape, early treatment, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The first infecting strain had the variant hpvhagpIa. The CTL response was higher to the second superinfecting variant, HPVHAGPVA.

HXB2 Location p24 (84–92)
Author Location (B consensus)
Epitope HPVHAGPVA
Epitope name HA9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A03, B07, Cw7
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location p24 (84–92)
Author Location Gag (216–224)
Epitope HPVHAGPIA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location p24 (84–92)
Author Location Gag
Epitope HPVHAGPIA
Epitope name B7-HA9(Gag)

CTL CD8+

Immunogen HIV-1 infection
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (84–92)
Author Location Gag
Epitope HPVHAGPIA
Epitope name HA9-B09
Subtype B, F
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Argentina
Keywords dynamics, HLA associated polymorphism
References Dilernia *et al.* 2008

- Dynamics of CTL escape mutations was studied theoretically by analyzing plasma samples from 302 subjects (collected over 20 years). HLA associated polymorphisms accumulated in a subtype-specific manner.
- Epitope HPVHAGPIA with anchor residues at H(P)VHAGPIA mutates to variant HPaHAGPvA and HPVHAGPvA; the latter increases over time.

HXB2 Location p24 (84–92)
Author Location Gag
Epitope HPVHAGPVA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-B7-restricted epitope HPVHAGPVA is from a subtype B peptide library, and is reactive as part of peptide HPVHAGPVAQMRE in a subtype B-carrying subject.

HXB2 Location p24 (84–92)
Author Location Gag
Epitope HPVHAGPVA
Epitope name Gag1156
Subtype C
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Epitope HPVHAGPVA elicits IFN-gamma ELISpot responses in 2/7 subjects; and bound HLA-B7 with high affinity in cell-based assays. Previously published HLA restriction of this epitope includes B7 (LANL database).

HXB2 Location p24 (84–92)
Author Location Gag
Epitope HPVHAGPIA
Epitope name Gag237
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- HPVHAGPIA is a Gag epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location p24 (84–92)
Author Location Gag
Epitope HVPHAGPIA
Epitope name Gag237
Subtype B, C, D
Immunogen HIV-1 infection
Species (MHC) human, mouse (B7 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope HVPHAGPIA of the HLA-B7 supertype bound most strongly to HLA-B*3501, -B*0702 and -B*5401 and also to -B*5301 but not to -B*5101. It was conserved 74% in subtype B, 38% in C and 25% in subtype D. 3/16 supertype B7 positive subjects mounted a positive ELISpot response to this epitope.

HXB2 Location p24 (84–92)
Author Location Gag
Epitope HPVHAGPVA
Subtype B, C, D, A1
Immunogen HIV-1 infection
Species (MHC) human
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- HPVHAGPVA was predicted to be supertype B7-restricted. It was recognized by at least 4 patients with restricting HLA supertype who were infected with several different HIV subtypes.

HXB2 Location p24 (84–100)
Author Location p24 (87–101)
Epitope HPVHAGPIAPGQMREPR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, HPVHAGPIAPGQMREPR, was detected within overlapping peptides LHPVHAGPIAPGQMREPR, LKETINEEAAEWDRLHPV and AAEWDRLHPVHAGPIA.

HXB2 Location p24 (87–101)
Author Location p24 (219–233 BRU)
Epitope HAGPIAPGQMREPRG
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Claverie *et al.* 1988

- One of 4 epitopes predicted then shown to stimulate HLA-A2 restricted CTL line.

HXB2 Location p24 (87–101)
Author Location p24 (87–101)
Epitope HAGPIAPGQMREPRG
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 19 patients recognized this epitope.

HXB2 Location p24 (87–101)
Author Location Gag
Epitope HAGPIAPGQMREPRG
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A1, A19, B*3501, B44, Cw16, Cw7; A*0201, A19, B14, B44, Cw16, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
References Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-A2 restricted epitope, HAGPIAPGQMREPRG was mutated to qAGPIAPGQMREPRG in the daughter D2 isolate.

HXB2 Location p24 (87–101)
Author Location Gag (219–233 LAI)
Epitope `HAGPIAPGQMREPRG`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Buseyne *et al.* 1993a

- Vertical transmission of HIV ranges from 13% to 39%.
- Primary assays showed that cytotoxic activity against at least one HIV protein detected in 70% of infected children.
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
- Patient EM28 (CDC P2A) had a CTL response to four epitopes in Gag.

HXB2 Location p24 (89–96)
Author Location p24
Epitope `GPIAPGQM`
Subtype D
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC A23, A24, B35, B58, Cw4, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

HXB2 Location p24 (89–96)
Author Location p24 (89–97)
Epitope `GPIAPGQM`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance, optimal epitope
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope GPIAPGQM was novel and conserved across clades B, C and D. It was putatively restricted by HLA-B*35.

HXB2 Location p24 (91–105)
Author Location (C consensus)
Epitope `IAPGQMREPRGSDIA`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*13)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location p24 (91–110)
Author Location p24 (223–242 SF2)
Epitope `IAPGQMREPRGSDIAGTTST`
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A2, A24, B13, B35.

HXB2 Location p24 (93–107)

Author Location Gag (225–239)
Epitope PGQMREPRGSDIAGT
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*03, A*24, B*35, B*40
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, superinfection, characterizing CD8+ T cells
References Yang *et al.* 2005b

- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
- An early response to this peptide was detected that waned prior to superinfection. The embedded epitope and HLA presenting molecule were not resolved. The initial and superinfecting strains carried a perfect match to the peptide sequence.

HXB2 Location p24 (94–104)
Author Location Gag (226–236)
Epitope GQMREPRGSDI
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*13)
Donor MHC A*0301, A*3001, B*1301, B*1402, Cw*0602, Cw*0802
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords epitope processing, immune evasion, viral fitness and reversion, HLA associated polymorphism
References Honeyborne *et al.* 2007

- To determine whether HLA-B*13-restricted CTL responses could partially explain low viremic loads in patients, a cohort of chronic C-clade infected subjects was studied. 6 novel B*13-restricted CTL epitopes were defined from both C- and B-clade viruses, 3 of which were within Gag. B*13-restricted CTL responses correlated with lower viremia, with most immunity targeted against Gag epitopes (p15, p17, p24). Gag epitope escape variants may exact a high viral fitness cost, mutations being seen within and around the optimal epitope.

HXB2 Location p24 (94–104)
Author Location p24
Epitope GQMREPRGSDI
Epitope name G11(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*13)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords optimal epitope
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B13-restricted epitope GQMREPRGSDI elicited an immune response in Chinese HIV-1 positive subjects as part of peptide IAPGQMREPRGSDIA.
- 10 of the 29 HLA-B13 carriers responded to GQMREPRGSDI-containing peptide with average magnitude of CTL response of 266 SFC/million PBMC.

HXB2 Location p24 (94–104)
Author Location
Epitope GQMREPRGSDI
Epitope name GI11
Immunogen
Species (MHC) human (B13)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B13 epitope.

HXB2 Location p24 (94–105)
Author Location Gag (229–239)
Epitope GQMREPRGSDIA
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p24 (101–120)
Author Location p24 (233–252 SF2)
Epitope GSDIAGTTSTLQEQIGWMTN
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A26, A30, B38.

CTL CD8+

HXB2 Location p24 (102–119)
Author Location Gag (245–252)
Epitope SDIAGTTSTVDEQIQWMY
Subtype HIV-2
Immunogen HIV-2 infection
Species (MHC) human
Country Guinea-Bissau
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords rate of progression, optimal epitope, HIV-2
References Leligdowicz *et al.* 2007

- To find the factors involved in attenuated disease course and long term non-progression, HIV-2 and immune control were studied. HIV-2 viral load was used as a predictor of patient survival. HIV-2 viral load correlated inversely with magnitude of IFN-gamma response, relative dominance of Gag-specific peptides' responses over other proteins' responses, and the breadth of different peptide-specific immune responses. The most frequently recognized peptides were in Gag protein, followed by Env and Pol, while Nef and accessory proteins (Vif, Vpx, Vpr, Tat and Rev) rarely elicited responses. The 6 most recognized peptides were clustered in a highly conserved region of Gag.
- This peptide, SDIAGTTSTVDEQIQWMY, was recognized by 10 out of 65 subjects. It is found in the 149 amino-acid long HIV-2 proteome region of Gag 175-323.

HXB2 Location p24 (105–119)
Author Location
Epitope AGTTSTLQEQIGWMT
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A11, A2, B60, B7; A2, A24, B15, B40; A11, A2, B44, B60
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 60 (NIH ARRP Cat# 7931), AGTTSTLQEQIGWMT, which contains an epitope restricted by HLA-A2 in different patients, elicited the following CTL responses: (1) >100 sfc/million PBMC for 22+ years in a living non-progressor (2) >100 sfc/million PBMC for 22+ years in another living non-progressor (3) for 12+ years in a former non-progressor who succumbed to non-AIDS death.

HXB2 Location p24 (107–115)
Author Location Gag (239–247 SF2)
Epitope TTSTLQEQI
Immunogen vaccine
Vector/Type: Listeria monocytogenes *Strain:* B clade HXB2 *HIV component:* Gag
Species (MHC) mouse (H-2K^d)
References Mata *et al.* 1998

- BALB/c mice were immunized with recombinant Listeria monocytogenes (Lm-Gag) expressing HIV-1 HXB2 Gag.
- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted L. monocytogenes antigens are processed and presented by both class I and class II pathways.

HXB2 Location p24 (107–115)
Author Location Gag
Epitope TTSTLQEQI
Epitope name T
Subtype A, B, C
Immunogen vaccine
Vector/Type: DNA with CMV promotor, modified vaccinia Ankara (MVA), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade, B clade, C clade Du422, Other *HIV component:* Gag, Nef, RT
Species (MHC) mouse (H-2K^d)
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords subtype comparisons, vaccine-induced epitopes, variant cross-recognition or cross-neutralization, antagonism
References Larke *et al.* 2007

- Cross-clade vaccine recognition was studied using either single-, multi or several anatomically separated single-clade vaccines. Limited cross-clade response was seen with single-clade administrations. Multi-clade vaccines gave immune interference (antagonism and original antigenic sin), reducing CTL response. Simultaneously administered but anatomically separated vaccines from clades A, B, C decreased antagonism and increased immune responses.

HXB2 Location p24 (108–117)
Author Location Gag
Epitope TSTLQEQIGW
Epitope name TW10
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather

than IFN-gamma responses, showed better correlation with the plasma viral variants.
- Several mutations in this epitope were found to potentially act as CTL escape mutations. These are: E245D, G248E, and a triple mutation Q244T/I247V/G248A.

HXB2 Location p24 (108–117)
Author Location p24 (108–118)
Epitope TSTLQEQIGW
Epitope name TW10
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country United Kingdom, Kenya
Assay type CD8 T-cell Elispot - IFNγ
Keywords TCR usage, structure, characterizing CD8+ T cells
References Gillespie *et al.* 2006
- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B*57-peptide complexes were studied.
- In addition, immunodominancy of the previously mapped B*57 epitopes during chronic infection was assessed. KGFNPEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

HXB2 Location p24 (108–117)
Author Location Gag (241–249)
Epitope TSTLQEQIGW
Epitope name TW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Donor MHC A*310102, A*6603, B*440302, B*570301, Cw*040101, Cw*07
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords rate of progression, escape, viral fitness and reversion, drug resistance
References Bailey *et al.* 2007
- In this study the entire HIV-1 genome was analyzed before and after virologic escape for the first time and escape mutations were temporarily associated with an increased viremia in an otherwise B*57-elite controller of viral load. It is suggested that HLA-B*57-restricted CTL mutations were the major cause of escape because other multiple drug resistance mutations in Pol and RT (M184V and T215Y) did not result in a marked increase in viral replication capacity in vitro.
- CTLs detecting this Gag epitope, TSTLQEQIGW, were detectable and levels remained unchanged over 20 months. TW10 changed over time from TSTLQEQIaW to TSTLQEQIgW to TSTLQEQIeW to TSTLQEQIdW.

HXB2 Location p24 (108–117)
Author Location Gag (240–249)
Epitope TSTLQEQIGW
Epitope name TW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, compensatory mutation
References Bailey *et al.* 2008
- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Supresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- In this epitope, all isolates from both patients contained T242N mutation, the ES had also G248A mutation (TSnLQEQIaW) and the Progressor had also G248T mutation (TSNLQEQItW). In the previous studies T242N has been shown to affect the fitness of the virus, and compensatory mutations were shown to restore the fitness of T242N containing isolates. Here, the isolates from the Progressor, but not the ES had compensatory substitutions (H219Q and M228I). The uncompensated T242N mutation likely contributes to the reduced fitness of the isolates from the ES.

CTL CD8+

HXB2 Location p24 (108–117)
Author Location p24 (240–249)
Epitope TSTLQEQIAW
Epitope name TW10
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country Kenya
References Peters *et al.* 2008a
- Gag sequences from 468 HIV-1 positive sex workers from the Kenyan Pumwani cohort were analyzed to bioinformatically identify positively selected residues that could be related to antigen processing. Mutation effects on disease progression were followed by mean CD4 counts. This method is also one way of identifying potential CTL epitopes and classifying them.
- A Gag positive selection map was generated and sites were classified as beneficial or harmful to HIV. They were correlated to antigen processing (proteasomal cleavage), antigen presentation (TAP transport efficiency) and T-cell receptor binding.
- p17 and p24's structural constraints limited their diversity, while p7-p1-p6 showed a higher average entropy.
- This HLA-B*57-restricted immunodominant epitope, TSTLQEQIAW, is located in the p24 region.

HXB2 Location p24 (108–117)
Author Location Gag (240–249)
Epitope TSTLQEQIGW
Epitope name TW10
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country Canada, South Africa
Keywords escape

References Carlson *et al.* 2008

- A statistical model, the phylogenetic dependency network (PDN), was developed to differentiate the confounding effects of codon variation, linkage disequilibrium of HLA alleles and HIV phylogeny from HLA-associated evolution including HIV selection by HLA-pressure and codon evolution.
- This approach was applied to 2 cohorts of 1144 Gag sequences from HIV-infected individuals, generating associations between HIV codons themselves and codons with HLA alleles. Results generated predicted escapes that confirmed that escape kinetics and compensating mutations are consistent across clades. General patterns of covariation and CTL adaptation were determined. Some clade-based differences were identified.
- HLA-B*57-restricted TW10, TSTLQEQIGW, has an escape mutation, T242N, TSnLQEQIGW which can partially abrogate B*57 binding, but comes with fitness cost. PDN confirms that partial compensatory mutations to offset fitness cost are found in H219Q, I223V and M228I.
- T242N, TSnLQEQIGW, also predicts G248A, TSTLQEQIaW as well as E210D. G248A, TSTLQEQIaW, predicts compensatory substitutions V218A and M228V; while G248T, TSTLQEQItW, predicts H219Q and M228I. These are examples of distal compensations where compensatory mutations are distal in three-dimensional space but alter functional dependencies.
- A putative epitope, pSG9, showed escape that was correlated with escape at this epitope, TW10 (as well as epitopes IW9, ISPRTLNAW, and QW9, Gag 308-316).

HXB2 Location p24 (108–117)
Author Location p24 (108–117)
Epitope `TSTLQEQIGW`
Epitope name TW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*57, B*58)
Country Switzerland
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, viral fitness and reversion, HLA associated polymorphism
References Frater *et al.* 2007

- To study whether CTL responses restricted by "good" HLA I molecules exert stronger immune selection than other HLA I molecules, 54 and 70 optimal epitopes within HIV-1 Gag, Pol and Nef genes for Caucasian and African cohorts were tested in patients over a mean of 14 months. "Good", advantageous HLA allele-restricted epitopes were much more polymorphic than epitopes restricted by other, non-advantageous HLA in patients, suggesting that benefits associated with HLA Class I alleles of elite controllers of disease progression are epitope-specific. Such "driver" epitopes with high polymorphism had high frequency of immune response, allowing them to be ranked for recognition and polymorphism.
- Patients with higher proportions of mutated epitopes also had lower plasma viral loads, and mean epitope variability correlated negatively with relative hazard of disease progression.
- Variants TSnLQEQIGW and TSTLQEQIaW at positions 3 and 9, were present in 86.7% of HLA-matched patients and 28.3% of HLA-unmatched patients. Phylogenetic analysis identified the threonine at position 3 to be under strong positive selective pressure.

HXB2 Location p24 (108–117)
Author Location Gag
Epitope `TSTLQEQIAW`
Epitope name TW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*57, B*58)
Country Canada
Keywords HLA associated polymorphism
References Brumme *et al.* 2008b

- A large chronically infected, treatment naïve cohort was studied to identify and organize HLA I-associated polymorphisms in Gag into an immune escape map. Insertion polymorphisms at p17 C-terminus were associated with HLA-B*44, -A*32, -C*05. Inverse correlations were found between number to HLA-associated sites and pVL as well as escaped Gag residues and pVL. pVL positively correlates with CD4 T-cell count. No enrichment for HLA-associated polymorphisms are seen at anchor residues, showing that CTL escape is primarily not through abrogation of peptide-HLA binding.
- B*57/B*58-restricted p24 TW10 epitope has HLA-associated substitutions at codons 242 and 248.

HXB2 Location p24 (108–117)
Author Location p24 (240–249)
Epitope `TSTLQEQIGW`
Epitope name TW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*57, B*58)
Country Australia, Canada, Germany, United States
Keywords escape, immune evasion, viral fitness and reversion, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- Escape (and reversion) rates for B*57-restricted epitopes were highest for Gag-TW10 (TSTLQEQIGW) > RT-IW9 (IVLPEKDSW) > Nef-YY9 (YTPGPGIRY) > Nef-HW9 (HTQGYFPDW) > Gag-IW9 (ISPRTLNAW) > Gag-KF11 (KAFSPEVIPMF) .
- HLA-B*58 and B*57-associated substitutions within optimally defined epitope TSTLQEQIGW are at positions T3 and G9, TStLQEQIgW. TW10, restricted by the protective HLA-B*57 allele, was most rapidly escaping, evolving and frequently targeted (70%). Escape mutations at codon 172 were the most rapidly reverting in Gag-TW10.

HXB2 Location p24 (108–117)
Author Location Gag (240–249)
Epitope TSTLQEQIAW
Epitope name TW10
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*57, B*5801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, viral fitness and reversion, compensatory mutation
References Chopera *et al.* 2008

- Transmission of HIV-1-escape variants from individuals with protective HLA-B*57/-B*5801 alleles to those without these alleles was studied to determine if infection with such replication-deficient mutants offered any advantage to the new host. Dependency between slower rate of disease progression in the newly infected subject and protective genotype of the infecting individual was suggested.
- 2 Gag polymorphisms in epitopes TW10 (TSTLQEQIAW) and ISW9 (ISPRTLNAW) associated with low viral loads and high CD4+ counts during acute and chronic infection were followed in HLA-B*57 and HLA-B*5801 negative subjects for minimum 12 months. A correlation was suggested between rate of disease progression and genotype of the individual HLA-B*57/-B*5801 positive) from whom virus was contracted.
- Epitope TW10, TSTLQEQIAW, was found with mutation T242N to TSnLQEQIAW, an escape mutation in 6/21 subjects. 2 of 9 individuals carrying T242N and another mutation, A146X, had compensating H219Q to partially restore replicative fitness. While A146X/T242N+ subjects show no significant difference from A146X/T242N- subjects in magnitude or breadth of CTL response to other Gag-epitope-containing peptides, they do have lower viremia.
- Over time, reversion to consensus sequence at position 242 was seen. Other variants of TW10 found were (T)TSTLQEQIAW(i), (T)TSnLQEQIvW(M), (T)TSsLQEQIAW(M), (T)TSTLQEQvAW(M), (T)TSTLaEQIAW(M) and (T)TSTLQEQIAW(i).

HXB2 Location p24 (108–117)
Author Location Gag (240–249)
Epitope TSTLQEQIGW
Epitope name TW10
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human (B*57, B*5801)
Assay type Other
Keywords escape, viral fitness and reversion
References Martinez-Picado *et al.* 2006

- Escape patterns of TSTLQEQIGW epitope were studied in 258 C-clade infected subjects from Durban, South Africa, and 187 B-clade infected subjects from diverse sources. 206 subjects were B*57/5801-positive.
- TS[t/n]LQEQIGW (T242N) escape mutation was present in 153/206 of B*57/5801-positive subjects and only in 2/239 B*57/5801-negative subjects.
- TS[t/n]LQEQIGW (T242N) mutation reduced viral replicative capacity based on in-vitro growth competition assays, supporting the inference of a fitness cost of T242N mutaion from observations of reversion in B*57/5801-negative subjects.
- Structural analysis suggested a critical role for T in Gag 242 position in defining the start point and in stabilizing helix 6 with p24 Gag, explaining the significant cost of escape.
- TW10-associated mutations were found in Gag positions 248,250,252 and for each a strong association with a potential compensatory mutation(s) was identified.

HXB2 Location p24 (108–117)
Author Location p24 (240–249 LAI)
Epitope TSTLQEQIGW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*5701 epitope.

HXB2 Location p24 (108–117)
Author Location
Epitope TSTLQEQIGW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords rate of progression, immunodominance
References Migueles & Connors 2001

- HLA B*5701 was found in a very high frequency in HIV-1 infected non-progressors, 11/13 (85%) versus 19/200 (9.5%) of progressors. Non-progressors tended to have an immune response that was highly focused on four p24 epitopes that were presented by B*5701, ISPRTLNAW, KAFSPEVIPMF, TSTLQEQIGW, and QASQEVKNW.

HXB2 Location p24 (108–117)
Author Location
Epitope TSTLQEQIGW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords rate of progression, immunodominance
References Migueles & Connors 2001

- CTL activity was monitored in 27 individuals, including 10 LTNP with an over-expression of HLA B*5701 – these individuals have viral loads below the threshold of infection without therapy, and their immune response tends to be focused on peptides that contain B*5701 epitopes ISPRTLNAW, KAFSPEVIPMF, TSTLQEQIGW, and QASQEVKNW.
- CTL responses are broader in B*5701+ individuals with progressive viremia than those that control viremia.
- The HLA-A*0201 SLYNTVATL epitope response was not as strong in individuals that carried both A2, B57.

HXB2 Location p24 (108–117)
Author Location
Epitope TSTLQEQIGN
Subtype B

CTL CD8+

Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Assay type Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Migueles *et al.* 2003

- cDNA Gag sequences from a set of 17 HLA-B*5701+ progressors and 10 LTNPs were obtained, and the variation in four p24 B*5701 epitopes examined. Sequence variants were more common ($p < 0.01$) in the epitopes in the progressors (median 3, range 1-7) than LTNPs (median 2, range 0-4).
- In general, use of the autologous protein in a target cell did not diminish the overall CD8+ T-cell responses.

HXB2 Location p24 (108–117)
Author Location p24 (1513–)
Epitope TSTLQEQIGW
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Country Australia
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, HLA associated polymorphism
References Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore et al., Science 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- The third position of this epitope TStLQEQIGW has a mutational pattern that is correlated with the host carrying HLA B*5701.

HXB2 Location p24 (108–117)
Author Location p24 (108–117)
Epitope TSTLQEQIGW
Epitope name TST
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells
References Turnbull *et al.* 2006

- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.
- This epitope, B57-TST (that is strongly associated with delayed progression to AIDS) and its alanine-substituted variants are efficiently cross-recognized.

HXB2 Location p24 (108–117)
Author Location p24
Epitope TSTLQEQIAW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5702, B*5703, B*5801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- TSTLQEQIAW is a previously described HLA-B*5702, -B*5703 and -B*5801-restricted epitope (part of Gag reacting peptide RGSDIAGTTStLQEQIAWMTS/RGSDIAGTTSTLQEQiAWMTS) that contains a B*5703-associated reversion at residue I (TSTLQEQiAW) and an HLA-B*5702, -B*5703 or -B*5801-associated reversion at residue T (TStLQEQIAW).

HXB2 Location p24 (108–117)
Author Location (C consensus)
Epitope TSTLQEQIAW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5703)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the T3 and A9 residues of TSTLQEQIAW are associated with the presence of the HLA presenting molecule in the host.
- TSTLQEQIAW is cross presented by both B*5801 and B*5703.

HXB2 Location p24 (108–117)
Author Location Gag
Epitope TSTLQEQIAW
Epitope name TW10
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5703, B*5801)
Country South Africa

Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords rate of progression, escape, HLA associated polymorphism
References Frater *et al.* 2007

- To study whether CTL responses restricted by "good" HLA I molecules exert stronger immune selection than other HLA I molecules, 54 and 70 optimal epitopes within HIV-1 Gag, Pol and Nef genes for Caucasian and African cohorts were tested in patients over a mean of 14 months. "Good", advantageous HLA allele-restricted epitopes were much more polymorphic than epitopes restricted by other, non-advantageous HLA in patients, suggesting that benefits associated with HLA Class I alleles of elite controllers of disease progression are epitope-specific. Such "driver" epitopes with high polymorphism had high frequency of immune response, allowing them to be ranked for recognition and polymorphism.
- Patients with higher proportions of mutated epitopes also had lower plasma viral loads, and mean epitope variability correlated negatively with relative hazard of disease progression.
- Variant TSnLQEQIGW at position 3 was often found in conjunction with a second polymorphism at positions 5, 8 or 9.

HXB2 Location p24 (108–117)
Author Location p24 (240–249 LAI)
Epitope TSTLQEQIGW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5801)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*5801 epitope. Variant TSTveEQqiW also noted.

HXB2 Location p24 (108–117)
Author Location Gag (240–249)
Epitope TSTVEEQIQW
Epitope name TSTV
Subtype HIV-2
Immunogen HIV-2 infection
Species (MHC) human (B*5801)
Country Gambia
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells, HIV-2
References Gillespie *et al.* 2005

- CD8 T-cell responses were evaluated and compared in HIV-1 and HIV-2 infected individuals. A significantly greater magnitude and breadth of Gag-specific responses were found in HIV-1 infected individuals, possibly because of undetectable viral load in HIV-2 infected individuals. This finding suggests that responses in HIV-2 infection reflect antigen load in plasma, as is the case in HIV-1 infection. No correlation was found between immune control of HIV-2 and the frequency of perforin-expressing virus-specific CD8 T-cells.
- 4/5 HIV-2-infected B*5801-positive subjects recognized TSTVEEQIQW, the HIV-2 version of this epitope. 0/4 HIV-1-infected B*5801-positive subjects responded to TSTLQEQIGW, the HIV-1 version of this epitope.

HXB2 Location p24 (108–117)
Author Location Gag (240–249)
Epitope TSTLQEQIGW
Epitope name TSTL
Immunogen HIV-1 infection
Species (MHC) human (B*5801)
Country Gambia
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells, HIV-2
References Gillespie *et al.* 2005

- CD8 T-cell responses were evaluated and compared in HIV-1 and HIV-2 infected individuals. A significantly greater magnitude and breadth of Gag-specific responses were found in HIV-1 infected individuals, possibly because of undetectable viral load in HIV-2 infected individuals. This finding suggests that responses in HIV-2 infection reflect antigen load in plasma, as is the case in HIV-1 infection. No correlation was found between immune control of HIV-2 and the frequency of perforin-expressing virus-specific CD8 T-cells.
- 4/5 HIV-2-infected B*5801-positive subjects recognized TSTVEEQIQW, the HIV-2 version of this epitope. 0/4 HIV-1-infected B*5801-positive subjects responded to TSTLQEQIGW, the HIV-1 version of this epitope.

HXB2 Location p24 (108–117)
Author Location (C consensus)
Epitope TSTLQEQIAW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the T3 residue of TSTLQEQIAW are associated with the presence of the HLA presenting molecule in the host.
- TSTLQEQIAW is cross presented by both B*5801 and B*5703.

HXB2 Location p24 (108–117)
Author Location Gag (1513–)
Epitope TSTLQEQIGW
Epitope name TW10
Immunogen HIV-1 infection
Species (MHC) human (B*5801)
Country Australia
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, HLA associated polymorphism
References Bhattacharya *et al.* 2007

HXB2 Location p24 (108–117)

CTL CD8+

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore et al., Science 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- This HLA-B*5801 HIV mutation association was only picked up using statistics that incorporate the phylogeny. The Thr at TStLQEQIGW at the third position is the HLA-correlated amino acid. A B57 association was also found for this cross-presented epitope.

HXB2 Location p24 (108–117)
Author Location p24
Epitope TSTLQEQIGW
Immunogen peptide-HLA interaction
Species (MHC) human (B*5801)
Assay type Tetramer binding
Keywords binding affinity
References Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, TSTLQEQIGW (MHC Class I restriction, serotype Bw4Ile80) complexed with MHC B*5801 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C.

HXB2 Location p24 (108–117)
Author Location Gag (241–250 HIV-2 ROD)
Epitope TSTVEEQIQW
Epitope name TSTV
Subtype HIV-2
Immunogen HIV-2 infection
Species (MHC) human (B*5801)
Donor MHC A*0101, A*2402, B*07, B*5801
Country India
Keywords escape, HIV-2
References Kageyama *et al.* 2008

- This longitudinal case study found 3 amino acid substitutions - V286I in Gag and K303T, N337K/R in Env with an increase in HIV-2 load. Sites encompassing these 3 substitutions are candidates for HIV-2 epitopes.
- Epitope TSTVEEQIQW of Gag 241-250 (relative to strain SMM239), restricted by HLA-B*5801, showed no changes in this patient.

HXB2 Location p24 (108–117)
Author Location (C consensus)
Epitope TSTLQEQIAW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords cross-presentation by different HLA, characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p24 (108–117)
Author Location p24 (233–252)
Epitope TSTLQEQIGW
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Bernard *et al.* 1998

- This study focuses on six rare long-term survivor HIV-infected people who were infected for many years without exhibiting immune dysregulation – such immunologically normal HIV-infected (INHI) cases occur at a frequency between 0.1 and 1% in the infected population.
- No direct CTL were found in any of the six INHIs, but above background CTLp activity was found in 3/6 INHIs.
- Epitope sequences were deduced from larger reactive peptides based on HLA binding motifs – XSXXXXXXXW is a B57 binding motif, and CTL activity against TSTLQEQIGW has been found in two other B57 long-term non-progressors.

HXB2 Location p24 (108–117)
Author Location Gag (SF2)
Epitope TSTLQEQIGW
Epitope name TW10
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords HAART, ART, acute/early infection
References Goulder *et al.* 2001a

- Dominant epitope in acute infection in patient PI004, who did not receive any antiviral therapy.
- 1-2 months post seroconversion, subject PI004 displayed a significant decrease in TW10 peptide recognition, followed by an increased CTL response against epitope SL9, SLYNTVATL and other epitopes.
- Three CTL responses, to epitopes TSTLQEQIGW, ISPRTLNAW, and KAFSPEVIPMF were evident early after infection; CTL responses to SLYNTVATL, QASQEVKNW, EIYKRWII, and FLKEKGGL were detectable at 5 months post-infection and beyond.

HXB2 Location p24 (108–117)
Author Location p24 (108–117)
Epitope TSTLQEQIGW
Epitope name TST
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords HAART, ART, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- None of the 8 study subjects recognized this epitope but none were HLA B57+.

HXB2 Location p24 (108–117)
Author Location p24 (108–117)
Epitope TSTLQEQIGW
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (108–117)
Author Location p24
Epitope TSTLQEQIGW
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2002

- Neisseria gonorrhea cervititis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
- Ghonorrhea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

HXB2 Location p24 (108–117)
Author Location p24
Epitope TSTLQEQIGW
Epitope name TST
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords HAART, ART, supervised treatment interruptions (STI)
References Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFN? Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

HXB2 Location p24 (108–117)
Author Location Gag (147–155)
Epitope TSTLQEQIAW
Epitope name TW10
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords epitope processing, escape
References Draenert *et al.* 2004b

- 174 people who have C clade infections were studied – those who carried B57 have 2 positions in which their HIV Gag consensus is different than the C consensus. One mutation is within this epitope, TW10, at position 3, and is believed to be an anchor residue. The other is in the N-terminal flanking position of the epitope ISPRTLNAW and is thought to impact processing.

HXB2 Location p24 (108–117)
Author Location Gag (240–249)
Epitope TSTLQEQIAW
Epitope name TW10
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords escape, viral fitness and reversion
References Leslie *et al.* 2004

- TSTLQEQIAW (the consensus form in the C clade) responses dominate the immune response in HLA-B57 individuals, and this epitope is also recognized in HLA-B5801 individuals. TSnLQEQIAW is shown to be an escape mutant correlated with HLA-B57 and HLA-B5801 alleles. The variant can be transmitted to HLA-B57/B5801 negative individuals, but reverts to wild-type in those. A second escape mutation within the epitope is, however, maintained after transmission; TSNLQEQIGW is the most common from of the epitope in the B clade, and a G substitution to some other amino acid, often A, was frequently noted in B57+ individuals; transmission of these variants persist in the new host.

HXB2 Location p24 (108–117)
Author Location p24 (108–117)
Epitope TSTLQEQIGW
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

CTL CD8+

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 7 patients recognized this epitope.

HXB2 Location p24 (108–117)
Author Location (B consensus)
Epitope TSTLQEQIGW
Epitope name TW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country United Kingdom
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords immunodominance, escape, characterizing CD8+ T cells
References Allen *et al.* 2004

- This study characterizes an escape mutation in a C-terminal flanking residue of the HLA-A3 gag p17 KK9 epitope that inhibits processing, and is embedded in the overlapping HLA-A3 RK9 epitope.
- The immune response was tracked in subject AC-38. The acute immunodominant response was to the B57 TW10 epitope; this response declined following viral escape (tsNlqeqigw) by day 64. The p17 KK9 and RK9 became immunodominant, but then declined as the escape mutation arose. TW10 is 1 of 3 other strong responses that persisted, along with 1 sub-dominant response.

HXB2 Location p24 (108–117)
Author Location Gag
Epitope TSTLQEQIGW
Epitope name TW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Two escape mutations, at positions 3 (T242N) and 9 (G248A), were found in the most polymorphic residues in the epitope. Both were shared between clades B and C. Both were significantly more variable in persons expressing HLA-B57.

HXB2 Location p24 (108–117)
Author Location p24 (240–249)
Epitope TSTLQEQIAW
Epitope name TW10
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Ethiopia
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance, escape, variant cross-recognition or cross-neutralization
References Currier *et al.* 2005

- Epitope sequence variation and CD8 T-cell responses were analyzed in C subtype infected HLA-B57-positive individuals from Ethiopia. KF11 was the immunodominant response.
- 9/10 B57 subjects had the T3N TSnLQEQIAW substitution relative to the C consensus, while this form was found in only 2/9 B57- subjects, so it appears to be selected and an immune escape form (p=0.001). Both forms of the TW10 epitope (TSTLQEQIAW and TSnLQEQIAW) were tested in 2 B57-positive subjects; neither responded. The authors suggest this may be due to the dominance of the TW10 response in acute infection, as the response may have been lost by the time of sampling.

HXB2 Location p24 (108–117)
Author Location Gag
Epitope TSTLQEQIGW
Epitope name TW10
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type Other
Keywords rate of progression, escape
References Gao *et al.* 2005b

- Three distinct HLA alleles known to alter the rate of AIDS progression were studied. B*57-mediated protection occurs early in infection and the protective effect of this allele subsides after CD4 cell count drops. In contrast, B*27 shows no protection against progression to CD4<200, but rather delays progression to an AIDS-defining illness after the CD4 counts have dropped. B*35-mediated rapid progression to AIDS is probably a function of early decline in CD4 counts.
- TW10 is typically the immunodominant B57 epitope. TW10 responses are rapid, and escape occurs but presumably with a fitness cost, because reversion occurs after the escape variant is transmitted to a B57- person. High CD4 counts may be maintained in individuals because of immune selection for a less fit form of the virus.

HXB2 Location p24 (108–117)
Author Location Gag (240–249)
Epitope TSTLQEQIAW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A*3001, A*66, B*4201, B*5802, Cw*0602, Cw*1701; A*66, A*68, B*57, B*5802, Cw*0602, Cw*0701
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, acute/early infection
References Pillay *et al.* 2005

- HIV-specific CTLs in infants were shown to be able to select for viral escape variants early in life, despite a lack of escape with the same CTL specificity in the mother. Infant CTL responses may be compromised by transmission of escape variants that arose in the mother and also those that arose in the father, if the father was the source of the mother's infection.
- TSTLQEQIAW is the C consensus form of the epitope and the autologous form in the mother was TSTLQEQItW, and this was the form transmitted to her infant. The mother does not carry B57, and the B57 escape footprint was inherited paternally. By 33 weeks a new dominant form of the epitope had emerged in the infant, TSnLQEQIAW, and the consensus form was also present in the infant.

HXB2 Location p24 (108–117)
Author Location p24
Epitope `TSTLQEQIGW`
Epitope name B57-TW10(p24)
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.
- This epitope, TSTLQEQIGW (TW10), elicits the HLA-B57 restricted response that is most dominant of the immune responses generated.

HXB2 Location p24 (108–117)
Author Location
Epitope `TSTLQEQIGW`
Epitope name B57-TW10
Immunogen
Species (MHC) (B57)
Keywords review, immunodominance, escape, vaccine antigen design
References Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.

HXB2 Location p24 (108–117)
Author Location Gag
Epitope `TSTLQEQIGW`
Epitope name TW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Australia, Canada, United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, escape, immune evasion, viral fitness and reversion, optimal epitope
References Streeck *et al.* 2007a

- To characterize HIV-1 proteome areas that are targeted in early, effective CTL responses, two cohorts were studied. Responses in early infection were against fewer epitopes and of lower magnitude than during chronic infection. While no region of the proteome was favored, Nef was the predominant target based on length of proteins.
- When based on the expression of protective versus nonprotective HLA I alleles, it was found that HLA-B27 and -57 possessing slow progressors to disease directed the majority of their responses to Gag in early infection, as opposed to those with HLA-B*3501 or B*3502, i.e. rapid progressors to AIDS, who had negligible responses to Gag. As compared with HLA-B57-/B27- subjects and HLA-B35 subjects, HLA-B57+/27+ subjects responded most to the p24 component of Gag. By using overlapping peptides within Gag p24, two were picked as being consistently targeted, and both contained previously described epitopes TSTLQEQIGW and KRWIIL-GLNK.
- TSTLQEQIGW, i.e. epitope TW10 is one of two immunodominant epitopes targeted during early infection in long term non-progressors to AIDS. After the acute phase of infection most subjects develop a variant, TSnLQEQIGW. Reversion to wild type is seen rapidly upon viral transmission to an HLA-B57- individual.

HXB2 Location p24 (108–117)
Author Location p24
Epitope `TSTLQEQIGW`
Epitope name TW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- 61 days after first testing, epitope TSTLQEQIGW showed no variation in a treated patient. Previously published HLA-restriction for TW10 is HLA-B57.

HXB2 Location p24 (108–117)

Author Location Gag
Epitope TSTLQEQIGW
Epitope name TW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- TW10, TSTLQEQIGW, is a known HLA-B57-restricted epitope used as a positive control for eliciting CTL IFN-gamma response.

HXB2 Location p24 (108–117)
Author Location p24
Epitope TSTLQEQIGW
Epitope name TW10
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Keywords review, rate of progression, immunodominance, escape, acute/early infection, viral fitness and reversion
References Goulder & Watkins 2004

- This paper is a review of the role of CTL in HIV infection, and it uses the TW10 epitope as an example. HLA B*57 and B*5801 both can present this epitope, and are associated with successful containment of HIV infection. The early response to TW10 is immunodominant, and often followed by rapid escape due to the T->N substitution, tsNlqeqigw. Some long term survivors do not carry the escape form, possibly because the CTL response to this epitope is able to suppress viremia. Others do carry the N escape form, and presumably control viremia due to viral attenuation; in support of this the N rapidly back mutates to T in a new host, so there is likely to be a high fitness cost. In contrast, the epitope sometimes contains a G-> A substitution at position 9, and the A can persist in a new host after transmission.

HXB2 Location p24 (108–117)
Author Location Gag
Epitope TSTLQEQIGW
Epitope name TW10
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords responses in children, mother-to-infant transmission, escape
References Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children did not respond to TSTLQEQIGW but showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.
- TW10 was found to be more frequently recognized by adults than by children. Among B57-positive subjects, TW10 was recognized by 10 out of 12 acutely infected adults, 11/22 chronically infected adults, and only 1/14 infected children. All 14 children carried mutations of this epitope, commonly T3N and G9A (TSnLQEQIaW), but the children were able to recognize the autologous variant. These mutations were rare in adults. One child carried T3N, Q5A, and G9A, and also recognized the autologous variant, TSnLaEQIaW.

HXB2 Location p24 (108–117)
Author Location p24
Epitope TSTLQEQIGW
Epitope name TW10
Immunogen
Species (MHC) (B*5801, B57)
Keywords review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion
References Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

HXB2 Location p24 (108–117)
Author Location Gag (240–249)
Epitope TSTLQEQIGW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Keywords HLA associated polymorphism
References Rousseau *et al.* 2008

- 3 phylogenetic correction methods—MLL (maximum likelihood character state analysis followed by likelihood ratio test), MLF (maximum likelihood character state analysis followed by Fisher test), and parsimony character state analysis were used to identify points in the HIV-1 subtype C proteome that conferred susceptibility or resistance to CTLs. Associations of HLA-epitope combinations that were inferred to be susceptible or resistant were organized into immunological sets that would help identify the best residues and genes as candidates for vaccines. While all proteins were interrogated, Gag, Pol, Env and Nef were focused upon. Amino acid changes were evaluated for association with plasma viral load.

- Proteome maps may be seen at `http://www.hiv.lanl.gov/content/immunology/hlatem/study5/index.html` with information showing single or multiple sites involving escape and reversion.
- HLA- B and -C alleles associated more with aa changes than HLA-A, suggesting that the former two are more important in driving viral evolution.
- The ratio of susceptible to resistant residues in HIV proteins was in descending order, Vpr>Gag>Rev>Pol>Nef>Vif>Tat>Env>Vpu, showing that epitopes from the earlier proteins are more conserved owing to viral fitness cost upon mutation.
- This previously described Gag p24 HLA B*57 or B*5801-restricted epitope, TSTLQEQIGW was susceptible at T3. Variants TSnLQEQIGW and TSsLQEQIGW were resistant to CTL response, but associated with lower viral loads. This epitope is 1 of 7 that suggest a fitness cost to immune escape.

HXB2 Location p24 (108–117)
Author Location p24 (235–243)
Epitope `TSTLQEQIGW`
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B57, B58)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- TSTLQEQIGW cross reacts with both A and B clades.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location p24 (108–117)
Author Location p24 (108–117)
Epitope `TSTLQEQIGW`
Immunogen HIV-1 infection
Species (MHC) human (B57, B58)
Donor MHC A1, A26, B35, B57, Cw*0601, Cw4; A1, A30, B42, B52, Cw17, Cw7; A*0201, A1, B44, B57, Cw5, Cw6
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins, cross-presentation by different HLA
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- This epitope was recognized in three of the acutely infected individuals and was presented by both HLA-B57 and B58.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.

HXB2 Location p24 (108–117)
Author Location Gag (240–249)
Epitope `TSTLQEQIGW`
Epitope name gag 240-9
Immunogen HIV-1 infection, HIV-2 infection
Species (MHC) human (B57, B58)
Country Gambia
Assay type Intracellular cytokine staining
Keywords escape, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells, HIV-2
References Lopes *et al.* 2003

- CD8+ T cells from HIV-2 infected patients had more polyclonal TCR responses than HIV-1 infected patients, who tended to have oligoclonal responses. This results in limited plasticity of T cell responses to amino acid substitutions within epitopes in HIV-1 infections. HIV-2-specific CD8+ T-cells showed a more diverse TCR usage associated with enhanced CD8 expansion and IFN-gamma production on cross-recognition of variant epitopes.
- This peptide was recognized by a CD8+ T-cell clonotype with Vbeta5.1 usage in one HIV-1 infected patient, and all HIV-1 patients had narrow TCR usage, while HIV-2 patients used multiple TCR Vbeta chains. The HIV-2 variant of this peptide is: tstVEeqiQw. 5/6 HIV-2 infected individuals could recognize both the HIV-1 and HIV-2 peptides, while 0/5 HIV-1 infected patients that could react with the HIV-1 peptide could also react with the HIV-2 peptide.

HXB2 Location p24 (108–117)
Author Location p24 (108–117)
Epitope `TSTLQEQIGW`
Epitope name TW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57, B58)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, subtype comparisons, acute/early infection
References Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (ANC) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants

are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- Epitope sequences for this eptiope, TW10 are invariant between CON B, COT B, ANC B and M-group. Cross-recognition is seen only to the C-clade variant. Anchor residues are at positions 2 and 10; while the A-clade variant contains a non-conservative change at position 4 to TSTpQEQIGW, and the C-clade variant has a semi-conservative substitution at position 9 to TSTLQEQIaW. Reduced avidity was seen with the clade-C variant. HLA-B57 and -58 restriction was inferred based on 4 subjects' possessing appropriate HLA class I allele and prior publication.

HXB2 Location p24 (108–117)
Author Location p24
Epitope TSTLQEQIGW
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B57, B58, B63)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, cross-presentation by different HLA, optimal epitope
References Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This epitope was recognized by 30% of B63-positive subjects and 22% of B57/58-positive subjects.

HXB2 Location p24 (108–117)
Author Location p24 (241–250)
Epitope TSTVEEQQIW
Subtype HIV-2
Immunogen HIV-2 infection
Species (MHC) human (B58)
Country Gambia
Keywords HIV-2
References Bertoletti 1998

- HIV-2 epitope defined from an infection in Gambia, Bertoletti, pers. comm.
- All HIV-2 sequences from the database are TSTVEEQIQW in this region, not TSTVEEQQW as in the paper.

HXB2 Location p24 (108–117)
Author Location p24
Epitope TSTLQEQIGW
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B58)
References Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective.
- HIV-2 sequence: TSTVEEQIQW, CTL are cross-reactive, Bertoletti *et al.* [1998]

HXB2 Location p24 (108–117)
Author Location p24 (240–249)
Epitope TSTLQEQIGW
Subtype HIV-2
Immunogen HIV-2 infection
Species (MHC) human (B58)
Keywords subtype comparisons, rate of progression, immunodominance, HIV-2
References Bertoletti *et al.* 1998

- CTL responses in HLA-B*5801 positive HIV-2 infected individuals have a dominant response to Gag and tolerate extensive substitution, thus HLA-B*5801+ individuals may have an enhanced potential for cross-protection between HIV-1 and HIV-2.
- This can be an immunodominant epitope in HLA-B57 and B*5801 infected individuals, and is associated with long-term non-progression Goulder *et al.* [1996b]
- HIV-2 sequence: HIV-2 ROD has the epitope sequence TSTVEEQIQW, and the CTL from a person infected with HIV-2 was cross-reactive with HIV-1 epitopes.
- The epitope is TSTLQEQIGW in HIV-1 B clade, and TSTVEEQIQW in HIV-2 ROD.
- HLA B*5801 and B35 may preferentially select HIV-1 and HIV-2 cross-reactive epitopes.

HXB2 Location p24 (108–117)
Author Location p24 (240–249 SF2)
Epitope TSTLQEQIGW
Immunogen HIV-1 infection
Species (MHC) human (B58)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B58+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 1/1 group 2, and 0/0 group 3.

HXB2 Location p24 (108–117)
Author Location p24 (108–117)
Epitope TSTLQEQIGW
Epitope name TW10
Immunogen HIV-1 infection

Species (MHC) human (B58)
Keywords acute/early infection
References Goulder *et al.* 2001c

- Responses to this dominant A3-restricted Gag epitope are present during the time of decreasing viral load in acute infection.
- Mutations in this epitope were observed in autologous clones of subjects who were B58-positive with a higher frequency than those who were B58-negative (P = 0.02)
- These mutations are being sexually transmitted in adult infections.

HXB2 Location p24 (108–117)
Author Location p24
Epitope TSTLQEQIGW
Epitope name TW10(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B58)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B58-restricted epitope TSTLQEQIGWF elicited an immune response in Chinese HIV-1 positive subjects as part of peptide SDIAGTTSTLQEQIGWM. This epitope differs from another previously described epitope TSTVEEQQIW, at 3 residues.
- 4 of the 14 HLA-B58 carriers responded to TSTLqEQigWF-containing peptide with average magnitude of CTL response of 90 SFC/million PBMC.

HXB2 Location p24 (108–117)
Author Location p24 (108–117)
Epitope TSTLQEQIGW
Immunogen HIV-1 infection
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate reversion rates for this epitope, TSTLQEQIGW, in 3 different subjects were found to be 0.016, 0, and 0.005/day with SEs of 0.007, 0, and 0.001 respectively.
- Gag p24 T110N confers escape in subjects expressing HLA-B57 and HLA-B5801. On transmission from an HLA-B57+ donor to an B57/B5801- recipient, the mutation rapidly reverted to wild type (a=0.016/day). Gag p24 G116A confers escape in subjects expressing B57 and B5801. On transmission from an HLA-B57+ donor to an B57/B5801- recipient, the mutation did not revert to wild type over the 8-year observation period, suggesting that the mutation was neutral (a=0/day). The escape variant in Gag p24 T110N was studied in a further HLA-B57+ to HLA-B57/B5801- transmission pair where it reverted to wild type (a=0.005/day).

HXB2 Location p24 (108–117)
Author Location
Epitope TSTLQRQIGW
Immunogen HIV-1 infection
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 1/22 HEPS sex worker controls (ML1250).

HXB2 Location p24 (108–117)
Author Location Gag (B57)
Epitope TSTLQEQIGW
Epitope name TW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a

CTL CD8+

previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Characteristic changes in B57 epitopes in B57+ people were mapped: TSNLQEQIGW often has one or both of the substitutions: tsNlqeqygw, tstlqeqy[A/G]w.

HXB2 Location p24 (108–117)
Author Location (108–117)
Epitope TSTLQEQIAW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country Botswana, South Africa
Assay type Other
Keywords HLA associated polymorphism
References Boutwell & Essex 2007
- Publicly available HIV-1 subtype C sequences from South Africa and Botswana were analyzed, and 94 HLA-associated amino acid polymorphisms were found. Many polymorphisms were associated with multiple HLA allele classes. 12% associations were negative: association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles accounted for 50% of associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes.
- TSTLQEQIAW encompassed a B*57/B*5801 associated polymorphism, TStLQEQIAW, in the third position. The B clade analog, TSNLQEQIgW was previously described as being HLA-B*5701/B*5801 restricted.

HXB2 Location p24 (108–117)
Author Location
Epitope TSTLQEQIGW
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101, A*2902; B*1501, B*5701
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b
- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- TSTLQEQIGW was recognized by a placebo patient after infection.

HXB2 Location p24 (108–118)
Author Location p24 (240–249 LAI)
Epitope TSTLQEQIGWF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*57, B*5801)
Keywords rate of progression
References Goulder *et al.* 1996b
- Response to this epitope was found in 4 slow progressing HLA-B*57 individuals, in 2 it was dominant or very strong.
- For one donor (from Zimbabwe) this was defined as the optimal peptide.
- This epitope can be presented in the context of the closely related HLA molecules B*5801 and B*57.

HXB2 Location p24 (108–118)
Author Location
Epitope TSTLQEQIGWF
Epitope name Gag-TF11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Sabbaj *et al.* 2003
- Among HIV+ individuals who carried HLA B57, 2/5 (40%) recognized this epitope.

HXB2 Location p24 (108–118)
Author Location Gag
Epitope TSTLQEQIGWF
Subtype B, F
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Argentina
Keywords dynamics, escape, HLA associated polymorphism
References Dilernia *et al.* 2008
- Dynamics of CTL escape mutations was studied theoretically by analyzing plasma samples from 302 subjects (collected over 20 years). HLA associated polymorphisms accumulated in a subtype-specific manner.
- Epitope TSTLQEQIGWF with anchor residues at T(S)TLQEQIGW(F) mutates to TSnLQEQIGWF. This mutation is strongly supported as escape by phylogenetic correction.

HXB2 Location p24 (109–117)
Author Location Gag (241–249 LAI)
Epitope STLQEQIGW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701, B*5801)
Keywords rate of progression
References Klein *et al.* 1998
- B57 has been associated with long-term non-progression in the Amsterdam cohort.
- The most pronounced CTL responses in HLA B*5701 LTS were to RT and Gag.

HXB2 Location p24 (109–117)
Author Location
Epitope STLQEQIGW
Epitope name Gag-SW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Sabbaj *et al.* 2003

CTL CD8+

- Among HIV+ individuals who carried HLA B57, 1/5 (20%) recognized this epitope.
- Among HIV+ individuals who carried HLA B58, 1/4 (25%) recognized this epitope.

HXB2 Location p24 (109–117)
Author Location p24
Epitope STLQEQIGW
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human (B58)
Donor MHC A23, A24, B35, B58, Cw4, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The epitope sequence in this person had a single G8A change, STLQEQIaW.

HXB2 Location p24 (109–118)
Author Location p24 (110–118)
Epitope STLQEQIGWM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, STLQEQIGWM, was detected within overlapping peptides SDIAGTTSTLQEQIGWM and WMTNNPPIPVGEIYKRWI.

HXB2 Location p24 (109–118)
Author Location Gag
Epitope STLQEQIGWM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-A2-restricted epitope STLQEQIGWM is from a subtype B peptide library, and is reactive as part of peptide STLQEQIGWMTNNPP in a subtype B-carrying subject.

HXB2 Location p24 (109–123)
Author Location
Epitope STLQEQIGWMTNNPP
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, A24, B15, B40; A11, A2, B44, B60
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 61 (NIH ARRP Cat# 7932), STLQEQIGWMTNNPP, which contains an epitope restricted by HLA-A2 in different patients, elicited the following CTL responses: (1) for 22+ years in a living non-progressor (2) for 12+ years in a former non-progressor who succumbed to non-AIDS death.

HXB2 Location p24 (110–118)
Author Location Gag (242–)
Epitope TLQEQIGWM
Epitope name Gag242
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* p24 Gag *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human (A2)

CTL CD8+

Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was an intermediate A2 binder that did not induce CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 2/17 HIV+ HLA-A2 subjects.

HXB2 Location p24 (110–118)
Author Location Gag (242–250 Henan isolate)
Epitope `NLQEQIGWM`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- NLQEQIGWM was among 5 mostly recognized epitopes (69%).

HXB2 Location p24 (110–118)
Author Location
Epitope `TLQEQIGWM`
Epitope name Gag 242
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Gag 242 TLQEQIGWM was found in 8 patients but only 2 had a CTL immune response to it.

HXB2 Location p24 (110–118)
Author Location Gag (242–)
Epitope `TLQEQIGWM`
Epitope name Gag242
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Gag epitope TLQEQIGWM, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients. A variant of this epitope, sLQEQIGWM, was seen in DK1.

HXB2 Location p24 (110–119)
Author Location Gag (Henan isolate)
Epitope `NLQEQIGWMT`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p24 (114–128)
Author Location Gag
Epitope `QIGWMTNNPPIPVGE`
Subtype A, AG, B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*23, B*15, B*49, Cw*02, Cw*07, DPA1*0201, DPB1*0101, DPB1*1301, DQB1*05, DRB1*11, DRB1*1301

Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- Epitope-containing peptide QIGWMTNNPPIPVGE, seen in a subtype-A/G carrying subject was derived from subtype A and B libraries and was not previously associated with host class I alleles A*23/*23; B*15/*49, Cw*02/*07.

HXB2 Location p24 (117–126)
Author Location p24 (Henan isolate)
Epitope `WMTNNPPIPV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- WMTNNPPIPV was among 5 mostly recognized epitopes (69%).

HXB2 Location p24 (117–131)
Author Location
Epitope `WMTNNPPIPVGEIYK`
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A11, A2, B44, B60
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 63 (NIH ARRP Cat# 7934), WMTNNPPIPVGEIYK, which contains an epitope restricted by HLA-A2, elicited a CTL responses for 12+ years in a former non-progressor who succumbed to non-AIDS death.

HXB2 Location p24 (117–134)
Author Location p24
Epitope `WMTNNPPIPVGEIYKRWI`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This frequently targeted overlapping peptide, WMTNNPPIPVGEIYKRWI, was differentially targeted across ethnic groups and had an overall frequency of recognition of 16% - 25.4% AA, 23.1% C, 2.3% H, 9.5% WI (P value = 0.0035). This peptide is included in a 41 aa Gag-p24 highly reactive region to be used for vaccine design. HLA-B53 and -B8 were the most commonly present HLA alleles among individuals with responses to this peptide.

HXB2 Location p24 (117–134)
Author Location Gag (251–268)
Epitope `MYRQQNPVPVGNIYRRWI`
Subtype HIV-2
Immunogen HIV-2 infection

CTL CD8+

Species (MHC) human
Country Guinea-Bissau
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords rate of progression, optimal epitope, HIV-2
References Leligdowicz *et al.* 2007

- To find the factors involved in attenuated disease course and long term non-progression, HIV-2 and immune control were studied. HIV-2 viral load was used as a predictor of patient survival. HIV-2 viral load correlated inversely with magnitude of IFN-gamma response, relative dominance of Gag-specific peptides' responses over other proteins' responses, and the breadth of different peptide-specific immune responses. The most frequently recognized peptides were in Gag protein, followed by Env and Pol, while Nef and accessory proteins (Vif, Vpx, Vpr, Tat and Rev) rarely elicited responses. The 6 most recognized peptides were clustered in a highly conserved region of Gag.
- This peptide, MYRQQNPVPVGNIYRRWI, was recognized by 11 out of 65 subjects. It is found in the 149 amino-acid long HIV-2 proteome region of Gag 175-323.

HXB2 Location p24 (118–126)
Author Location p24 (118–126)
Epitope `MTNNPPIPV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, HPVHAGPIAPGQMREPR, was detected within overlapping peptideS LHPVHAGPIAPGQMREPR, LKETINEEAAEWDRLHPV and AAEWDRLHPVHAGPIA.

HXB2 Location p24 (118–126)
Author Location Gag
Epitope `MTSNPPIPV`
Epitope name Gag 271
Subtype M
Immunogen vaccine, in vitro stimulation or selection
Vector/Type: DNA, peptide *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, mouse (A*0201)
Assay type Cytokine production, T-cell Elispot
Keywords subtype comparisons, computational epitope prediction, escape, TCR usage, variant cross-recognition or cross-neutralization
References McKinney *et al.* 2004

- This study examined variant recognition of epitopes presented by A*0201 and A*1101. Numerous amino acid substitutions can be introduced into epitopes without disrupting their recognition by CTLs, although epitopes with multiple substitutions were less recognized. An algorithm was constructed for prediction of epitopes capable of inducing responses to a great number of variant epitopes.
- MTSNPPIPV form is most common in subtype C while MTnNPPIPV form is mostly found in subtype B.
- A total of 14 variant forms of Gag 271 were identified. Immunization with MTSNPPIPV form induced CTLs recognizing 11 of the variant forms while MTnNPPIPV form induced CTLs recognizing only 3 of the epitope variants.

HXB2 Location p24 (118–126)
Author Location Gag (271–)
Epitope `MTNNPPIPV`
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (A*0201)
Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008

- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location p24 (118–126)
Author Location p24 (118–126)
Epitope `MTNNPPIPV`
Epitope name MV9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A*02, A*23, B*07, B*51, Cw*15
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, acute/early infection, viral fitness and reversion
References Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.

- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- The mother was A02- and carried a variant form of the epitope, MThNPPIPV, which she passed to her A02+ child. This form persisted in her child for 12 months.

HXB2 Location p24 (118–126)
Author Location Gag
Epitope MTNNPPIPV
Epitope name Gag271
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- MTNNPPIPV is a Nef epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location p24 (118–126)
Author Location Gag (282–290)
Epitope MTNNPPIPV
Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind three of the five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802).

HXB2 Location p24 (118–126)
Author Location Gag
Epitope MTNNPPIPV
Epitope name Gag271
Subtype B
Immunogen HIV-1 infection
Species (MHC) human, mouse (A2 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope MTNNPPIPV of the HLA-A2 supertype bound most strongly to HLA-A*6802, -A*0203 and -A*0601 and also to -A*0206 and -A*0202. It was conserved 89% in subtype B. 0/22 HLA-A2 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Gag271.

HXB2 Location p24 (118–126)
Author Location p24
Epitope MTSNPPIPV
Epitope name MV9
Subtype D
Immunogen HIV-1 infection
Species (MHC) human
Country Kenya
Keywords epitope processing, escape
References Peters *et al.* 2008a

- Gag sequences from 468 HIV-1 positive sex workers from the Kenyan Pumwani cohort were analyzed to bioinformatically identify positively selected residues that could be related to antigen processing. Mutation effects on disease progression were followed by mean CD4 counts. This method is also one way of identifying potential CTL epitopes and classifying them.
- A Gag positive selection map was generated and sites were classified as beneficial or harmful to HIV. They were correlated to antigen processing (proteasomal cleavage), antigen presentation (TAP transport efficiency) and T-cell receptor binding.
- p17 and p24's structural constraints limited their diversity, while p7-p1-p6 showed a higher average entropy.
- Decreased TAP binding affinity indicating a possible TAP escape mutant was seen in HLA-A*0201-restricted S252N positively selected residue of epitope MTSNPPIPV to MTnNPPIPV.

HXB2 Location p24 (121–129)
Author Location Gag
Epitope NPPIPVGEI
Epitope name Gag1144
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

CTL CD8+

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Epitope NPPIPVGEI elicits IFN-gamma ELISpot responses in 1/7 subjects; and bound HLA-B7 with low affinity in cell-based assays. Previously published HLA restrictions of this epitope include a B8 association (LANL db), A*0201 restriction (Immune Epitope Database).

HXB2 Location p24 (121–135)
Author Location
Epitope NPPIPVGEIYKRWII
Immunogen HIV-1 infection
Species (MHC) human (B44)
Donor MHC A11, A2, B44, B60
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 64 (NIH ARRP Cat# 7935), NPPIPVGEIYKRWII, which contains an epitope restricted by HLA-B44, elicited a CTL responses for 12+ years in a former non-progressor who succumbed to non-AIDS death.

HXB2 Location p24 (121–135)
Author Location p24 (253–267)
Epitope NPPIPVGEIYKRWII
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Gotch *et al.* 1990

- High frequency of memory and effector Gag-specific CTL.

HXB2 Location p24 (121–135)
Author Location p24 (255–274 SF2)
Epitope NPPIPVGEIYKRWII
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords review, immunodominance, escape
References Goulder *et al.* 1997a; Phillips *et al.* 1991

- Longitudinal study of CTL escape mutants in people with the appropriate HLA types – little variation was observed in the immunodominant B27 epitope, relative to B8 epitopes, which varied over time.
- Goulder *et al.* [1997a] is a review of immune escape that points out that there may be a protective effect associated with B27, and that HLA-B8 individuals tend to progress more rapidly than HLA B27 patients.

HXB2 Location p24 (121–135)
Author Location p24 (121–135)
Epitope NPPIPVGEIYKRWII
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (121–135)
Author Location p24 (121–135 HXB2)
Epitope NPPIPVGEIYKRWII
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 19% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location p24 (121–140)
Author Location p24 (253–272)
Epitope NPPIPVGEIYKRWIILGLNK
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

HXB2 Location p24 (121–140)
Author Location p24 (253–272 SF2)

Epitope NPPIPVGEIYKRWIILGLNK
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- Two of these 12 had CTL response to this peptide.
- The responding subjects were HLA-A2, A3, B8, B62, and HLA-A1, B8, B18.

HXB2 Location p24 (121–140)
Author Location p24 (253–272 SF2)
Epitope NPPIPGEIKRWIILGNIK
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

HXB2 Location p24 (121–140)
Author Location p24 (255–274 SF2)
Epitope NPPIPVGEIYKRWIILGLNK
Immunogen HIV-1 infection
Species (MHC) human
References van Baalen *et al.* 1993

- Gag CTL epitope precursor frequencies were estimated and peptide mapping was performed.

HXB2 Location p24 (121–142)
Author Location p24 (253–274 BH10)
Epitope NPPIPVGEIYKRWIILGLNKIV
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Johnson *et al.* 1991

- Gag CTL response studied in three individuals.

HXB2 Location p24 (121–152)
Author Location Gag
Epitope NPPIPVGEIYKRWIILGLNKIVRMYSPTSILD
Immunogen HIV-1 infection, vaccine
Vector/Type: lipopeptide *HIV component:* Gag
Species (MHC) human (A*0201)
References Seth *et al.* 2000

- Immunization of 2/4 HIV seropositive HLA selected individuals with a 32 amino acid Gag lipopeptide that contains CTL epitopes restricted by HLA A33, B8, B27, B35, and Bw62 gave a transient increase in peptide-specific bulk CTL response, but they did not decrease plasma viral load.
- Placebo and HLA mis-matched controls showed no change in CTL.
- The responders carried HLA Bw62 and B35 – the two HLA-matched that did not respond carried B35 and B8.

HXB2 Location p24 (121–152)
Author Location Gag (183–214 LAI)
Epitope NPPIPVGEIYKRWIILGLNKIVRMYSPTSILD
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide
Species (MHC) human
References Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long amino acid peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 9/10 reacted to this peptide.
- 9/12 tested mounted a CTL response to at least one of the six peptides; each of the six peptides elicited a CTL response in at least one individual – this peptide was particularly immunogenic, eliciting a CTL response in four vaccinees.
- All of the 12 tested had an IgG response to this peptide.

HXB2 Location p24 (122–130)
Author Location (C consensus)
Epitope PPIPVGDIY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the D7 residue of PPIPVGDIY are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location p24 (122–130)
Author Location (C consensus)
Epitope PPVPVGDIY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- PPVPVGDIY is an optimal epitope.

HXB2 Location p24 (122–130)
Author Location Gag
Epitope NPVPVGNIY
Subtype A, CRF02_AG
Immunogen HIV-2 infection, HIV-1 or HIV-2 infection
Species (MHC) human (B*35)
Country Gambia

CTL CD8+

Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, variant cross-recognition or cross-neutralization, HIV-2
References Ondondo *et al.* 2008

- To comprehensively compare Gag-specific cellular immunity against HIV-1 versus HIV-2, 20 subjects each infected with HIV-1 or -2, and with similar CD4+ counts were tested for CTL response to Gag peptide pools. No significant difference was seen in magnitude/breadth of CTL response, immunodominance and frequency of targeted Gag peptides, and cross-recognition.
- HIV-2 epitope NPVPVGNIY is cross-reactive with its HIV-1 variant, PPIPVGDIY. B*35 restriction of this eptiope is previously published.

HXB2 Location p24 (122–130)
Author Location Gag
Epitope `PPIPVGDIY`
Subtype A, CRF02_AG
Immunogen HIV-1 infection, HIV-1 or HIV-2 infection
Species (MHC) human (B*35)
Country Gambia
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, variant cross-recognition or cross-neutralization, HIV-2
References Ondondo *et al.* 2008

- To comprehensively compare Gag-specific cellular immunity against HIV-1 versus HIV-2, 20 subjects each infected with HIV-1 or -2, and with similar CD4+ counts were tested for CTL response to Gag peptide pools. No significant difference was seen in magnitude/breadth of CTL response, immunodominance and frequency of targeted Gag peptides, and cross-recognition.
- HIV-1 epitope PPIPVGDIY is cross-reactive with its HIV-2 variant epitope, NPVPVGNIY. B*35 restriction of this eptiope is previously published.

HXB2 Location p24 (122–130)
Author Location Gag
Epitope `PPIPVGDIY`
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Country Canada, South Africa
Keywords escape
References Carlson *et al.* 2008

- A statistical model, the phylogenetic dependency network (PDN), was developed to differentiate the confounding effects of codon variation, linkage disequilibrium of HLA alleles and HIV phylogeny from HLA-associated evolution including HIV selection by HLA-pressure and codon evolution.
- This approach was applied to 2 cohorts of 1144 Gag sequences from HIV-infected individuals, generating associations between HIV codons themselves and codons with HLA alleles. Results generated predicted escapes that confirmed that escape kinetics and compensating mutations are consistent across clades. General patterns of covariation and CTL adaptation were determined. Some clade-based differences were identified.
- HLA-B*35-restricted epitope PPIPVGDIY has a resistant, mutant form, PPIPVGeIY found mostly in clade B. The optimal epitope is found mostly in clade C.

HXB2 Location p24 (122–130)
Author Location Gag
Epitope `NPVPVGNIY`
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Country Canada, South Africa
Keywords escape
References Carlson *et al.* 2008

- A statistical model, the phylogenetic dependency network (PDN), was developed to differentiate the confounding effects of codon variation, linkage disequilibrium of HLA alleles and HIV phylogeny from HLA-associated evolution including HIV selection by HLA-pressure and codon evolution.
- This approach was applied to 2 cohorts of 1144 Gag sequences from HIV-infected individuals, generating associations between HIV codons themselves and codons with HLA alleles. Results generated predicted escapes that confirmed that escape kinetics and compensating mutations are consistent across clades. General patterns of covariation and CTL adaptation were determined. Some clade-based differences were identified.
- HLA-B*35-restricted epitope NPVPVGNIY has a resistant, mutant form, NPVPVGeIY found mostly in clade B. This optimal epitope is found mostly in clade C.

HXB2 Location p24 (122–130)
Author Location p24 (254–262)
Epitope `PPIPVGDIY`
Epitope name PY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*35-associated substitution within optimally defined epitope PPIPVGDIY is at positions D7, PPIPVGdIY.

HXB2 Location p24 (122–130)
Author Location p24 (260–268 LAI)
Epitope `PPIPVGDIY`
Subtype B
Immunogen HIV-1 or HIV-2 infection

Species (MHC) human (B*3501)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*3501 epitope. Variant nPvPVGDIY also noted.

HXB2 Location p24 (122–130)
Author Location p24 (245–253)
Epitope NPVPVGNIY
Subtype HIV-2
Immunogen HIV-1 or HIV-2 infection
Species (MHC) human (B*3501)
Country Gambia
Keywords HIV exposed persistently seronegative (HEPS), HIV-2
References Rowland-Jones *et al.* 1995

- HIV-2 epitope NPVPVGNIY was recognized by CTL from HIV-1-infected and HIV-2-infected B35+ subjects.

HXB2 Location p24 (122–130)
Author Location p24
Epitope PPIPVGDIY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- PPIPVGDIY is a previously described HLA-B*3501-restricted epitope (part of Gag reacting peptide MT-SNPPIPVGdIYKRWIILGL) that contains a B*3501-associated sequence polymorphism at residue D (PPIPVGdIY).

HXB2 Location p24 (122–130)
Author Location Gag
Epitope PPIPVGDIY
Epitope name PY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*3501, B*3502)
Country Australia, Canada, United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, immune evasion, optimal epitope
References Streeck *et al.* 2007a

- To characterize HIV-1 proteome areas that are targeted in early, effective CTL responses, two cohorts were studied. Responses in early infection were against fewer epitopes and of lower magnitude than during chronic infection. While no region of the proteome was favored, Nef was the predominant target based on length of proteins.
- When based on the expression of protective versus nonprotective HLA I alleles, it was found that HLA-B27 and -57 possessing slow progressors to disease directed the majority of their responses to Gag in early infection, as opposed to those with HLA-B*3501 or B*3502, i.e. rapid progressors to AIDS, who had negligible responses to Gag. As compared with HLA-B57-/B27- subjects and HLA-B35 subjects, HLA-B57+/27+ subjects responded most to the p24 component of Gag. By using overlapping peptides within Gag p24, two were picked as being consistently targeted, and both contained previously described epitopes TSTLQEQIGW and KRWIIL-GLNK.
- PPIPVGDIY, i.e. epitope PY9 was targeted in 10% of rapid progressors to disease.

HXB2 Location p24 (122–130)
Author Location p24 (260–268 LAI)
Epitope PPIPVGDIY
Subtype B
Immunogen HIV-1 or HIV-2 infection
Species (MHC) human (B35)
Keywords HIV exposed persistently seronegative (HEPS), HIV-2
References Rowland-Jones *et al.* 1995

- Defined as minimal peptide by titration curve, PPIPVGEIY; HIV-2 form NPVPVGNIY is also recognized.

HXB2 Location p24 (122–130)
Author Location p24 (260–268 LAI)
Epitope PPIPVGDIY
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (B35)
References Lalvani *et al.* 1997

- A peptide-based protocol was optimized for restimulation of CTLp using optimized peptide and IL-7 concentrations – importantly this protocol does not stimulate a primary response, only secondary – peptide-specific CTLp counts could be obtained via staining with peptide-Class I tetramers.
- This peptide was one of the B35 presented test peptides used in control experiments showing that the assay gave no activity using lymphocytes from 21 healthy B35 seronegative donors.

HXB2 Location p24 (122–130)
Author Location p24 (260–268 LAI)
Epitope PPIPVGDIY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords review
References McMichael & Walker 1994

- Review of HIV CTL epitopes.

HXB2 Location p24 (122–130)
Author Location p24 (subtype B)
Epitope PPIPVGEIY
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B35)
Keywords subtype comparisons

CTL CD8+

References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among B and D clade viruses.
- The Clade A version of the epitope, PPIPVGDIY, was preferentially recognized by CTL.

HXB2 Location p24 (122–130)
Author Location
Epitope PPIPVGEIY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords acute/early infection
References Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers—high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load.
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B2705; and A*0201, A*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK.
- The subject with A*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705.
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

HXB2 Location p24 (122–130)
Author Location p24
Epitope PPIPVGDIY
Immunogen
Species (MHC) human (B35)
References Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective.
- HIV-2 version of this epitope is not conserved: NPVPVGNIY, but the CTLs are cross-reactive – one of five B35 CTL epitopes that are cross-reactive, see also Rowland-Jones *et al.* [1995]

HXB2 Location p24 (122–130)
Author Location p24 (260–268)
Epitope PPIPVGDIY
Epitope name PPI
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords HAART, ART, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- One of two HLA B35+ among the eight study subjects recognized this epitope.
- Patient SC15 (HLA A1/68, B8/35, Bw4/6, Cw4/0704) was given acute and sustained therapy and recognized epitopes PPIPVGDIY and VPLRPMTY during 331 days of HAART treatment.

HXB2 Location p24 (122–130)
Author Location p24 (122–130)
Epitope PPIPVGDIY
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (122–130)
Author Location p24 (254–262 SF2)
Epitope PPIPVGDIY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with preseroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 0/2 group 1, 0/2 group 2, and 1/1 group 3.

HXB2 Location p24 (122–130)
Author Location p24 (260–268)
Epitope PPIPVGDIY

CTL CD8+

Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B35)
Keywords HIV exposed persistently seronegative (HEPS), immunodominance
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B35 women, 1/3 HEPS and 3/4 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in the 1/3 HEPS case and in the all 3/4 responsive HIV-1 infected women.
- Subject ML 857 shifted from a A*6802 DTVLEDINL and B35 (H/N)PDIVIYQY response prior to seroconversion to a B35 PPIPVGDIY and B35 VPLRPMTY response post-seroconversion.

HXB2 Location p24 (122–130)
Author Location
Epitope PPIPVGDIY
Epitope name Gag-PY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B35, 2/21 (10%) recognized this epitope.
- Among HIV+ individuals who carried HLA B*5301, 0/11 (0%) recognized this epitope.

HXB2 Location p24 (122–130)
Author Location p24
Epitope PPIPVGEIY
Subtype A, B, C, D
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human (B35)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location p24 (122–130)
Author Location p24 (260–268)
Epitope PPIPVGDIY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords characterizing CD8+ T cells
References Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- None of three patients responded to this peptide with GzB producing cells and one of the patients responded with IFN-gamma producing cells.

HXB2 Location p24 (122–130)
Author Location Gag
Epitope PPIPVGEIY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords HIV exposed persistently seronegative (HEPS)
References Koning *et al.* 2004

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A*11, A*31 and Cw*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
- No one, 0/3 HLA B35+ infection-resistant men, and 0/5 pre-seroconversion men who went on to become infected, reacted to this epitope.

HXB2 Location p24 (122–130)
Author Location p24 (122–130)
Epitope PPIPVGDIY

CTL CD8+

Immunogen HIV-1 infection
Species (MHC) human (B35)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 4/9 patients recognized this epitope.

HXB2 Location p24 (122–130)
Author Location (C consensus)
Epitope PPVPVGDIY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p24 (122–130)
Author Location p24
Epitope PPIPVGEIY
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human (B35, B53)
Donor MHC A23, A24, B35, B58, Cw4, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence in this person matched the known epitope. In another D subtype infected individual, it was predicted to be a B53 epitope based on HLA typing of the individual and motifs within the reactive peptide.

HXB2 Location p24 (122–130)
Author Location Gag (254–262)
Epitope PPIPVGEIY
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (B7 supertype)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

HXB2 Location p24 (122–130)
Author Location p24
Epitope PPIPVGDIH
Immunogen HIV-1 infection
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 1/22 HEPS sex worker controls, ML887.

HXB2 Location p24 (122–130)
Author Location
Epitope PPIPVGDIY
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp160 boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A2A2; B35, B62

Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location p24 (122–130)
Author Location p24
Epitope `PPIPVGEIY`
Epitope name PY9(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope PPIPVGEIY elicited an immune response in Chinese HIV-1 positive subjects as part of peptide WMTNNPPIPVGEIYKRWI. This epitope differs from the previously described HLA-B35-restricted epitope, PPIPVGDIY, at 1 residue, PPIPVGeIY; and from another previously described epitope, NPVPVGNIY, at 3 residues, pPiPVGeIY.
- 3 of the 12 HLA-B35 carriers responded to PPIPVGeIY-containing peptide with average magnitude of CTL response of 150 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p24 (124–138)
Author Location p24 (256–270 LAI)
Epitope `IPVGEIYKRWIILGL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Buseyne *et al.* 1993b

- Clustering of Gag p24 CTL epitopes recognized in 29 HIV-infected people.

HXB2 Location p24 (124–138)
Author Location Gag (256–270 LAI)
Epitope `IPVGEIYKRWIILGL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Buseyne *et al.* 1993a

- Vertical transmission of HIV ranges from 13% to 39%.
- Primary assays showed that cytotoxic activity against at least one HIV protein was detected in 70% of infected children.
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
- Two children, EM16 (CDC P2A+D2) and EM18 (CDC P2A), had a CTL response to this epitope, and it was shown to be presented by B8 in EM18.

HXB2 Location p24 (124–138)
Author Location Gag
Epitope `IPVGEIYKRWIILGL`
Subtype A, B, C
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-B8-restricted epitope IPVGEIYKRWIILGL is from subtype A,B and C peptide libraries, and is reactive in a subtype B-carrying subject.

HXB2 Location p24 (125–135)
Author Location Gag (264–274)
Epitope `PVGDIYKRWII`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p24 (125–139)
Author Location
Epitope `PVGEIYKRWIILGLN`
Immunogen HIV-1 infection

Species (MHC) human (A24, B60)
Donor MHC A2, A24, B15, B40; A11, A2, B44, B60
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 65 (NIH ARRP Cat# 7936), PVGEIYKRWIILGLN, which contains epitopes restricted by HLA-A24 and -B60 in different patients, elicited the following CTL responses: (1) for 12+ years in a former non-progressor who succumbed to non-AIDS death (2) for 22+ years in a living non-progressor.

HXB2 Location p24 (125–139)
Author Location Gag (257–271 SF2)
Epitope PVGEIYKRWIILGLN
Epitope name Peptide 65
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF2 *HIV component:* Gag, Tat *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse (H-2^d)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes
References Cellini *et al.* 2008

- In order to increase the known number of epitopes in Gag protein so that they can be assayed for reactivity in vaccine studies, BALB/c mice were inoculated with Gag or Gag+Tat. OLPs were used to elicit T-cell immune responses from mouse splenocytes, tested for by cytotoxicity or ELISpot assays. 5 novel predicted optimal CTL epitopes, 2 novel predicted CD4 epitopes and 2 immune response eliciting peptides were found.
- Reactive peptide PVGEIYKRWIILGLN, besides containing potential CTL epitope, IYK, also contains a potential CD4 epitope.

HXB2 Location p24 (125–139)
Author Location Gag (257–271)
Epitope PVGEIYKRWIILGLN
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized both by mice co-immunized with Gag and Tat, and by mice immunized with Gag alone.

HXB2 Location p24 (125–139)
Author Location Gag (257–271)
Epitope PVGEIYKRWIILGLN
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the ES. The ES had N271H substitution.

HXB2 Location p24 (125–142)
Author Location p24
Epitope PVGEIYKRWIILGLNKIV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This frequently targeted overlapping peptide, PVGEIYKRWIILGLNKIV, was differentially targeted across ethnic groups and had an overall frequency of recognition of 22% - 30.5% AA, 42.3% C, 9.1% H, 4.8% WI (P value = 0.001). This peptide is included in a 41 aa Gag-p24 highly reactive region to be used for vaccine design. HLA-B27 and -B8 were the most commonly present HLA alleles among individuals with responses to this peptide.

HXB2 Location p24 (125–142)
Author Location Gag (259–276)
Epitope `PVGNIYRRWIQIGLQKCV`
Subtype HIV-2
Immunogen HIV-2 infection
Species (MHC) human
Country Guinea-Bissau
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords rate of progression, optimal epitope, HIV-2
References Leligdowicz *et al.* 2007

- To find the factors involved in attenuated disease course and long term non-progression, HIV-2 and immune control were studied. HIV-2 viral load was used as a predictor of patient survival. HIV-2 viral load correlated inversely with magnitude of IFN-gamma response, relative dominance of Gag-specific peptides' responses over other proteins' responses, and the breadth of different peptide-specific immune responses. The most frequently recognized peptides were in Gag protein, followed by Env and Pol, while Nef and accessory proteins (Vif, Vpx, Vpr, Tat and Rev) rarely elicited responses. The 6 most recognized peptides were clustered in a highly conserved region of Gag.
- This peptide, PVGNIYRRWIQIGLQKCV, was recognized by 9 out of 65 subjects. It is found in the 149 amino-acid long HIV-2 proteome region of Gag 175-323.

HXB2 Location p24 (126–140)
Author Location p24 (126–140 HXB2)
Epitope `VGEIYKRWIIGLNK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 19% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location p24 (127–134)
Author Location Gag
Epitope `GDIYWKRWI`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Chopera *et al.* 2008

- Transmission of HIV-1-escape variants from individuals with protective HLA-B*57/-B*5801 alleles to those without these alleles was studied to determine if infection with such replication-deficient mutants offered any advantage to the new host. Dependency between slower rate of disease progression in the newly infected subject and protective genotype of the infecting individual was suggested.
- HLA-B*0801-restricted epitope GDIYWKRWI, within peptide WMTSNPPVPVGDIYWKRWI was able to elicit CTL response in a T242N/A146X viral-mutation-carrying subject.

CTL CD8+

HXB2 Location p24 (127–135)
Author Location p24 (127–135)
Epitope GEIYKRWII
Epitope name GI9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*08)
Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords rate of progression, immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-B*08-restricted autologous epitope GEIYKRWII elicited CTL responses at the earliest time point, with a reduction in response frequency just before disease progression at the second time point and an increase at the third sample point. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location p24 (127–135)
Author Location p24 (259–267 SF2)
Epitope GDIYKRWII
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
References McAdam *et al.* 1998

- GDIYKRWII specific CTL clone also recognized GEIYKRWII.

HXB2 Location p24 (127–135)
Author Location p24 (127–135)
Epitope GEIYKRWII
Epitope name GEI
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells
References Turnbull *et al.* 2006

- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.
- This epitope, B8-GEI, that is associated with rapid progression to AIDS, and its natural as well as alanine-substituted variants are either not cross-recognized or show high interpatient variability in cross-recognition. At lower peptide concentrations, efficiency of variant cross-recognition was reduced, even while interepitopic differences in variant cross-recognition efficiency were maintained. CTLs responding to this epitope expressed the same predominant TCR Vbeta family.

HXB2 Location p24 (127–135)
Author Location p24 (261–269)
Epitope GEIYKRWII
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Sutton *et al.* 1993

- Predicted epitope based on B8-binding motifs, from larger peptide NPPIPVGEIYKRWII.

HXB2 Location p24 (127–135)
Author Location p24 (259–267)
Epitope GEIYKRWII
Immunogen in vitro stimulation or selection
Species (MHC) human (B8)
Keywords dendritic cells
References Zarling *et al.* 1999

- This study compares the ability of macrophages and dendritic cells to stimulate primary responses in CD8+ lymphocytes isolated from HLA-appropriate HIV-uninfected donors using peptide-pulsed APC – the dendritic cells performed better as APC for the stimulation of primary responses.
- Strong CTL responses were elicited by the epitopes DRFYKTLRA and GEIYKRWII when presented by either immature or mature dendritic cells – macrophages were not able to prime a CTL response against DRFYKTLRA.
- A weak response to KLTPLCVSL was stimulated using macrophages as the APC.
- No detectable response was observed for the following previously-defined HIV epitopes: KIRLRPGGK, ILKEPVHGV, IRLRPGGK, GPKVKQWPL.

HXB2 Location p24 (127–135)
Author Location p24 (259–267 LAI)
Epitope GEIYKRWII
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Klenerman *et al.* 1994

- Naturally occurring variant GDIYKRWII may act as antagonist.

HXB2 Location p24 (127–135)
Author Location p24 (259–267)
Epitope GEIYKRWII
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the HLA A2+ was HLA A*0201, A31, B8, B51 and responded to this epitope as well as seven others.

HXB2 Location p24 (127–135)
Author Location p24 (259–267)
Epitope GEIYKRWII
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords dynamics, escape
References Nowak *et al.* 1995

- Longitudinal study of CTL response and study of immune escape – GDIYKRWII could also stimulate CTL, reactivity fluctuated.

HXB2 Location p24 (127–135)
Author Location p24 (259–267)
Epitope GEIYKRWII
Immunogen HIV-1 infection
Species (MHC) human (B8)
References McAdam *et al.* 1995

- Equivalent sequence GDIYKRWII also recognized by CTL from some donors.

HXB2 Location p24 (127–135)
Author Location p24 (259–267)
Epitope GEIYKRWII
Epitope name GEI
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART, supervised treatment interruptions (STI), immunodominance, escape, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- Six of the 7/8 study subjects that were HLA B8 recognized this epitope.
- Patient SC2 (HLA A1, B7/8, Cw0701/0702, DR4/53, DQ7) had CTL responsiveness against epitopes FLKEKGGL, GPKVKQWPL, and GEIYKRWII peptides – FLKEKGGL tetramer staining steadily declined and at day 1340 the FLKEKGGL stained cells were no longer detected and the escape mutant FLKENGGI was found in 8/10 clones.
- Patient SC9 (HLA A1/2, B8/13, Cw0/0701, DR2/11, DQ6/7) had a CTL response against epitopes FLKEKGGL, ILKEPVHGV, SQRRQDILDLWIYHTQGYFPDWQNY, and GEIYKRWII and all responses declined during therapy initiated at day 390 but were restored when therapy become intermittent.
- Patient SC19(HLA A11/12, B8/44, Cw06/0701, DR3/7, DR52/53, DQ 2/8) had a CTL response to epitopes FLKEKGGL, GEIYKRWII, ACQGVGGPGHK, AVDLSHFLK, and FNCGGEFFY that declined during therapy initiated at day 197.
- Patient SC10(HLA A1/3, B8/35, DR1/8, DQ 4/5) had sustained therapy started during acute infection and maintained an immunodominant response to FLKEKGGL and a response to GEIYKRWII through day 1088.
- Patient SC12(HLA A1, B8/39, Cw0701/0702, DR2/3, DR51/52, DQ2/6) had sustained therapy started during acute infection and maintained an immunodominant response to FLKEKGGL throughout and minor responses to GEIYKRWII, DCKTILKAL, GGKKKYKLK – GEIYKRWII and GGKKKYKLK responses were stimulated by a brief period off therapy.
- Patient SC11(HLA A1, B8, Cw0201, DR3/11, DR52, DQ2/7) started therapy early, remained on therapy for 40 days, then reinitiated HAART at day 640 had a CTL response to FLKEKGGL, GPKVKQWPL, and GEIYKRWII throughout and received a benefit from the early limited course therapy.

HXB2 Location p24 (127–135)
Author Location p24 (259–267 SF2)
Epitope GEIYKRWII
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with preseroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B8+ individuals that had a CTL response to this epitope broken down by group: 2/3 group 1, 2/3 group 2, and 2/2 group 3.

HXB2 Location p24 (127–135)
Author Location p24

Epitope GEIYKRWII
Epitope name GEI
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART, supervised treatment interruptions (STI)
References Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFNgamma Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

HXB2 Location p24 (127–135)
Author Location p24
Epitope GEIYKRWII
Subtype A, B, C, D
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human (B8)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location p24 (127–135)
Author Location Gag (259–267)
Epitope GEIYKRWII
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (B8)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the most frequently recognized of the 31 epitopes that the vaccinated volunteers responded to.

HXB2 Location p24 (127–135)
Author Location p24 (259–267)
Epitope GEIYKRWII
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords Th1, characterizing CD8+ T cells
References Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- None of three patients responded to this peptide with GzB producing cells and one of the patients responded with IFN-gamma producing cells.

HXB2 Location p24 (127–135)
Author Location p24
Epitope GEIYKRWII
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A1A1, B55, B8, Cw3, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence matched the peptide.

HXB2 Location p24 (127–135)
Author Location Gag (259–267 BRU)
Epitope GEIYKRWII
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 1/9 CRF02_AG-infected Ivorians, and 2/9 B-infected French subjects.

HXB2 Location p24 (127–135)
Author Location p24 (127–135)
Epitope GEIYKRWII
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country Switzerland
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords HAART, ART
References Rehr *et al.* 2008

- By following T-cell function in ART-regimented patients over time, it was shown that ART resulted in reduced viral replication and the restoration of CTLs to polyfunctionality. It is concluded that in vivo antigenic exposure during declining viremia has a positive influence on CTL function.
- Epitope GEIYKRWII was used to interrogate CTL function in 37 chronically infected HIV-1 positive subjects, with respect to cytokine production.

HXB2 Location p24 (127–136)
Author Location
Epitope GEIYKRWIIL
Epitope name Gag-GL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Donor MHC A*0101, A*0301, B*0801, B*5802, Cw*0602, Cw*0701
Assay type Chromium-release assay
Keywords HAART, ART
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Among HIV+ individuals who carried HLA B08, 3/6 (50%) recognized this epitope.

HXB2 Location p24 (128–135)
Author Location
Epitope EIYKRWII
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*08)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Addo *et al.* 2007

- Maturation phenotypes of CTLs were compared between HIV-1 Controller and Progressor subjects. Controllers were found to recognize a median of 18 epitopes compared to 15 by Progressors. While Controllers certainly had higher frequencies of terminally differentiated effector CTLs (CD45RA+/CCR7-), Progressors had higher mean frequencies of CD45RA-/CCR7- effector memory, CD45RA-/CCR7+ central memory (statistically significant) and CD45RA+/CCR7+ naive CTLs. No correlation was seen between CTL effector phenotype and either HLA-type or epitope.
- B*08-restricted epitope EIYKRWII does not correlate with any particular CTL maturation phenotype.

HXB2 Location p24 (128–135)
Author Location p24 (260–267 LAI)
Epitope EIYKRWII
Subtype B
Immunogen
Species (MHC) human (B*0801)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*0801 epitope.

HXB2 Location p24 (128–135)
Author Location (C consensus)
Epitope DIYKRWII
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p24 (128–135)
Author Location (C consensus)

Epitope DIYKRWII
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- DIYKRWII is an optimal epitope.

HXB2 Location p24 (128–135)
Author Location p24
Epitope DIYKRWII
Epitope name DI8
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Country South Africa
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization
Keywords rate of progression
References Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naive patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer B*0801 DI8 was used to test 27 patients and gave a median ex vivo tetramer frequency of 0.55.

HXB2 Location p24 (128–135)
Author Location p24
Epitope DIYKRWII
Immunogen peptide-HLA interaction
Species (MHC) human (B*0801)
Assay type Tetramer binding
Keywords binding affinity
References Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, DIYKRWII (MHC Class I restriction, serotype Bw6) complexed with MHC B*0801 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C.

HXB2 Location p24 (128–135)
Author Location
Epitope DIYKRWII
Epitope name DI8
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Country South Africa
Assay type proliferation, Tetramer binding, Intracellular cytokine staining
References Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

HXB2 Location p24 (128–135)
Author Location p24 (260–267 LAI)
Epitope EIYKRWII
Subtype B
Immunogen
Species (MHC) human (B8)
References Goulder *et al.* 1997g

- Defined in a study of the B8 binding motif.

HXB2 Location p24 (128–135)
Author Location p24 (SF2)
Epitope EIYKRWII
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in an HIV+ Caucasian living in Boston – this epitope did not fall within the three most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa.

HXB2 Location p24 (128–135)
Author Location p24 (C consensus)
Epitope DIYKRWII
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in an HIV+ South African – this epitope did not fall within the five most recognized peptides in the study.

- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa.

HXB2 Location p24 (128–135)
Author Location p24 (SF2)
Epitope EIYKRWII
Epitope name EI8
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Goulder *et al.* 2001a

- This peptide elicited a weak CTL response during acute HIV-1 infection in patient PI004.
- Three CTL responses to epitopes, TSTLQEQIGW, ISPRTLNAW, and KAFSPEVIPMF, were evident early after infection; CTL responses to SLYNTVATL, QASQEVKNW, EIYKRWII, and FLKEKGGL were detectable at 5 months post-infection and beyond.

HXB2 Location p24 (128–135)
Author Location p24
Epitope EIYKRWII
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords rate of progression
References Kostense *et al.* 2001

- HLA tetramers to six epitopes were used to study HLA-A2, B8 and B57 CTL in 54 patients – HIV-specific tetramer positive cells were inversely correlated with viral load in patients with high CD4, but in patients with CD4 T-cells below 400 high tetramer frequencies were found despite high viral load.
- Most patients have high levels of HIV-specific T-cell expansions, but many of these cells aren't functional.
- In 15 of the patients, the proportion of IFN gamma producing tetramer cells correlated with AIDS-free survival.
- 4/13 patients that reacted with EIYKRWII displayed epitope mutations in a minority of sequences, which did not correlate with disease progression or viral load – these mutations were: Patient 156 (KIYKRWMI), Patient 36 (EIYKRRII), Patient 656 (KIYKRWII, EIYERWMI), and Patient 159 (EIYKRWVI).
- Stimulation with HLA-B8 p24 and Nef epitopes significantly increased Nef-specific T-cell numbers in 2 patients (748 and 1113)
- There were more functional IFN-gamma producing Nef-specific T-cells within the T-cell population than there were active p24 Gag-specific T-cells.

HXB2 Location p24 (128–135)
Author Location p24 (259–267)
Epitope DIYKRWII
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Appay *et al.* 2000

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α

HXB2 Location p24 (128–135)
Author Location p24 (128–135)
Epitope EIYKRWII
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Day *et al.* 2001

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual.

HXB2 Location p24 (128–135)
Author Location Gag
Epitope EIYKRWII
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Goulder *et al.* 2000b

- Tetramer assays were compared with three functional assays in 42 people with chronic HIV infection: ELISPOT, intracellular cytokine staining, and precursor frequency (limiting dilution assay [LDA])
- HIV-specific tetramer staining CTLs appeared to be active, and inert CTL were not found to play a significant role in chronic pediatric or adult HIV infection.

HXB2 Location p24 (128–135)
Author Location p24
Epitope DIYKRWII
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A11, A2, B60, B8, Bw6
Keywords HAART, ART
References Appay *et al.* 2002

- Four HIV patients with prolonged clinically successful anti-viral therapy but with ongoing evidence of replication and Nef mRNA transcription, showed specific T-cell responses by Elispot and Tetramer staining, maintained for 2-4 years after initiation of HAART.
- Nef epitope recognition was detected in all 4 subjects, gp120, Pol and Gag-specific in 1 or 2 subjects.
- The HIV-specific CD8+ T-cells had an intermediate maturation phenotype characterized by low levels of perforin and high levels of CD27 expression.

HXB2 Location p24 (128–135)
Author Location Gag (260–267 IIIB)
Epitope EIYKRWII
Subtype B
Immunogen HIV-1 infection

Species (MHC) human (B8)
Assay type Chromium-release assay
References Kurane *et al.* 2003

- Three CD8+ CTL cell clones were derived from 2 HIV-1 positive asymptomatic patients, and their epitope specificities and HLA presenting proteins were defined.

HXB2 Location p24 (128–135)
Author Location Gag (B con)
Epitope EIYKRWII
Epitope name E18
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Draenert *et al.* 2004c

- CD8+ T-cell responses that persisted in individuals with advanced disease were studied; most of the optimal epitopes defined were recognized with intermediate to high avidity. On average 13 (range, 2-39) epitopic regions were targeted in an average of 6 proteins (range, 1-8). HAART resulted in decrease in antigen and reduction in gamma IFN EliSpot responses, suggesting active responses to autologous virus. The lack of mutations within most viral epitopes suggest that persistent CTL through late disease do not exert strong immune selection pressure, yet the Elispot assays show robust responses, suggesting to the authors that gamma IFN-based screening methods may not reveal functional CD8+ T-cell impairment in patients with AIDS.
- 3 subjects recognized this epitope with intermediate functional avidity. Autologous sequence revealed one substitution, Diyrkwil, in 1 of the 3; this version of the epitope also had intermediate functional avidity with the donor's cells.

HXB2 Location p24 (128–135)
Author Location Gag
Epitope EIYKRWII
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords HIV exposed persistently seronegative (HEPS)
References Koning *et al.* 2004

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A*11, A*31 and Cw*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
- 3/9 HLA B8+ infection-resistant men, compared to 1/3 pre-seroconversion men who went on to become infected, reacted to this epitope.

HXB2 Location p24 (128–135)
Author Location (B consensus)
Epitope EIYKRWII
Epitope name EI8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A02, A03, B08, B62, Cw10, Cw7; A11, A29, B08, B44, Cw4, Cw7; A25, A32, B08, B14, Cw7, Cw8; A01, A03, B08, B14, Cw7, Cw8
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 4/9 individuals recognized this epitope, presented by HLA-B8.

HXB2 Location p24 (128–135)
Author Location p24
Epitope DIYKRWII
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country United Kingdom
Assay type Tetramer binding, T-cell Elispot, Intracellular cytokine staining
Keywords rate of progression, acute/early infection, characterizing CD8+ T cells, immune dysfunction
References Papagno *et al.* 2004

- Acute HIV-1 infection induces massive activation of HIV-specific and non-HIV-specific CD8+ T-cells resulting in differentiation of these cells. High differentiation of CD8+ T-cells is correlated with disease progression. Differentiation is a natural process but it can be driven by elevated immune activation, such as in HIV infection.

HXB2 Location p24 (128–135)
Author Location p24 (128–135)
Epitope EIYKRWII
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A1, A3, B35, B8
Country United States
Assay type Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, escape, variant cross-recognition or cross-neutralization
References Casazza *et al.* 2005

CTL CD8+

- Evidence of continued viral evolution during HAART therapy despite low viral load was found in 1/5 patients studied.
- Diykrwii sequence was found in 12/17 clones after the initiation of therapy, while eVykrwii sequence was found in 5/17, and the peptide used to initially detect the response was not found, EIYKRWII. The less frequent clone was most often recognized. No dramatic shift towards escape was observed after the initiation of therapy.

HXB2 Location p24 (128–135)
Author Location Gag
Epitope EIYRKWII
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country Netherlands
Assay type Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords binding affinity, rate of progression, escape, characterizing CD8+ T cells
References Jansen *et al.* 2005

- Number and responsiveness of CD8 T-cells directed to different Gag peptides presented by HLA-A2, -B8 and B57 were compared. It was shown that T-cells specific for an HLA-B57 peptide responded to a higher extent and more readily to antigenic stimulation than those specific for HLA-A2 and -B8 peptides did. Moreover, it was shown that the higher functionality of B57-restricted T-cells was not correlated to higher number of epitope escape mutations in A2- and B8-restricted T-cells.
- Tetramer decay experiments indicate that the HLA-B57 peptide has a higher half-life than the A2 and B8 peptides. The authors point out that CD8+ T cells with high binding affinity may require less help.
- In 1/2 B8+ individuals that were sequenced, 2 epitope variants were present: EfYRKWII and rIYRKWII, but the form EIYRKWII was found most often.

HXB2 Location p24 (128–135)
Author Location Gag (260–267 B consensus)
Epitope EIYKRWII
Epitope name EI8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A*01, A*11, B*08, B*15, Cw*04, Cw*07
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords escape, variant cross-recognition or cross-neutralization, optimal epitope
References Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- The EI8 variant dIYKRWII was the only form of the epitope detected over a 5 year time period in this person. Elispot reactions were comparable between the autologous form and the B clade consensus form, EIYKRWII .

HXB2 Location p24 (128–135)
Author Location p24
Epitope EIYKRWII
Epitope name B8-EI8(p24)
Immunogen HIV-1 infection
Species (MHC) human (B8)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (128–135)
Author Location p24 (128–135)
Epitope EIYKRWII
Epitope name EI8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, subtype comparisons, acute/early infection
References Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (ANC) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- Epitope sequences for this eptiope, EI8 are invariant between CON B, COT B, ANC B and M-group. Cross-recognition is seen to both A- and C-clade variants. Anchor residues are at positions 4 and 5; while both A- and C- variants contain a

CTL CD8+

change at position 1 to dIYKRWII. HLA-B08 restriction was inferred based on subject possessing appropriate HLA class I allele and prior publication.

HXB2 Location p24 (128–135)
Author Location
Epitope `EIYKRWII`
Immunogen
Species (MHC) (B8)
Keywords review, immunodominance, escape, vaccine antigen design
References Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection (recognized by >30% of subjects).

HXB2 Location p24 (128–135)
Author Location
Epitope `EIYKRWII?`
Epitope name EI8
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country United States, South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords memory cells
References Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

HXB2 Location p24 (128–135)
Author Location p24
Epitope `EIYKRWII`
Epitope name EI8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- 350 days after first testing, this epitope, EIYKRWII, decreased from triple-functional to monofunctional in the nature of response it was able to elicit in untreated patients, without any change in sequence. Previously published HLA-restriction for EI8 is HLA-B8.

HXB2 Location p24 (128–135)
Author Location
Epitope `EIYKRWII`
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A1, A2; B38, B8
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location p24 (128–135)
Author Location
Epitope `EIYKRWII`
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords binding affinity, acute/early infection
References Lichterfeld *et al.* 2007b

- Differences in early versus chronic AIDS include a decline in CTL number accompanied by a reducing viremia. Comparative analysis of such CTLs in this study show that early infection is characterized by a different clonotypic composition and higher functional avidity of CTLs followed by their selective depletion during transition to chronic disease. The total magnitude of CTL cytokine production is lower in early infection. Intraindividual, early CTLs' functional avidity for the same epitope decreases concomitantly with a reduction in clonotypic TCR repertoire especially of strongly activated and CD127lo, CD38+, Ki-67hi CTLs while progressing to chronic infection states.
- None of the target epitopes, including this epitope EIYKRWII seen in 2 patients, underwent sequence changes.

HXB2 Location p24 (128–136)
Author Location Gag (260–268 SUMA)
Epitope EIYKRWIIL
Epitope name Gag EIL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Donor MHC A*1103, A*2402, B*1402, B*1501, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, acute/early infection, characterizing CD8+ T cells
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape muations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

HXB2 Location p24 (128–136)
Author Location Gag (260–268)
Epitope EIYKRWIIL
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (A2)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the most frequently recognized of the 31 epitopes that the vaccinated volunteers responded to.

HXB2 Location p24 (128–136)
Author Location p24
Epitope EIYKRWIIL
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human (A24)
Donor MHC A23, A24, B35, B58, Cw4, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence in this person matched the known epitope.

HXB2 Location p24 (129–136)
Author Location p24 (263–270 SF2)
Epitope IYKRWIIL
Epitope name Gag263-8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Country Japan
References Ikeda-Moore *et al.* 1997

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402.
- This peptide induced CTL in 1/4 HIV-1 + people tested.
- IYKRWIIL bound to A*2402 with medium strength, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

HXB2 Location p24 (129–137)
Author Location Gag (263–272 NL-432 or NL-M20A)
Epitope IYKRWIILG
Epitope name Gag263-10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Donor MHC A*2402
Country Japan
Assay type Chromium-release assay, CTL suppression of replication, HLA binding
References Fujiwara *et al.* 2008

CTL CD8+

- To clarify mechanisms of escape mutation accumulation in the population, the Japanese Nef138-10 (RYPLTFGWCF) epitope was studied amongst hemophiliacs and others, to determine replication suppression abilities of both the wild type and 2F (RfPLTFGWCF) mutant virus. This mutant is conserved due to reduced CTL suppression of viral replication, also preventing viral reversion to WT upon transfer to a new host.
- Epitope Gag263-10, IYKRWIILG, was used as a comparison for positive cytolytic activity of epitope-specific HLA-A*2402 clones against target cells prepulsed with corresponding peptide. These clones partially suppressed NL-M20A viral replication.

HXB2 Location p24 (129–138)
Author Location p24 (263–272 SF2)
Epitope `IYKRWIILGL`
Epitope name Gag263-10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Country Japan
References Ikeda-Moore *et al.* 1997

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402.
- This peptide induced CTL in 1/4 HIV-1 + people tested.
- IYKRWIILGL bound to A*2402 with medium strength, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

HXB2 Location p24 (129–138)
Author Location Gag (261–270)
Epitope `IYKRWIILGL`
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (A24)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

HXB2 Location p24 (129–138)
Author Location p24
Epitope `IYKRWIILGL`
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human (A24)
Donor MHC A23, A24, B35, B58, Cw4, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence in this person matched the known epitope.

HXB2 Location p24 (129–138)
Author Location p24 (263–272)
Epitope `IYKRWIILGL`
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the A2+ individuals was B27 and responded to IYKRWIILGL.

HXB2 Location p24 (129–138)
Author Location Gag (261–270 SF2)
Epitope `IYKRWIILGL`
Epitope name IYK
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF2 *HIV component:* Gag, Tat *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse (H-2^d)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes
References Cellini *et al.* 2008

- In order to increase the known number of epitopes in Gag protein so that they can be assayed for reactivity in vaccine studies, BALB/c mice were inoculated with Gag or Gag+Tat. OLPs were used to elicit T-cell immune responses from mouse splenocytes, tested for by cytotoxicity or ELISpot assays. 5 novel predicted optimal CTL epitopes, 2 novel predicted CD4 epitopes and 2 immune response eliciting peptides were found.

- Predicted epitope IYKRWIILGL was found in reactive peptide 65, PVGEIYKRWIILGLN.

HXB2 Location p24 (129–140)
Author Location Gag
Epitope IYKRWIILGLNK
Subtype A, B, C, AE
Immunogen HIV-1 infection
Species (MHC) human (A24)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-A24-restricted epitope IYKRWIILGLNK is from subtype A,B and C peptide libraries, and is reactive in subtype B and subtype AE-carrying subjects. This epitope is part of reacting peptide IYKRWIILGLNKIVR.

HXB2 Location p24 (129–143)
Author Location
Epitope IYKRWIILGLNKIVR
Immunogen HIV-1 infection
Species (MHC) human (A24, B27)
Donor MHC A25, A3, B18, B27; A2, A24, B15, B40; A2, A31, B27, B44
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 66 (NIH ARRP Cat# 7937), IYKRWIILGLNKIVR, contains epitopes restricted by HLA-A24 and -B27 in different patients and elicited the following CTL responses: (1) 1920 sfc/million PBMC at 12.5 years, and 2050 sfc/million PBMC at 22.8 years post-infection in a living non-progressor (2) for >22 years in another living non-progressor (3) for 22+ years in a former non-progressor who succumbed to loss of viremic control.

HXB2 Location p24 (129–143)
Author Location Gag (261–275)
Epitope IYKRWIILGLNKIVR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the ES. The ES had N271H substitution.

HXB2 Location p24 (129–148)
Author Location Gag (261–280)
Epitope IYKLWIILGLNKIVRMYSPT
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27, B62)
Donor MHC A3, A31, B27, B38; A24, B27, B62
Assay type Chromium-release assay
Keywords genital and mucosal immunity
References Musey *et al.* 2003

- CTL clones from blood, semen, cervix and rectum samples from 12 individuals were compared. CTL clones derived from blood and mucosal samples had similar high lysis efficiency, primarily perforin dependent, and TCRβ VDJ region sequencing revealed cases of expansion of the same clone in different compartments.
- CD8+ T cell clones directed at this epitope were derived from blood and rectum of one individual, and blood and semen of another. Both individuals are HLA-B27 positive, and within the peptide there is a B27 epitope that was recognied in the blood and rectum of the first patient, and in the blood of the second. A HLA-B62 epitope is also recognized in this peptide in the second individual, and the CD8+ T cells clones from both the blood and semen recognized this epitope.

HXB2 Location p24 (130–148)
Author Location p24 (265–280 BRU)
Epitope YKRWIILGLNKIVRMYSPT
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Dadaglio *et al.* 1991

- Used as a positive control for HLA specificity.

HXB2 Location p24 (131–139)
Author Location Gag (265–273)
Epitope KRWIILGLN
Immunogen HIV-1 infection

CTL CD8+

Species (MHC) chimpanzee (Patr-B*03)
References Balla-Jhagjhoorsingh *et al.* 1999b

- Certain HLA-alleles have been associated with long-term survival – among them are HLA-B*27 and HLA-B*57.
- Of more than 150 chimpanzees that have been reported to be infected with HIV-1, only one has developed AIDS.
- CTL responses were studied in two HIV-1 infected chimpanzees that have strong CTL responses, and they were found to respond to highly conserved epitopes that are recognized in humans in the context of HLA-B*27 and HLA-B*57.
- The human HLA protein which presents this Patr-B*03 epitope is HLA B*2705 but the amino acid sequences in the binding pockets of HLA-B*2705 and Patr-B*03 are distinctive.

HXB2 Location p24 (131–140)
Author Location p24 (263–272)
Epitope `KRWIILGLNK`
Immunogen HIV-1 infection
Species (MHC) human (B*27)
Keywords HAART, ART
References Huang *et al.* 2000

- The single cell ELISPOT assay was optimized and highly specific, and found to work well even after the primary cells had been frozen and thawed.
- Increases in gamma interferon producing cells were observed in response to anti-retroviral therapy using single cell IFN-gamma-production ELISPOT.
- In 3/3 HLA A*02, B*27 individuals, the dominant response in gag measured by both gamma IFN production and T cell lysis was to the B27 epitope, KRWIILLGLNK, not the A2 SLYNTVATL epitope.

HXB2 Location p24 (131–140)
Author Location p24 (263–272 SF2)
Epitope `KRWIILGLNK`
Immunogen HIV-1 infection
Species (MHC) human (B*27)
References McAdam *et al.* 1998

- Epitope invariant across clades A, B, C, and D.

HXB2 Location p24 (131–140)
Author Location Gag
Epitope `KRWIILGLNK`
Epitope name KK10
Immunogen HIV-1 infection
Species (MHC) human (B*27)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- Epitope KRWIILGLNK is B*27-, non-B*57-restricted.
- An N271H variant, KRWIILGLhK, was found in resting CD4+ T cells and could elicit immune responses.
- An L268M variant, KRWIImGLNK, found in plasma virus elicited at least as great immune response as wild type virus.

HXB2 Location p24 (131–140)
Author Location p24 (131–140)
Epitope `KRWIILGLNK`
Epitope name KK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*27)
Country Switzerland
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, HLA associated polymorphism
References Frater *et al.* 2007

- To study whether CTL responses restricted by "good" HLA I molecules exert stronger immune selection than other HLA I molecules, 54 and 70 optimal epitopes within HIV-1 Gag, Pol and Nef genes for Caucasian and African cohorts were tested in patients over a mean of 14 months. "Good", advantageous HLA allele-restricted epitopes were much more polymorphic than epitopes restricted by other, non-advantageous HLA in patients, suggesting that benefits associated with HLA Class I alleles of elite controllers of disease progression are epitope-specific. Such "driver" epitopes with high polymorphism had high frequency of immune response, allowing them to be ranked for recognition and polymorphism.
- Patients with higher proportions of mutated epitopes also had lower plasma viral loads, and mean epitope variability correlated negatively with relative hazard of disease progression.
- Variants KkWIILGLNK and KRWIImGLNK/KRWIIiGLNK at positions 2 and 6 were found. Phylogenetic analysis identified the leucine at position 6 to be under strong positive selective pressure.

HXB2 Location p24 (131–140)
Author Location
Epitope `KRWIILGLNK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*27)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Addo *et al.* 2007

- Maturation phenotypes of CTLs were compared between HIV-1 Controller and Progressor subjects. Controllers were found to recognize a median of 18 epitopes compared to 15 by Progressors. While Controllers certainly had higher frequencies of terminally differentiated effector CTLs (CD45RA+/CCR7-), Progressors had higher mean frequencies of CD45RA-/CCR7- effector memory, CD45RA-/CCR7+ central memory (statistically significant) and CD45RA+/CCR7+ naive CTLs. No correlation was seen between CTL effector phenotype and either HLA-type or epitope.

CTL CD8+

- B*27-restricted epitope KRWIILGLNK does not correlate with any particular CTL maturation phenotype even though Controllers had similar viral loads.

HXB2 Location p24 (131–140)
Author Location p24 (131–140)
Epitope KRWIILGLNK
Epitope name KK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*27)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords rate of progression, acute/early infection, memory cells
References Sabbaj *et al.* 2007

- CD127 hi memory CTLs were correlated with different patient groups - subjects with chronic HIV-1 infection or controllers or those treated early with ART. For patients with chronic infection, CD127 hi CTL levels decrease greatly. Early ART treatment alone maintained these long-lived memory T cells.
- In response to epitope KK10, KRWIILGLNK, IFN-gamma was produced by CD127 lo cells in chronic patients without viremia. IL-2 and TNF-alpha were not secreted. In patients with early ART, IFN-gamma was secreted by both CD127 hi and lo cells before treatment but was maintained in CD127 hi cells after treatment. CD127 hi cells were responsible for producing IL-2 and TNF-alpha after ART. HLA-restriction to KK10 was -B*27.

HXB2 Location p24 (131–140)
Author Location Gag
Epitope KRWIILGLNK
Epitope name KK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*27)
Country Canada
Keywords HLA associated polymorphism
References Brumme *et al.* 2008b

- A large chronically infected, treatment naïve cohort was studied to identify and organize HLA I-associated polymorphisms in Gag into an immune escape map. Insertion polymorphisms at p17 C-terminus were associated with HLA-B*44, -A*32, -C*05. Inverse correlations were found between number to HLA-associated sites and pVL as well as escaped Gag residues and pVL. pVL positively correlates with CD4 T-cell count. No enrichment for HLA-associated polymorphisms are seen at anchor residues, showing that CTL escape is primarily not through abrogation of peptide-HLA binding.
- B*27-restricted p24 KK10 epitope has HLA-associated substitutions at codons 264 and 268.

HXB2 Location p24 (131–140)
Author Location Gag (263–272)
Epitope KRWIILGLNK
Epitope name KK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*27)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, CTL suppression of replication
Keywords rate of progression, escape
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- In this epitope, the ES had N271H substitution (KRWIILGLhK), which is very rare in B clade isolates. N271H substitution caused a 40% reduction in infectivity, likely contributing to the reduced fitness of the isolates from the ES.
- N271H substitution in this epitope (KRWIILGLhK) is a partial escape mutation. Mutant elicited lower level of IFN-γ secretion and activated fewer polyfunctional KK10-specific CD8+ T cells. However, at high concentrations both peptides induced robust clonal expression and proliferation.

HXB2 Location p24 (131–140)
Author Location Gag (263–272)
Epitope KRWIILGLNK
Epitope name KK10
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*27)
Country Canada, South Africa
Keywords escape, HLA associated polymorphism, compensatory mutation
References Carlson *et al.* 2008

- A statistical model, the phylogenetic dependency network (PDN), was developed to differentiate the confounding effects of codon variation, linkage disequilibrium of HLA alleles and HIV phylogeny from HLA-associated evolution including HIV selection by HLA-pressure and codon evolution.
- This approach was applied to 2 cohorts of 1144 Gag sequences from HIV-infected individuals, generating associations between HIV codons themselves and codons with HLA alleles. Results generated predicted escapes that confirmed that escape kinetics and compensating mutations are consistent across clades. General patterns of covariation and CTL adaptation were determined. Some clade-based differences were identified.
- In these cohorts HLA-B27 is found to correlate with escape at position 264 of its restricted epitope KK10, KRWIILGLNK, to KkWIILGLNK and KgWIILGLNK. Moreover, most KK10 compensations are proximal where codon pairs in a compensatory pathway are in close proximity and are likely required to maintain structural fidelity.

CTL CD8+

- As reported before, the KkWIILGLNK mutation is preceded by L268M, KRWIImGLNK in this prediction. L268M, KRWIImGLNK, itself is predicted by the HLA, B*27. Substitution A146P is associated with wildtype L268 sequence.
- A replicative compensation, S173A, was previously described for R264K, KkWIILGLNK. A strong association was confirmed using PDN, with new associations with I267V, KRWIvLGLNK and L215M. I267V, KRWIvLGLNK is predicted by the substitution A163X.
- Another association confirmed by PDN is that E260D compensates for the R264G mutation KgWIILGLNK but not R264K. Also, regardless of position 260's being E in clade B and D in clade B, if a viral sequence possessed mutant R264G i.e. KgWIILGLNK, then it was always a 260D. KgWIILGLNK is strongly associated with the Q136R substitution.

HXB2 Location p24 (131–140)
Author Location p24 (263–272)
Epitope `KRWIILGLNK`
Epitope name KK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*27)
Country Australia, Canada, Germany, United States
Keywords immune evasion, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*27-associated substitutions within optimally defined epitope KRWIILGLNK are at positions R2 (R264K) and L6 (L268M), KrWIIlGLNK. In spite of being the most frequently targeted epitope in early infection, KK10 is only the 20th most rapidly evolving. 5/11 subjects selected R264K and 2 more selected both R264K and L268M.

HXB2 Location p24 (131–140)
Author Location p24 (260–269 HIV-2)
Epitope `RRWIQLGLQK`
Immunogen
Species (MHC) human (B*2703)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*2703 epitope.

HXB2 Location p24 (131–140)
Author Location p24
Epitope `KRWIILGGLNK`
Immunogen HIV-1 infection
Species (MHC) human (B*2705)
Keywords dynamics, acute/early infection
References Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B2705; and A*0201, A*0301, B2705, B39.
- Tetramers with peptide variants KRWIILGGLNK and KRWIIMGGLNK were used – CTL from most B27 donors recognize both variants, although one of the three subjects recognized only KRWIILGGLNK.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK.
- The subject with A*0201 had a moderately strong strong response to SLYNTVATL.
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705.
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

HXB2 Location p24 (131–140)
Author Location p24 (263–272 LAI)
Epitope `KRWIILGLNK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*2705)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*2705 epitope.

HXB2 Location p24 (131–140)
Author Location p24 (263–272)
Epitope `KRWIILGLNK`
Immunogen HIV-1 infection
Species (MHC) human (B*2705)
Keywords escape
References Kelleher *et al.* 2001b

- A mutation in 4/5 B*2705 patients had substitution to lysine (K) at HIV-1 gag residue 264 (R264K), in three the change occurred late in infection – in one patient a substitution of glycine at HIV-1 gag residue 264 (R264G) was detected – these substitutions reduce binding to B27.
- The R264K mutations were associated with a L268M mutation that may be compensatory, and R264G occurred in conjunction with E260D.
- Positions 260, 264, and 268 all lie along one aspect of helix seven of the capsid protein, a region that is important for capsid self-association and assembly.
- R264G and R264K escape mutation outgrowth occurred in conjunction with high viral loads.

HXB2 Location p24 (131–140)
Author Location p24 (263–272)
Epitope KRWIIMGLNK
Immunogen HIV-1 infection
Species (MHC) human (B*2705)
References Appay *et al.* 2000

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α

HXB2 Location p24 (131–140)
Author Location p24
Epitope KRWIILGLNK
Subtype A, B, C, D
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human (B*2705)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location p24 (131–140)
Author Location Gag (263–272)
Epitope KRWIILGLNK
Epitope name KK10
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Protease
Species (MHC) human (B*2705)
Donor MHC A2, B27, B44, Cw2, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay, Degranulation, CD107a and b cell surface mobilization
Keywords vaccine-specific epitope characteristics, vaccine-induced epitopes, immunodominance, escape, TCR usage, characterizing CD8+ T cells
References Betts *et al.* 2005

- A vaccinated HIV-negative individual exhibited features predicted to be necessary for vaccine-induced protection: killing ability, cytokine production, multifunctionality, proliferative capacity, polyclonality, memory phenotype, and a CD8 T-cell response directed against a highly immunodominant epitope correlated with long-term nonprogression. In spite of this, the subject became infected with HIV through homosexual contact. The subject progressed more rapidly than expected for an HLA-B27-positive individual.
- After infection, CD4+ and CD8+ T cells acquired functional characteristics typical of chronic HIV infection. The infecting virus escaped the vaccine-induced T-cell response with an R264G substitution, KgWIILGLNK, which diminishes binding to B27, between the second and third year of infection.

HXB2 Location p24 (131–140)
Author Location p24 (131–140)
Epitope KRWIILGLNK
Epitope name KRW
Immunogen HIV-1 infection
Species (MHC) human (B*2705)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells
References Turnbull *et al.* 2006

- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.
- This epitope, B27-KRW is very strongly associated with delayed disease progression and its alanine-substituted variants are highly efficiently cross-recognized.

HXB2 Location p24 (131–140)
Author Location
Epitope KRWIILGLNK
Immunogen HIV-1 infection
Species (MHC) human (B*2705)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding

Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope KRWIILGLNK elicited a magnitude of response of 1510 SFC with a functional avidity of 0.001nM.

HXB2 Location p24 (131–140)
Author Location Gag
Epitope `KRWIILGLNK`
Epitope name KK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*2705)
Assay type Cytokine production, proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, escape, dendritic cells, immune evasion
References Lichterfeld *et al.* 2007a

- A variant of this epitope KK10, KRWIImGLNK (L6M), arises due to CTL escape and increases binding to Immunoglobulin-like transcritp-4 (ILT4), leading to functional inhibition of DCs. Not only was KK10-L6M not recognized by CTLs but other variants like R2K and R2T were. During chronic infection, this variant recruited an alternative TCRalpha and beta, being immunogenic enough to elicit a de novo CTL response. Finally, enhanced binding of this HLA-B*2705-KK10-L6M complex to ILT4 occurred, resulting in an impairment of DC function as measured by the markers HLA-DR, CD83, CD40, CD180 and CD86.

HXB2 Location p24 (131–140)
Author Location p24 (263–272)
Epitope `KRWIILGLNK`
Epitope name KK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*2705)
Country United States
Assay type Chromium-release assay, Other
Keywords escape, compensatory mutation
References Schneidewind *et al.* 2008

- Variants at position R264 of epitope KK10, KRWIILGLNK, were studied in an in vitro coculture assay. HLA-B*27 subjects can control HIV-1 through its immunodominant epitope KK10. Escape at KK10 usually occurs through R264K, KkWIILGLNK, along with an upstream compensatory S173A mutation. While alternative mutations at R264 - KgWIILGLNK, KqWIILGLNK, KtWIILGLNK - have less severe replicative defects, R264K is still preferred. Viral replication is least impaired with the R264K plus S173A double mutant.
- Since the double variant, R264K+S173A, is the dominant one, and also has least impact on viral replication, it is suggested that functionally, a minimal threshold of HIV replication may be necessary to select the dominant quasispecies.
- During HIV-1 replication cycles, there is a bias in frequency of G-to-A substitutions, providing an initial structural reason for selection of the R264K mutation.
- Other KK10 variants that may be seen are KRWIImGLNK, KkWIImGLNK KqWIImGLNK and KtWIImGLNK.
- Upstream of KK10, 2 variants that may be seen are (1) the previously discussed, relatively common S173A change from PMFSALS (Gag170-176) to PMFaALS along with R264K,L268M (KkWIImGLNK); as well as (2) the rare change from PVGEIY (Gag257-262) to PVGdIY along with R264G, KgWIILGLNK. Both are double variants.

HXB2 Location p24 (131–140)
Author Location p24 (263–272 LAI)
Epitope `KRWIILGLNK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*2705, B27)
Keywords review, rate of progression, immunodominance, escape
References Goulder *et al.* 1997c; Goulder *et al.* 1997a

- HLA-B*2705 is associated with slow HIV disease progression.
- 11/11 HLA-B*2705 donors make a response to this epitope, usually an immunodominant response.
- This is a highly conserved epitope.
- The HLA-B*2705 binding motif includes R at position 2, and L in the C-term position.
- Goulder *et al.* [1997a] is a review on CTL immune escape that discusses this epitope in the context of the difficulty in detection of immune escape – KRWIILGLNK and an R2K change, KKWIILGLNK, show little difference in titration curves, yet the K2 variants fail to bind to targets for more than 1 hour, while the R2 form can sensitize lysis by CTL for over 24 hours – minigene transfection experiments confirmed the importance of this for the CTL response.

HXB2 Location p24 (131–140)
Author Location p24 (260–269 HIV-2)
Epitope `RRWIQLGLQK`
Immunogen
Species (MHC) human (B27)
References Brander & Walker 1996

- HIV-2, HLA-B*2703, S. Rowland-Jones, pers. comm.

HXB2 Location p24 (131–140)
Author Location p24 (263–272 LAI)
Epitope `KRWIILGLNK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords dendritic cells
References Fan *et al.* 1997

- The capacity of dendritic cells to process and present antigen and stimulate anti-HIV-1 CTL memory responses was studied.

HXB2 Location p24 (131–140)
Author Location Gag (263–272)
Epitope KRWIILGLNK
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords epitope processing, dendritic cells
References Zheng *et al.* 1999

- Protein delivery (gp160 LAV, p66 LAV, and p24 NY5) to human dendritic cells (DC) with liposomes provides enhanced memory CTL response relative to delivery of protein alone.
- Chloroquine administration enhanced epitope presentation, and brefeldin A and peptide aldehyde inhibitors inhibited antigen presentation, suggesting epitopes were processed by classical proteasome pathway.
- The CTL response to p24 was measured in individuals with a response to B27-KRWIILGLNK.

HXB2 Location p24 (131–140)
Author Location p24 (263–272 LAI)
Epitope KRWIILGLNK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords dynamics, TCR usage
References Wilson *et al.* 1998a

- HIV+ individuals were followed longitudinally using MHC tetramers in combination with 14 anti-BV chain MAbs, and clonal expansion of HIV-specific T cells was followed *in vivo*.
- Seven HIV+ people were studied, and all showed expansions of particular TCR BV clones, often several, relative to uninfected controls.
- Three patients were followed in detail, TCR VB expansions persisted for 2 to 3 years, with occasional transient increases.

HXB2 Location p24 (131–140)
Author Location p24
Epitope KRWIILGLNK
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords review
References Rowland-Jones *et al.* 1997

- Described in this review as the first identified HIV CTL epitope.

HXB2 Location p24 (131–140)
Author Location p24 (263–272 LAI)
Epitope KRWIILGLNK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Buseyne *et al.* 1993b

- Clustering of Gag p24 CTL epitopes recognized in 29 HIV-infected people.

HXB2 Location p24 (131–140)
Author Location p24 (263–272 LAI)
Epitope KRWIILGLNK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords review
References McMichael & Walker 1994

- Review of HIV CTL epitopes.

HXB2 Location p24 (131–140)
Author Location p24 (263–272)
Epitope KRWIIMGLNK
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Klenerman *et al.* 1994

- Naturally occurring variant KRWIILGLNK may act as antagonist.

HXB2 Location p24 (131–140)
Author Location p24 (263–272)
Epitope KRWIIMGLNK
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Klenerman *et al.* 1995

- Naturally occurring variant KRWIILGLNK may act as antagonist.

HXB2 Location p24 (131–140)
Author Location p24 (265–274)
Epitope KRWIILGLNK
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords dynamics, TCR usage
References Moss *et al.* 1995

- In one individual, TCR usage changed over time indicating that new populations of CTL can be recruited.
- TCR usage showed a CTL clonal response to this epitope that persisted over 5 years.
- CTL clones specific for HIV epitopes may represent between 0.2 and 1% of the total CD8+ population of T cells.

HXB2 Location p24 (131–140)
Author Location p24 (265–276)
Epitope KRWIILGLNK
Immunogen
Species (MHC) human (B27)
References Carreno *et al.* 1992

- Included in HLA-B27 binding peptide competition study.

HXB2 Location p24 (131–140)
Author Location p24 (265–274 SF2)
Epitope KRWIILGLNK
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords dynamics, review, immunodominance, escape
References Goulder *et al.* 1997a; Phillips *et al.* 1991

- Longitudinal study of CTL escape mutants – little variation was observed in the immunodominant B27 epitope, relative to B8 epitope.

CTL CD8+

- Goulder *et al.* [1997a] is a review of immune escape that points out that there may be a protective effect associated with B27, and that HLA-B8 individuals tend to progress more rapidly than HLA B27 patients.

HXB2 Location p24 (131–140)
Author Location p24 (263–272)
Epitope KRWIILGLNK
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords review, escape
References Goulder *et al.* 1997a; Nietfeld *et al.* 1995

- Single point mutations were introduced and viral viability and CTL recognition tested – an Arg to Lys change at anchor position P2 abrogates binding to B27, but doesn't change viral viability *in vitro*.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

HXB2 Location p24 (131–140)
Author Location p24 (263–272)
Epitope KRWIIMGNK
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords escape
References Nowak *et al.* 1995

- Longitudinal study of CTL response and immune escape – the form KRWIILGNK was also found, and both forms stimulate CTL.

HXB2 Location p24 (131–140)
Author Location p24 (263–272)
Epitope KRWIILGNK
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords subtype comparisons
References Durali *et al.* 1998

- Cross-clade CTL response was studied by determining the CTL activity in seven patients from Bangui, (6 A subtype, and 1 AG recombinant infections) and one A subtype infection from a person living in France originally from Togo, to different antigens expressed in vaccinia.
- Pol reactivity: 8/8 had CTL to A subtype, and 7/8 to B subtype, and HIV-2 Pol was not tested.
- Gag reactivity: 7/8 reacted with A or B subtype gag, 3/8 with HIV-2 Gag.
- Nef reactivity: 7/8 reacted with A subtype, and 5/8 with B subtype, none with HIV-2 Nef.
- Env reactivity: 3/8 reacted with A subtype, 1/8 with B subtype, none with HIV-2 Env.
- One of the patients was shown to react to this epitope: KRWIILGNK.

HXB2 Location p24 (131–140)
Author Location p24 (263–272)
Epitope KRWIIMGLNK
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords review, immunodominance, escape
References Goulder *et al.* 1997f; Goulder *et al.* 1997a

- Six HLA-B27 donors studied make a strong response to this epitope.
- In 4/6 cases, this was the immunodominant or only CTL response.
- Two of the cases had an epitope switch to the form KKWIIMGLNK during a period of rapid decline to AIDS, following their asymptomatic period.
- The arginine to lysine switch is in an anchor residue, and results in immune escape due to severely diminished binding to the B27 molecule.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study in the context of CTL escape to fixation.

HXB2 Location p24 (131–140)
Author Location p24
Epitope KRWIILGLNK
Immunogen
Species (MHC) human (B27)
References Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective.
- HIV-2 sequence: RRWIQLGLQK – this epitope was not HIV-1 and HIV-2 cross-reactive.

HXB2 Location p24 (131–140)
Author Location Gag (263–)
Epitope KRWIILGLNK
Immunogen computer prediction
Species (MHC) (B27)
Keywords subtype comparisons
References Schafer *et al.* 1998

- This study uses EpiMatrix for T cell epitope prediction to identify possible HLA-B27 and A-2 CTL epitopes in HIV.
- Based on EpiMatrix predictions, 28 peptides were synthesized and tested using T2 binding assays for potential HLA A2 or B27 binding, and 12 of these were shown to bind to the predicted HLA molecule.
- Two of these 12 peptides had been previously identified as CTL epitopes: HLA-B27 KRWILGLNK and HLA-A2 ILKEPVHGV.
- This peptide sequence is not conserved between clades, but is found in most B clade isolates.

HXB2 Location p24 (131–140)
Author Location p24 (263–282)
Epitope KRWIILGLNK
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Bernard *et al.* 1998

- This study focuses on six rare long-term survivor HIV-infected people who were infected for many years without exhibiting immune dysregulation – such immunologically normal HIV-infected (INHI) cases occur at a frequency between 0.1 and 1% in the infected population.
- No direct CTL were found in any of the six INHIs, but above background CTLp activity was founded in 3/6 INHIs.

- Epitope sequences were deduced from larger reactive peptides based on HLA binding motifs – XRXXXXXXXK is a B*2705 binding motif.

HXB2 Location p24 (131–140)
Author Location p24 (265–274 SF2)
Epitope KRWIILGLNK
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B27+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/0 group 2, and 1/1 group 3.

HXB2 Location p24 (131–140)
Author Location p24 (263–272)
Epitope KRWIILGLNK
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B27)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Subject ML 1760 had an A2 response to ILK(D/E)PVHGV prior to seroconversion, and gained responses to epitopes A2 SL(F/Y)NTVATL and B27 KRWII(L/M)GLNK post-seroconversion.

HXB2 Location p24 (131–140)
Author Location p24 (131–140)
Epitope KRWIILGLNK
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Day *et al.* 2001

HXB2 Location p24 (131–140)
Author Location p24 (260–299)
Epitope RRWIQLGLQK
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Day *et al.* 2001

HXB2 Location p24 (131–140)
Author Location p24 (131–140)
Epitope KRWIILGLNK
Epitope name KK10
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords responses in children, mother-to-infant transmission, immunodominance, escape, acute/early infection
References Goulder *et al.* 2001b

- 85% of B27+ adults have CTL that recognize this epitope, but only 2/6 children did.
- Responses to this dominant B27-restricted Gag epitope are present during the time of decreasing viral load in acute infection.
- Three children who shared B27 with their mothers did not respond to this epitope and inherited escape mutations from their mothers.
- A transmitted R132T anchor residue mutation abrogated binding to B27.
- In the three children infected with the non-binding KK10 variants, the dominant CTL specificity was still HLA-B27-restricted, but it was directed against an epitope in p17, IRLRPGGKK, only rarely recognized in adults when KRWIILGLNK is the dominant response.
- Mutations in this epitope were observed in autologous clones of subjects who were B27-positive with a higher frequency than those who were B27-negative (P = 0.0005)
- These mutations are being sexually transmitted in adult infections.

HXB2 Location p24 (131–140)
Author Location
Epitope KRWIILGLNK
Epitope name Gag-KK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B27, 2/3 (66%) recognized this epitope.

HXB2 Location p24 (131–140)
Author Location p24 (263–272 LAI)
Epitope KRWIIMGLNK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords HAART, ART, epitope processing, immunodominance
References Kelleher *et al.* 2001a

CTL CD8+

- Ritonavir (RTV) inhibits chymotryptic activity in the 20S proteasome *in vitro*, as does Saquinavir (SQV) to a lesser extent; Indinavir (IDV) does not. Thus there is concern protease inhibitors may adversely effect CTL epitope processing, but this paper indicates that processing is not inhibited at therapeutically relevant concentrations of RTV when the proteasome is functioning in an intracellular context.
- RTV did not reduce antigen presentation and concentration of the two immunodominant Gag CTL epitopes (KRWIIMGLNK (B27) and SLYNTVATL (A2)).
- RTV did not inhibit the processing and assembly of HLA-B35 or -A2, which are assembled with a rapid and moderate time course, respectively, or of HLA-A3, -B27 and -B39.

HXB2 Location p24 (131–140)
Author Location p24
Epitope KRWIILGLNK
Epitope name B27-KK10(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Donor MHC A24, B27, B7; A30, A32, B18, B27
Keywords HAART, ART, supervised treatment interruptions (STI)
References Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient C displayed the greatest response to B27-KK10(p24), and in decreasing order also responded to A24-RW8(Nef), B7-IL9(gp41), A24-RL9(gp41), A24-YL8(gp41), and B7-TM9(Nef). Patient D also displayed the greatest response to B27-KK10(p24), and also responded to A30-RY11(p17), A32-PW10(RT), A30-KY11(RT), A32-RW10(gp120), and B18-YY9(Nef).

HXB2 Location p24 (131–140)
Author Location Gag (263–272)
Epitope KRWIILGLNK
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (B27)
Donor MHC B27
Keywords subtype comparisons
References Currier *et al.* 2002a

- Cross-reactive responses were found in PBMC isolated from individuals infected with either B or CRF01_AE clade viruses, as determined by Elispot assays of target cells expressing recombinant vaccinia viruses expressing HIV-1 gag, env, nef and pol from many clades.
- Subject AIHP-6 (Thai, CDF01-AE infected) recognized this epitope. This subject showed cross-subtype CTL responses to gag constructs derived from subtypes A, B, C, D, F, G, and H, and this epitope was perfectly preserved in all of these but subtype A which had the sequence KRWMILGLNK.
- This subject didn't respond to a Gag CRF01 sequence which had a R->K mutation in position 2.

HXB2 Location p24 (131–140)
Author Location Gag
Epitope KRWIILGLNK
Epitope name KK10
Immunogen HIV-1 infection
Species (MHC) human (B27)
Donor MHC A26, B27
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, rate of progression, immunodominance, escape
References Feeney *et al.* 2004

- Viral load in a perinatally infected child remained low until emergence of an escape variant (kTwiilglnk) in the immunodominant CTL epitope KRWIILGLNK when the child was 7.4 years old. The emergence of this escape mutation was followed by an increase in viremia and an increase in the number of targeted CTL epitopes, measured again when the child was 9.2 years old. The timing suggests that the loss of recognition of this epitope may have resulted in the subsequent loss of immune control.
- The mutation krwillMglnk has been suggested to be compensatory and required for the emergence of the previously described escape mutation kKwillMglnk (Kelleher 2001). The L136M mutation does appear in this child, but not in conjunction with the R132T escape mutation.

HXB2 Location p24 (131–140)
Author Location
Epitope KRWIIMGLNK
Epitope name KK10
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords review, responses in children, vaccine-specific epitope characteristics, rate of progression, escape
References Goulder & Watkins 2004

- This paper is a review of the role of CTL in HIV infection, and it uses KK10 as an example of an epitope that has late escape mutations associated with loss of immune control of the virus and decline to AIDS.

- A study where a vaccine response to KK10 was stimulated in a individual who subsequently got infected and had rapid escape from the KK10 response and an unexpectedly high steady state viral load for a B27+ person is recounted as a cautionary note regarding the delicate balance of effects that might contribute to CTL mediated immune control.

HXB2 Location p24 (131–140)
Author Location Gag
Epitope KRWIILGLNK
Epitope name KK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 6, krwiiMglnk, was found in the most polymorphic residue in the epitope.This was shared between clades B and C. One escape mutation, at position 2, kTwiilglnk, was found not to correspond to the most polymorphic residue in the epitope.

HXB2 Location p24 (131–140)
Author Location Gag (263–272 BRU)
Epitope KRWIILGLNK
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 0/9 CRF02_AG-infected Ivorians, and 3/9 B-infected French subjects.

HXB2 Location p24 (131–140)
Author Location p24
Epitope KRWIILGLNK
Epitope name KK10
Immunogen
Species (MHC) (B27)
Keywords review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion
References Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

HXB2 Location p24 (131–140)
Author Location Gag (263–272)
Epitope KRWIILGLNK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Barbados
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, acute/early infection
References Pillay *et al.* 2005

- HIV-specific CTLs in infants were shown to be able to select for viral escape variants early in life, despite a lack of escape with the same CTL specificity in the mother. Infant CTL responses may be compromised by transmission of escape variants that arose in the mother and also those that arose in the father, if the father was the source of the mother's infection.
- A B27 escape footprint was passed from a B27+ father to his partner, who then passed the variant to their child. KRWIILGLNK is the B consensus form of this epitope, the paternal form was KqWIIiGLNK, the maternal form, KqWvImGLNK, and this was the form passed on to the child.

HXB2 Location p24 (131–140)
Author Location Gag (263–272)
Epitope KRWIILGLNK
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Australia
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, rate of progression, immunodominance, escape
References Ammaranond *et al.* 2005

- B27-positive subjects have an immunodominant response to Gag epitope KRWIILGLNK, with R264 KrWIILGLNK being a crucial anchor residue. Among a group of 20 long-term non-progressive B27-positive subjects, 14 carried wild-type sequence, 5 carried known escape mutants (K264 or G264), and 1 carried a novel Q264 mutant. This mutant was also shown to be a likely escape mutation. These escape mutations all lower the affinity for B27 binding; the Q264 variant has 30-fold lower binding affinity.

HXB2 Location p24 (131–140)
Author Location p24
Epitope KRWIILGLNK
Epitope name B27-KK10(p24)
Immunogen HIV-1 infection
Species (MHC) human (B27)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

CTL CD8+

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.
- This epitope, KRWIILGLNK (KK10), elicits the HLA-B27 restricted response that is most dominant of the immune responses generated.

HXB2 Location p24 (131–140)
Author Location p24 (131–140)
Epitope KRWIILGLNK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, subtype comparisons, acute/early infection
References Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (ANC) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- This epitope, KRWIILGLNK, is invariant across CON A, B, C and M-Group sequences, as well as clade B COT and ANC sequences. HLA-B27 restriction was inferred based on subject possessing appropriate HLA class I allele and prior publication

HXB2 Location p24 (131–140)
Author Location p24 (131–140)
Epitope KRWIIMGLNK
Immunogen HIV-1 infection
Species (MHC) human (B27)
Donor MHC A1, A3, B*2705, B35; A2, A22, B*2705, B35
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rates for this epitope, KRWIIMGLNK, were found in 3 subjects to be 0.002, 0.001 and 0.010/day, with SEs of 0.003, 0.003 and 0.011 respectively.
- The escape mutation was R132K in all cases.

HXB2 Location p24 (131–140)
Author Location p24
Epitope KRWIIMGLHK
Epitope name KK10 (263-272)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Donor MHC A2, A68, B27, B35
Country France
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, immunodominance, TCR usage, characterizing CD8+ T cells
References Almeida *et al.* 2007

- Since it is suggested that a single response to B27-KK10 epitope may be responsible for the association of HLA-B*2705 patients with AIDS-free survival, B27-KK10-specific CTLs were compared to other HLA-specific CTLs in phenotype, function, clonal diversity, and antigen sensitivity in 47 treatment-naive infected slow or nonprogressing patients.
- cVL, the cell-associated viral load (number of infected cells harboring HIV DNA) correlated inversely with Gag-specific CTLs. This was most significant in HLA-B27 donors, and KK10 was identified as the peptide generating strongest CTL responses.
- B27-KK10-specific CTLs had no significant phenotypic differences from other epitope-specific CTLs upon testing a large panel of markers; however, they released higher proportions of IFN-gamma, TNF-alpha, MIP-1beta and CD107a upon antigenic stimulation.
- B27-KK10-specific and other HLA-specific CTLs had strikingly consistent domination of single clonotypes. B27-KK10-specific CTLs showed no preferential usage of CDR3 motifs, indicating that they could be recognized by diverse clonotypes with differing binding properties. Over several years, B27-KK10-specific CTLs changed their dominant clonotype as compared to other CTLs. This temporal dominant clonal turnover was attributed to a decline in replicative capacity of

the dominant clonotype as seen by increases in CD57 expression, which is linked to replicative senescence.

- Studies involving functional avidity and different HLA-restricted responses proved that B27-KK10 responses had highest avidity. An inverse correlation between patient cVL and functional avidity of both dominant and highest subdominant responses suggested that functional avidity correlates with capacity to control HIV replication via infected cell elimination.
- Using the example seen in one patient, the authors stress the importance of maintaining protective stimulating activity of CTLs. When control by dominant clonotypes is lost, as in viral escape, ensuing viral replication is rapid.
- In one B27-positive patient studied, the dominantly-targeted epitope sequence changed over time from KRWIIMGLHK to KRWIIlGLnK. TCR sequences were studied in 11 patients.

HXB2 Location p24 (131–140)
Author Location
Epitope `KRWIILGLNK`
Epitope name KK10
Immunogen HIV-1 infection, peptide-HLA interaction
Species (MHC) human, mouse (B27)
Assay type Tetramer binding, Chromium-release assay, HLA binding
Keywords assay standardization/improvement, review, epitope processing, escape, structure, optimal epitope
References McMichael 2007a

- This historical essay recounts the discovery of antigenic peptide processing by MHC-I. New techniques, the first epitope in HIV (KK10), epitope identification, escape mutations and HLA type are discussed with respect to CTLs in HIV infection control.

HXB2 Location p24 (131–140)
Author Location
Epitope `KRWIILGLNK`
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (B27)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location p24 (131–140)
Author Location Gag
Epitope `KRWIILGLNK`
Epitope name KK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Australia, Canada, United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, escape, immune evasion, optimal epitope
References Streeck *et al.* 2007a

- To characterize HIV-1 proteome areas that are targeted in early, effective CTL responses, two cohorts were studied. Responses in early infection were against fewer epitopes and of lower magnitude than during chronic infection. While no region of the proteome was favored, Nef was the predominant target based on length of proteins.
- When based on the expression of protective versus nonprotective HLA I alleles, it was found that HLA-B27 and -57 possessing slow progressors to disease directed the majority of their responses to Gag in early infection, as opposed to those with HLA-B*3501 or B*3502, i.e. rapid progressors to AIDS, who had negligible responses to Gag. As compared with HLA-B57-/B27- subjects and HLA-B35 subjects, HLA-B57+/27+ subjects responded most to the p24 component of Gag. By using overlapping peptides within Gag p24, two were picked as being consistently targeted, and both contained previously described epitopes TSTLQEQIGW and KRWIIL-GLNK.
- KRWIILGLNK, epitope KK10, is one of two immunodominant epitopes targeted during early infection in long term nonprogressors to AIDS. Only in later phases of infection, after accumulation of compensatory mutations do most subjects develop variants.

HXB2 Location p24 (131–140)
Author Location p24
Epitope `KRWIIMGLNK`
Epitope name KK10 (263-272)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Donor MHC A2, A32, B27, B39; A24, A3, B27, B7; A3, A32, B27, B35
Country France
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, immunodominance, characterizing CD8+ T cells
References Almeida *et al.* 2007

- Since it is suggested that a single response to B27-KK10 epitope may be responsible for the association of HLA-B*2705 patients with AIDS-free survival, B27-KK10-specific CTLs were compared to other HLA-specific CTLs in phenotype, function, clonal diversity, and antigen sensitivity in 47 treatment-naive infected slow or nonprogressing patients.
- cVL, the cell-associated viral load (number of infected cells harboring HIV DNA) correlated inversely with Gag-specific CTLs. This was most significant in HLA-B27 donors, and KK10 was identified as the peptide generating strongest CTL responses.

- B27-KK10-specific CTLs had no significant phenotypic differences from other epitope-specific CTLs upon testing a large panel of markers; however, they released higher proportions of IFN-gamma, TNF-alpha, MIP-1beta and CD107a upon antigenic stimulation.
- B27-KK10-specific and other HLA-specific CTLs had strikingly consistent domination of single clonotypes. B27-KK10-specific CTLs showed no preferential usage of CDR3 motifs, indicating that they could be recognized by diverse clonotypes with differing binding properties. Over several years, B27-KK10-specific CTLs changed their dominant clonotype as compared to other CTLs. This temporal dominant clonal turnover was attributed to a decline in replicative capacity of the dominant clonotype as seen by increases in CD57 expression, which is linked to replicative senescence.
- Studies involving functional avidity and different HLA-restricted responses proved that B27-KK10 responses had highest avidity. An inverse correlation between patient cVL and functional avidity of both dominant and highest subdominant responses suggested that functional avidity correlates with capacity to control HIV replication via infected cell elimination.
- Using the example seen in one patient, the authors stress the importance of maintaining protective stimulating activity of CTLs. When control by dominant clonotypes is lost, as in viral escape, ensuing viral replication is rapid.
- In one B27-positive patient studied, the dominantly-targeted epitope sequence changed over time from KRWIIMGLNK to KRWIIGLqK. TCR sequences were studied in 11 patients.

HXB2 Location p24 (131–140)
Author Location p24
Epitope `KRWIILGLNK`
Epitope name KK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords immunodominance, superinfection
References Streeck *et al.* 2008b

- Loss of viral replication control by an elite controller after superinfection was found to coincide with rapid recombination events in 2, ∼50 residue regions of Gag and Env that include immunodominant epitopes KK10 (KRWIILGLNK) and CL9 (CAPAGFAIL). Viral escape was seen at both epitopes and consequent CTL responses against the epitope-variants.
- Previously described epitope KRWIILGLNK is HLA-B27 restricted. Early immunodominance of the KK10-specific CTL response was followed by the stereotypical L268M escape to KRWIImGLNK and then its equivalent control via variant-specific CTLs. Variant R264K to KkWIILGLNK did not appear in the primary infection.
- Superinfection resulted in new immunodominances, a reversion to WT KK10 and later escape of the reverted WT KK10 to KkWIILGLNK (R264K), KRWIImGLNK, KRWvILGLNK and KkWIImGLNK. 2 distinct mutations accompanied this last studied escape, T239V and N252S.

HXB2 Location p24 (131–140)
Author Location p24
Epitope `KRWIIILGLNK`
Epitope name KK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- Epitope KRWIIILGLNK varied to KRWIImLGLNK in 2 untreated patients. Previously published HLA-restriction for KK10 is HLA-B27.

HXB2 Location p24 (131–140)
Author Location Gag
Epitope `KRWIILGLNK`
Epitope name KK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- KK10(Gag-p24, 131-140), KRWIILGLNK, is a known HLA-B27-restricted epitope used as a positive control for eliciting CTL IFN-gamma response.

HXB2 Location p24 (131–140)
Author Location
Epitope `KIRWIIGLNK`
Epitope name KK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country United States

Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Chromium-release assay
Keywords TCR usage, characterizing CD8+ T cells
References Alter *et al.* 2008

- By studying HIV-1 dysregulation of CTLs at different infection stages induced by inhibitory KIRs (Killer Immunoglobulin-like receptors), it was determined that KIR surface expression on memory T cells correlates with HIV replication. It results in reduced activation, proliferation, cytokine secretion, and killing following TCR stimulation. Since non-TCR-dependent CTL stimulation was unaffected, TCR-mediated stimulation appears to be defective. KIR induced suppression of CTL function was found to be KIR-ligand-independent.
- KK10-specific CTLs had heterogeneous surface expression of KIR. Of these tetramer positive B27-CTLs, only KIR- cells were able to secrete IFN-gamma upon stimulation. These KK10-specific, HLA-B27-restricted CTL were also used for an HIV inhibition assay.

HXB2 Location p24 (131–140)
Author Location
Epitope KRWIILGLNK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- A broad CTL response was essential to elite control of disease. Immune escape at KRWIILGLNK was not a major cause of disease progression.
- Escape from the peptide sequence EIYKRWIILGLNK to dIYKgWIILGLNK was seen only in 1 subject who exhibited delayed progression to viremia and who initiated ART, but succumbed to non-AIDS death at age 83.

HXB2 Location p24 (131–140)
Author Location Gag (263–272 LAI)
Epitope KRWILLGLNK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Buseyne *et al.* 1993a

- Vertical transmission of HIV ranges from 13% to 39%.
- Primary assays showed that cytotoxic activity against at least one HIV protein was detected in 70% of infected children.
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
- Patient EM28 (CDC P2A) had a CTL response to four epitopes in Gag.

HXB2 Location p24 (131–140)
Author Location Gag (263–272 B27)
Epitope KRWIILGLNK
Epitope name KK10 (263-272)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords review, immunodominance, escape, dendritic cells, immune evasion, viral fitness and reversion, compensatory mutation
References McMichael 2007b

- This commentary summarizes work by Lichterfeld et al. [JEM Vol. 204: 2785-7 (2007)]. HLA-B27 restricted CTLs presented with epitope KK10 (KRWIILGLNK) are known to keep infection at bay in LTPs. However, a triple mutation resulting in viral escape can occur after several years. The mutations are L268M, R264K(T/G) and S173A. L268M occurs early in infection and becomes fixed when bound to HLA-B27, conferring unknown viral advantage that is suggested to be due to its 3-fold higher affinity for ILT4. This may result in impaired DC and monocyte function. It is thought that the triple mutations compensate for each other, stabilizing them.

HXB2 Location p24 (131–140)
Author Location
Epitope KRWIILGLNK
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* Other *HIV component:* gp160
Species (MHC) human
Donor MHC A3, A33; B15 (63), B27
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location p24 (131–140)
Author Location
Epitope KRWIILGLNK

Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords binding affinity, acute/early infection
References Lichterfeld *et al.* 2007b

- Differences in early versus chronic AIDS include a decline in CTL number accompanied by a reducing viremia. Comparative analysis of such CTLs in this study show that early infection is characterized by a different clonotypic composition and higher functional avidity of CTLs followed by their selective depletion during transition to chronic disease. The total magnitude of CTL cytokine production is lower in early infection. Intraindividual, early CTLs' functional avidity for the same epitope decreases concomitantly with a reduction in clonotypic TCR repertoire especially of strongly activated and CD127lo, CD38+, Ki-67hi CTLs while progressing to chronic infection states.
- None of the target epitopes, including this epitope KRWIILGLNK seen in 1 patient, underwent sequence changes.

HXB2 Location p24 (131–140)
Author Location Gag (263–272)
Epitope `KRWIILGLNK`
Epitope name KK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type Other
Keywords escape, acute/early infection, immune evasion, viral fitness and reversion, optimal epitope, compensatory mutation
References Schneidewind *et al.* 2007

- Epitope KK10 in HLA-B27 slow progressors to disease varies late in infection, leading to AIDS. The predominant escape mutation for this epitope is R264K, and it severely compromises virus replication, late in reverse transcription but unrelated to capsid stability. This can be restored by an in vivo upstream compensatory mutation, S173A and modulation of CypA binding in the presence of cyclosporine A. However, the first mutation to arise is the L268M, a prerequisite compensatory mutation to R264K.
- Four HLA-B27 subjects' virus were sequenced longitudinally to find that the KK10 epitope mutates from KRWIILGLNK (WT) to KkWIILGLNK (R264K), KRWIILGmNK (L268M), KkWIImGLNK (R264K/L268M), KRWIILGLNK (S173A), KkWIILGLNK (S173A/R264K), KkWIImGLNK (S173A/R264K/L268M) and KkWIImGLNK (A237T on R264K/L268M).

HXB2 Location p24 (131–142)
Author Location p24 (265–276)
Epitope `KRWIILGLNKIV`
Immunogen peptide-HLA interaction
Species (MHC) human (B27)
References Jardetzky *et al.* 1991

- Epitope examined in the context of peptide binding to HLA-B27.

HXB2 Location p24 (131–142)
Author Location p24 (263–274 LAI)
Epitope `KRWIILGLNKIV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords dendritic cells
References Fan *et al.* 1997

- The capacity of dendritic cells to process and present antigen and stimulate anti-HIV-1 CTL memory responses was studied.

HXB2 Location p24 (131–142)
Author Location p24 (131–142)
Epitope `KRWIILGLNKIV`
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (131–142)
Author Location p24 (265–275)
Epitope `KRWILGLNKIV`
Immunogen HIV-1 infection
Species (MHC) human (B27)
Donor MHC A2, A24, B27, B62
Country United Kingdom
Assay type Flow cytometric T-cell cytokine assay, Other
Keywords HAART, ART, immunodominance, TCR usage, memory cells
References Weekes *et al.* 2006

- The effect of HAART on the population size, phenotype and function of HIV- and HCMV-specific CTL clones was analyzed. It was determined that the clonal composition of gag and env HIV-specific CD8 T-cells did not change after HAART. Following HAART, the size of immunodominant HIV-specific CD8 T-cell clones was found to diminish even with the relative preservation of functional memory responses. Maintainance of such strong functional responses implied the preferential loss of HIV-specific cells that have reduced cloning efficiency in vitro. HCMV-specific CTL clones had different kinetics and phenotypes than HIV-specific CTL clones in the same subject.

HXB2 Location p24 (131–145)
Author Location p24 (263–277 LAI)
Epitope `KRWIILGLNKIVMRY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A33)
References Buseyne *et al.* 1993b

- Clustering of Gag p24 CTL epitopes recognized in 29 HIV-infected people.

HXB2 Location p24 (131–145)
Author Location p24 (266–277)
Epitope `KRWIILGLNKIVRMY`
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* Gag

Species (MHC) human (B27)
References Nixon *et al.* 1988

- Gag CTL epitope mapped with rec gag-vaccinia and synthetic peptides.
- This was the first HIV-1 epitope to be mapped.

HXB2 Location p24 (131–145)
Author Location p24 (266–277 LAI)
Epitope `KRWIILGLNKIVMRY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Meyerhans *et al.* 1991

- Longitudinal study showing persistence of epitope despite CTL activity.

HXB2 Location p24 (131–145)
Author Location p24 (265–279)
Epitope `KRWIILGLNKIVRMY`
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Nixon *et al.* 1990; Rowland-Jones *et al.* 1999

- HIV-1 and HIV-2 cross-reactive CTL clone, highly conserved epitope.
- Reviewed in Rowland-Jones99, notes that it did not appear cross-reactive with HIV-2 in Rowland-Jones98, HIV-2 form: RRWIQLGLQK.

HXB2 Location p24 (131–145)
Author Location p24 (SF2)
Epitope `KRWILGLNKIVRMY`
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a HIV+ African American living in Boston with unknown HLA – this epitope did not fall within the three most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa.

HXB2 Location p24 (131–145)
Author Location p24 (131–145 HXB2)
Epitope `KRWIILGLNKIVRMY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- Responses to this peptide were detected in 16% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location p24 (131–146)
Author Location p24 (265–279)
Epitope `KRWIILGLNKIVRMYC`
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Bouillot *et al.* 1989

- HLA-B27 restricted epitope also binds to HLA-A2 and HLA-B37 in solid phase assay.

HXB2 Location p24 (131–150)
Author Location p24 (265–284 SF2)
Epitope `KRWIILGLNKIVRMYSPTSI`
Immunogen HIV-1 infection
Species (MHC) human (B62?)
References van Baalen *et al.* 1993

- Gag CTL epitope precursor frequencies estimated.

HXB2 Location p24 (131–150)
Author Location p24 (263–282 SF2)
Epitope `KRWIILGLNKIVRMYSPTSI`
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 A-2 had CTL response to this peptide.
- The responding subject was HLA-A3, A32, B51, B62.

HXB2 Location p24 (131–152)
Author Location p24 (263–284 BH10)
Epitope `KRWIILGLNKIVRMYSPTSILD`
Immunogen HIV-1 infection
Species (MHC) human (B62)
References Johnson *et al.* 1991

- Gag CTL response studied in three individuals.

CTL CD8+

HXB2 Location p24 (132–140)
Author Location Gag (261–280)
Epitope RWIILGLNK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Donor MHC A24, A33, B14, B27; A2, A32, B27, B62
Assay type Chromium-release assay
Keywords genital and mucosal immunity
References Musey *et al.* 2003

- CTL clones from blood, semen, cervix and rectum samples from 12 individuals were compared. CTL clones derived from blood and mucosal samples had similar high lysis efficiency, primarily perforin dependent, and TCRβ VDJ region sequencing revealed cases of expansion of the same clone in different compartments.
- CD8+ T cell clones that recognize this epitope were derived from both blood and cervix from a woman, and the blood and semen from a man.

HXB2 Location p24 (132–145)
Author Location Gag
Epitope KWILGLNKIVRMY
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords TCR usage
References Weekes *et al.* 1999b

- Peptide 728: Almost all CD8+ T cells are CD28+ at birth, and the proportion of CD28-CD8+ cells increases with age – this study examines the contribution of CD8+CD28- cells to CTL memory pools for CTL clones specific for two persistent human viruses, CMV and HIV – clones were found to be similarly distributed the CD28 depleted cell population.
- HIV CTL responses to 3 Env and 2 Gag peptides were studied.
- The clonal composition of the TCR Vβ responses were studied and was found to be highly focused, with one TCR beta-chain sequence tending to dominate the peptide-specific response – clones to this epitope were Vβ22.1.

HXB2 Location p24 (132–145)
Author Location Gag
Epitope KWILGLNKIVRMY
Immunogen HIV-1 infection
Species (MHC) human
References Weekes *et al.* 1999a

- Peptide 728: Memory CTL specific for HIV-1 may contribute to oligoclonal expansions within the CD57+ CD28- CD8+ CTLp populations.

HXB2 Location p24 (133–147)
Author Location
Epitope WIILGLNKIVRMYSP
Immunogen HIV-1 infection
Species (MHC) human (A11, A3, B15, B27)
Donor MHC A25, A3, B18, B27; A2, A24, B15, B40; A11, A2, B44, B60; A2, A31, B27, B44
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 67 (NIH ARRP Cat# 7938), WIILGLNKIVRMYSP, contains epitopes restricted by HLA-A3, -A11, -B15 and -B27 in different patients and HLA-A3, -B27 in one patient. This peptide elicited the following CTL responses: (1) only at 22.8 years in one living non-progressor (2) for 22+ years in another living non-progressor (3) 76 sfc/million PBMC for 12 years in a former non-progressor who succumbed to non-AIDS death (4) >5000 sfc/million PBMC in a former non-progressor who succumbed to loss of viremic control.

HXB2 Location p24 (133–147)
Author Location Gag (265–279)
Epitope WIILGLNKIVRMYSP
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the Progressor, who had H441Y substitution.

HXB2 Location p24 (134–141)
Author Location p24 (266–273 SF2, HXBc2/Bal R5)
Epitope IILGLNKI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2, A3)
Donor MHC A2, A3, B15, B7, Cw3, Cw6
Country United States
Assay type Cytokine production, Flow cytometric T-cell cytokine assay, Degranulation, CD107a and b cell surface mobilization

Keywords supervised treatment interruptions (STI), immunodominance, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells, drug resistance
References Daucher *et al.* 2008

- A detailed analysis of 6 chronically infected patients' CTL responses to autologous virus was performed after ART and SIT (structured interruption of therapy). Qualitative responses including degranulation and production of IFN-gamma, MIP-1beta, TNF-alpha, IL-2, but not memory CD27, CD45RO and CD57 T cells correlated with extended low plasma viremia. Frequency and breadth of CTL response as well as immune escape did not influence virological outcome.
- One patient exhibited drug resistance mutations K170R (to NNRTI efavirenz) and D76N, K70R (to NRTIs).
- Data confirmed that autologous epitopes were preferentially recognized over optimal, consensus sequences.
- Patients with favorable virological outcomes demonstrated CTL recognition within multiple, conserved regions of Gag and Nef.
- Patients with poor virological outcomes recognized optimal epitopes with much lower frequencies, though this was not significant.
- HLA-A2 and -A3-restricted epitope, IILGLNKI, elicited a response in 1 patient and is found in Gag immunodominant region WIILGLNKIVRMYS. The patient autologous sequence was ImLGLNKI.

HXB2 Location p24 (134–142)
Author Location Gag (Henan isolate)
Epitope `IILGLNKIV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p24 (134–143)
Author Location Gag
Epitope `IILGLNKIVR`
Subtype A, B, C
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-A3-restricted epitope IILGLNKIVR is from subtype A,B and C peptide libraries, and is reactive in subtype B and subtype C-carrying subjects. This epitope is part of reacting peptide IYKRWIILGNKIVR.

HXB2 Location p24 (134–143)
Author Location Gag (266–275)
Epitope `IILGLNKIVR`
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (A11, A3)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

HXB2 Location p24 (134–143)
Author Location p24 (subtype B)
Epitope `IILGLNKIVR`
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A33)
Keywords subtype comparisons
References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among A, B and D clade viruses.

HXB2 Location p24 (134–143)
Author Location p24
Epitope `IILGLNKIVR`
Epitope name IR10(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A33)

CTL CD8+

Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords optimal epitope
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A33-restricted epitope IILGLNKIVR elicited an immune response in Chinese HIV-1 positive subjects as part of peptide WIILGLNKIVRMYSPTSI.
- 2 of the 20 HLA-A33 carriers responded to an IILGLNKIVR-containing peptide with average magnitude of CTL response of 90 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p24 (135–142)
Author Location Gag (267–274)
Epitope ILGLNKIV
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (A2)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the most frequently recognized of the 31 epitopes that the vaccinated volunteers responded to.

HXB2 Location p24 (135–142)
Author Location Gag (267–274 HXB2)
Epitope ILGLNKIV
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2, A3)
Country Viet Nam
Assay type HLA binding
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- ILGLNKIV is the epitope in the HXB2 reference strain sequence, and is also the most common form in CRF01.

HXB2 Location p24 (135–142)
Author Location p24 (135–142)
Epitope ILGLNKIV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*27)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, ILGLNKIV, was detected within overlapping peptide PVGEIYKRWIILGLNKIV.

HXB2 Location p24 (135–142)
Author Location p24 (135–142)
Epitope ILGLNKIV
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope ILGLNKIV is highly conserved across clades (100% to subtype A, >60% to subtype D, and is predicted to be restricted by HLA-A*0201, using 2 different peptides.

HXB2 Location p24 (135–143)

CTL CD8+

Author Location Gag (267–275)
Epitope ILGLNKIVR
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (A11, A3)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

HXB2 Location p24 (135–145)
Author Location Gag (267–277)
Epitope ILGLNKIVRMY
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (B7 supertype)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the most frequently recognized of the 31 epitopes that the vaccinated volunteers responded to.
- A response to this peptide was induced in three patients after immunization with lipopeptides alone (no adjuvant) after the third and the fourth boost, and induced in two patients after immunization with lipopeptides and QS21 adjuvant after the third boost. Variant IyGLNKIVRMY was also recognized in two patients.

HXB2 Location p24 (136–145)
Author Location p24 (268–277 LAI)
Epitope LGLNKIVRMY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62)
Keywords review
References McMichael & Walker 1994

- Predicted from larger peptide.
- Review of HIV CTL epitopes.
- Also P. Johnson, pers. comm.

HXB2 Location p24 (136–146)
Author Location p24 (271–281)
Epitope LGLNKIVRMYS
Immunogen HIV-1 infection
Species (MHC) human (B62)
Keywords TCR usage
References Lubaki *et al.* 1997

- Eighty two HIV-1-specific CTL clones from 5 long-term non-progressors were isolated and analyzed for breadth of response.
- A sustained Gag, Env and Nef response was observed, and clones were restricted by multiple HLA molecules, indicating a polyclonal response.
- A subject who was B62+ had CTL that recognized this peptide, p17 KIRLRPGGKKKYKL, and one additional unknown epitope.
- The two clones that recognized this epitope used two different Vβ genes, further demonstrating a polyclonal response.

HXB2 Location p24 (136–146)
Author Location p24 (136–146)
Epitope LGLNKIVRMYS
Immunogen HIV-1 infection
Species (MHC) human (B62)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (136–146)
Author Location Gag (275–285)
Epitope LGLNKIVRMYS
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p24 (136–150)
Author Location p24 (136–150 HXB2)
Epitope LGLNKIVRMYSPTSI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment

CTL CD8+

References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized—the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized. A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- Responses to this peptide were detected in 16% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location p24 (137–145)
Author Location p24 (272–280 LAI)
Epitope GLNKIVRMY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1501)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*1501 epitope.

HXB2 Location p24 (137–145)
Author Location Gag (269–277 SUMA)
Epitope GLNKIVRMY
Epitope name Gag GY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1501)
Donor MHC A*1103, A*2402, B*1402, B*1501, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, acute/early infection, characterizing CD8+ T cells
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape muations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

HXB2 Location p24 (137–145)
Author Location p24 (137–145)
Epitope GLNKIVRMY
Immunogen HIV-1 infection
Species (MHC) human (B*1501)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope GLNKIVRMY was predicted to be restricted by HLA A*0203, A1, B*1501.

HXB2 Location p24 (137–145)
Author Location
Epitope GLNKIVRMY
Immunogen HIV-1 infection
Species (MHC) human (B*1501)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.

- Epitope GLNKIVRMY elicited a magnitude of response of 510 SFC with a functional avidity of 0.25nM.

HXB2 Location p24 (137–145)
Author Location Gag (B con)
Epitope GLNKIVRMY
Epitope name GY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B15)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Draenert *et al.* 2004c

- CD8+ T-cell responses that persisted in individuals with advanced disease were studied; most of the optimal epitopes defined were recognized with intermediate to high avidity. On average 13 (range, 2-39) epitopic regions were targeted in an average of 6 proteins (range, 1-8). HAART resulted in decrease in antigen and reduction in gamma IFN EliSpot responses, suggesting active responses to autologous virus. The lack of mutations within most viral epitopes suggest that persistent CTL through late disease do not exert strong immune selection pressure, yet the Elispot assays show robust responses, suggesting to the authors that gamma IFN-based screening methods may not reveal functional CD8+ T-cell impairment in patients with AIDS.
- 1 subject recognized this epitope with intermediate functional avidity. The autologous sequence matched the B consensus.

HXB2 Location p24 (137–145)
Author Location p24
Epitope GLNKIVRMY
Epitope name B15-GY9(p24)
Immunogen HIV-1 infection
Species (MHC) human (B15)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (137–145)
Author Location Gag
Epitope GLNKIVRMY
Subtype A, B
Immunogen HIV-1 infection
Species (MHC) human (B15)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA B15-restricted epitope GLNKIVRMY is from subtype A and B peptide libraries, and is reactive in subtype A and B-carrying subjects as part of peptides IILGLNKIVRMYSPV and IIVGLNKIVRMYSPV respectively.

HXB2 Location p24 (137–145)
Author Location p24
Epitope GLNKIVRMY
Epitope name GY9(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B15)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B15-restricted epitope GLNKIVRMY elicited an immune response in Chinese HIV-1 positive subjects as part of peptide WIILGLNKIVRMYSPTSI.
- 5 of the 21 HLA-B15 carriers responded to GLNKIVRMY-containing peptide with average magnitude of CTL response of 204 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p24 (137–145)
Author Location p24 (269–277 SF2, HXBc2/Bal R5)
Epitope GLNKIVRMY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B15)
Donor MHC A2, A3, B15, B7, Cw3, Cw6
Country United States
Assay type Cytokine production, Flow cytometric T-cell cytokine assay, Degranulation, CD107a and b cell surface mobilization
Keywords supervised treatment interruptions (STI), immunodominance, characterizing CD8+ T cells, drug resistance

CTL CD8+

CTL CD8+

References Daucher *et al.* 2008

- A detailed analysis of 6 chronically infected patients' CTL responses to autologous virus was performed after ART and SIT (structured interruption of therapy). Qualitative responses including degranulation and production of IFN-gamma, MIP-1beta, TNF-alpha, IL-2, but not memory CD27, CD45RO and CD57 T cells correlated with extended low plasma viremia. Frequency and breadth of CTL response as well as immune escape did not influence virological outcome.
- One patient exhibited drug resistance mutations K170R (to NNRTI efavirenz) and D76N, K70R (to NRTIs).
- Autologous epitopes were preferentially recognized over optimal, consensus sequences.
- Patients with favorable virological outcomes demonstrated CTL recognition within multiple, conserved regions of Gag and Nef.
- Patients with poor virological outcomes recognized optimal epitopes with much lower frequencies, though this was not significant.
- HLA-B15-restricted epitope, GLNKIVRMY, elicited a response in 1 patient and is found in Gag immunodominant region WIILGLNKIVRMYS.

HXB2 Location p24 (137–145)
Author Location p24 (137–145)
Epitope GLNKIVRMY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B15, B62)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, subtype comparisons, acute/early infection
References Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (ANC) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- This epitope, GLNKIVRMY, is invariant across CON A, B, C and M-Group sequences, as well as clade B COT and ANC sequences. HLA-B15 and -62 restriction was inferred based on 2 different subjects possessing appropriate HLA class I allele and prior publication.

HXB2 Location p24 (137–145)
Author Location
Epitope GLNKIVRMY
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (B27)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location p24 (137–145)
Author Location p24 (272–280 LAI)
Epitope GLNKIVRMY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62)
Keywords review, escape
References Goulder *et al.* 1997a

- This paper is a review of CTL and immune evasion, but it presents a study of a shift from an HLA-A*0201 response to SLYNTVATL, to a B62 response to GLNKIVRMY.
- As long as a strong CTL response to SLYNTVATL was evident, the epitope variants SLFNTVATL or SLYNTIATL dominated the viral population – eventually the CTL response to the index peptide became undetectable, the CTL response shifted to a focus on GLNKIVRMY, and the index peptide SLYNTVATL once again established itself as the dominant form.

HXB2 Location p24 (137–145)
Author Location p24 (SF2)
Epitope GLNKIVRMY
Immunogen HIV-1 infection
Species (MHC) human (B62)
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a HIV+ African American living in Boston – this epitope did not fall within the three most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa.

HXB2 Location p24 (137–145)

Author Location p24 (267–277 SF2)
Epitope GLNKIVRMY
Immunogen HIV-1 infection
Species (MHC) human (B62)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B62+ individuals that had a CTL response to this epitope broken down by group: 0/1 group 1, 0/1 group 2, and 1/1 group 3.

HXB2 Location p24 (137–145)
Author Location p24 (137–145)
Epitope GLNKIVRMY
Immunogen HIV-1 infection
Species (MHC) human (B62)
Keywords immunodominance
References Day *et al.* 2001

- No immunodominant responses were detected to four B62-restricted epitopes tested.

HXB2 Location p24 (137–145)
Author Location p24 (137–145)
Epitope GLNKIVRMY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62)
Donor MHC A1, A3, B62, B8, Cw3, Cw7
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

HXB2 Location p24 (137–145)
Author Location Gag (269–277)
Epitope GLNKIVRMY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62)
Donor MHC A2, A24, B27, B62
Assay type Chromium-release assay
Keywords TCR usage, genital and mucosal immunity
References Musey *et al.* 2003

- CTL clones from blood, semen, cervix and rectum samples from 12 individuals were compared. CTL clones derived from blood and mucosal samples had similar high lysis efficiency, primarily perforin dependent, and TCRβ VDJ region sequencing revealed cases of expansion of the same clone in different compartments.
- CD8+ T cell clones directed at this epitope were derived from blood, rectum and semen.
- The TCRβ VDJ rearrangement of the CTL clones was Vβ22S1DJ1.2, demonstrating expansion of CTL clones in all three compartments from the same progenitor cell.

HXB2 Location p24 (137–145)
Author Location Gag (269–277)
Epitope GLNKIVRMY
Epitope name GY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62)
Donor MHC A*01, A*11, B*08, B*15, Cw*04, Cw*07
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords escape, optimal epitope
References Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- The autologous form of the GY9 matched the B clade consensus form of the epitope, GLNKIVRMY, throughout the 5 years of study.

HXB2 Location p24 (137–145)
Author Location Gag (269–277 HXB2)

CTL CD8+

Epitope GLNKVRMY
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (B62)
Country Viet Nam
Assay type HLA binding
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- GLNKVRMY is the epitope in the HXB2 reference strain sequence, and is also the most common form in CRF01.

HXB2 Location p24 (137–145)
Author Location p24 (C consensus)
Epitope GLNKIVRMY
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A2, B*5802, B62, Cw4, Cw6
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a HIV+ South African living in Durban, HLA A2/- B5802/62 Cw4/6 – this epitope did not fall within the three most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa.

HXB2 Location p24 (137–151)
Author Location
Epitope GLNKIVRMYSPTSIL
Immunogen HIV-1 infection
Species (MHC) human (A2, B15)
Donor MHC A2, A24, B15, B40; A11, A2, B44, B60
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 68 (NIH ARRP Cat# 7939), GLNKIVRMYSPTSIL, contains epitopes restricted by HLA-A2 and -B15 in different patients and elicited the following CTL responses: (1) >3000 sfc/million PBMC for 22+ years in a living non-progressor (2) >200 sfc/million PBMC for 12 years in a former non-progressor who succumbed to a non-AIDS death.

HXB2 Location p24 (139–153)
Author Location Gag
Epitope NKIVRMYSPVSILDI
Subtype A, AG
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*23, B*15, B*49, Cw*02, Cw*07, DPA1*0201, DPB1*0101, DPB1*1301, DQB1*05, DRB1*11, DRB1*1301
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- Epitope-containing peptide NKIVRMYSPVSILDI, seen in a subtype-A/G carrying subject was derived from a subtype A library and was not previously associated with host class I alleles A*23/*23; B*15/*49, Cw*02/*07.

HXB2 Location p24 (141–155)
Author Location
Epitope IVRMYSPTSILDIRQ
Immunogen HIV-1 infection
Species (MHC) human (A2, A24)
Donor MHC A2, A24, B15, B40; A11, A2, B44, B60; A2, A31, B27, B44
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.

- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 69 (NIH ARRP Cat# 7940), IVRMYSPTSILDIRQ, contains epitopes restricted by HLA-A2 and -A24 in one patient and HLA-A2 in different patients. This peptide elicited the following CTL responses: (1) 22+ years in a living non-progressor (2) >200 sfc/million PBMC for 12+ years in a former non-progressor who succumbed to a non-AIDS death (3) > 200 sfc/million PBMC for 22+ years in a former non-progressor who succumbed to loss of viremic control.

HXB2 Location p24 (141–155)
Author Location Gag (273–287)
Epitope `IVRMYSPTSILDIRQ`
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized by mice co-immunized with Gag and Tat, but not by mice immunized with Gag alone.

HXB2 Location p24 (141–155)
Author Location Gag (273–287)
Epitope `IVRMYSPTSILDIRQ`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the Progressor. Both patients had R286K substitution.

HXB2 Location p24 (142–150)
Author Location
Epitope `VRMYSPVSI`
Epitope name VI9
Immunogen
Species (MHC) human (Cw*18)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a Cw18 epitope.

HXB2 Location p24 (142–150)
Author Location (C consensus)
Epitope `VRMYSPVSI`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*1801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- VRMYSPVSI is an optimal epitope.

HXB2 Location p24 (142–150)
Author Location p24 (142–150)
Epitope `VRMYSPVSI`
Immunogen peptide-HLA interaction
Species (MHC) human (Cw*1801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords optimal epitope
References Honeyborne *et al.* 2006

- Novel epitopes are defined for four HLA-alleles common in South African Zulu/Xhosa populations: B*3910, B*4201, B*8101 and Cw*1801, by motif inference. HLA-A*2902 was found to overlap those of A1 and A24 supertypes.
- VRMYSPVSI was the optimal epitope for HLA-Cw*1801 with variants VRMYSPVS, RMYSPVSI, VRMYSPVSIl, iVRMYSPVSI having been tested.

HXB2 Location p24 (142–150)
Author Location Gag

CTL CD8+

Epitope VRMYSPVSI
Epitope name VI9-Cw18
Subtype B, F
Immunogen HIV-1 infection
Species (MHC) human (Cw18)
Country Argentina
Keywords dynamics, escape, HLA associated polymorphism
References Dilernia *et al.* 2008

- Dynamics of CTL escape mutations was studied theoretically by analyzing plasma samples from 302 subjects (collected over 20 years). HLA associated polymorphisms accumulated in a subtype-specific manner.
- Epitope VRMYSPVSI mutates to variant VRMYSPtSI with time.

HXB2 Location p24 (143–150)
Author Location p24 (275–282)
Epitope RMYSPTSI
Epitope name RI8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*52)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*52-associated substitution within optimally defined epitope RMYSPTSI is at positions T6, RMYSPtSI.

HXB2 Location p24 (143–150)
Author Location p24 (273–283 IIIB)
Epitope RMYSPTSI
Immunogen HIV-1 infection
Species (MHC) human (B*5201)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*5201 epitope.

HXB2 Location p24 (143–150)
Author Location p24 (273–283 IIIB)
Epitope RMYSPTSI
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (B52)
Keywords epitope processing, immunodominance, escape
References Brander *et al.* 1999

- Multiple natural variations in the SL9 flanking regions of the immunodominant epitope SLYNTVATL were tested and found not to adversely affect CTL recognition or prevent epitope processing, suggesting that viral escape from the HLA-A*0201-restricted CTL response against SLYNTVATL is probably not linked to variations in the flanking regions of this epitope.
- The CTL response to RMYSPTSI was used as a control.

HXB2 Location p24 (143–150)
Author Location p24 (273–283 IIIB)
Epitope RMYSPTSI
Immunogen HIV-1 infection
Species (MHC) human (B52)
Keywords responses in children, mother-to-infant transmission, escape
References Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- No variants of this epitope were found in a non-transmitting mother that had a CTL response to this epitope.

HXB2 Location p24 (143–150)
Author Location p24 (143–150)
Epitope RMYSPTSI
Immunogen HIV-1 infection
Species (MHC) human (B52)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (143–150)
Author Location Gag (275–282)
Epitope RMYSPTSI
Epitope name RI8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B52)
Donor MHC A*02, A*68, B*14, B*52, Cw*08, Cw*12
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords escape, optimal epitope
References Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.

- A form of this epitope that elicited a diminished Elispot response, RMYSPvSI, dominated the viral sequence for several years, and then reverted back to the B consensus form, RMYSPTSI.

HXB2 Location p24 (143–150)
Author Location
Epitope RMYSPTSI
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (B52)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location p24 (143–150)
Author Location Gag
Epitope RMYSPTSI
Epitope name RI8-B*52
Subtype B, F
Immunogen HIV-1 infection
Species (MHC) human (B52)
Country Argentina
Keywords HLA associated polymorphism
References Dilernia *et al.* 2008

- Dynamics of CTL escape mutations was studied theoretically by analyzing plasma samples from 302 subjects (collected over 20 years). HLA associated polymorphisms accumulated in a subtype-specific manner.
- Epitope RMYSPTSI contains a polymorphism RMYSPtSI.

HXB2 Location p24 (143–150)
Author Location p24
Epitope RMYSPTSI
Epitope name RI8(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B52)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B52-restricted epitope RMYSPTSI elicited an immune response in Chinese HIV-1 positive subjects as peptide WIILGLNKIVRMYSPTSI, but there was no response to peptide IVRMYSPTSILDIRQGPK.
- 1 of the 5 HLA-B52 carriers responded to RMYSPTSI-containing peptide with a magnitude of CTL response of 250 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p24 (143–151)
Author Location Gag (275–283)
Epitope RMYSPTSIL
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (A2)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

HXB2 Location p24 (143–151)
Author Location Gag (275–283 BRU)
Epitope RMYSPTSIL
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects
- This epitope was recognized by 1/9 CRF02_AG-infected Ivorians, and 0/9 B-infected French subjects.

HXB2 Location p24 (143–151)
Author Location Gag (275–283 HXB2)
Epitope RMYSPTSIL
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Viet Nam
Assay type HLA binding

CTL CD8+

Keywords subtype comparisons, computational epitope prediction, escape, variant cross-recognition or cross-neutralization, vaccine antigen design
References Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- The most common CRF01_AE variant rmyspVsil had a higher HLA-binding score than the HXB2 epitope. The rare variant, rmyspVsiW was predicted not to bind to A2.

HXB2 Location p24 (143–151)
Author Location Gag (Henan isolate)
Epitope `RMYSPTSIL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p24 (143–151)
Author Location p24 (143–151)
Epitope `RMYSPVSIL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope RMYSPVSIL is highly conserved across clades with >80% conservation to subtypes A, C and D. It is predicted to be restricted by HLA-A*0201.

HXB2 Location p24 (144–151)
Author Location Gag (276–283)
Epitope `MYSPTSIL`
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (A24)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the most frequently recognized of the 31 epitopes that the vaccinated volunteers responded to.

HXB2 Location p24 (144–153)
Author Location Gag (276–285 SF2)
Epitope `MYSPTSILDI`
Epitope name MYS
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF2 *HIV component:* Gag, Tat *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse (H-2^{d})
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes
References Cellini *et al.* 2008

- In order to increase the known number of epitopes in Gag protein so that they can be assayed for reactivity in vaccine studies, BALB/c mice were inoculated with Gag or Gag+Tat. OLPs were used to elicit T-cell immune responses from mouse splenocytes, tested for by cytotoxicity or ELISpot assays. 5 novel predicted optimal CTL epitopes, 2 novel predicted CD4 epitopes and 2 immune response eliciting peptides were found.
- Predicted epitope MYSPTSILDI was found in reactive Peptide 69, IVRMYSPTSILDIRQ.

HXB2 Location p24 (149–158)
Author Location Gag
Epitope `SILDIRQGPK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China

CTL CD8+

Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p24 (149–163)
Author Location Gag
Epitope `STLDIRQGPKEPFID`
Subtype CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide STLDIRQGPKEPFID from subtype CRF02_AG.

HXB2 Location p24 (149–163)
Author Location Gag
Epitope `SILDIKQGPKEPFRD`
Subtype A
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0308, A*24, B*15, B*18, DPA1*0103, DPB1, DQB1*03, DQB1*06, DRB1*12, DRB1*15, DRB3, DRB5
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- Epitope-containing peptide SILDIKQGPKEPFRD, seen in a subtype-A carrying subject was derived from a subtype A library and was not previously associated with host class I alleles A*0308,A*24,B*15,B*18.

HXB2 Location p24 (151–170)
Author Location p24 (283–302 SF2)
Epitope `LDIRQGPKEPFRDYVDRFYK`
Immunogen HIV-1 infection
Species (MHC) human
References McAdam *et al.* 1998

HXB2 Location p24 (152–162)
Author Location p24 (152–162)
Epitope `DIRQGPKEPFR`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*27)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, DIRQGPKEPFR, was detected within overlapping peptides SILDIRQGPKEPFRDYV and GPKEPFRDYVDRFYKTLR.

HXB2 Location p24 (153–177)
Author Location p24
Epitope `IRQGPKEPFRDYVDRFFKTLRAEQA`
Immunogen in vitro stimulation or selection
Species (MHC) human
Assay type Other
Keywords assay standardization/improvement, immunodominance, adjuvant comparison
References Singh *et al.* 2007

- To shorten serological latency and better immunodiagnosis of HIV-1 infection by ELISA, a synthetic p24 Gag epitope was conjugated to BSA (Bovine Serum Albumin) through a decaalanine spacer. This p24 epitope-spacer-BSA consistently gave better immunoreactivity and specificity than either recombinant epitope or p24 epitope-BSA when immobilized to microtiter wells and tested by inhibition ELISA.

HXB2 Location p24 (154–168)
Author Location Gag
Epitope `RQGPKEPFRDYVDRF`
Subtype A, AG, B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*23, B*15, B*49, Cw*02, Cw*07, DPA1*0201, DPB1*0101, DPB1*1301, DQB1*05, DRB1*11, DRB1*1301

CTL CD8+

Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- Epitope-containing peptide RQGPKEPFRDYVDRF, seen in a subtype-A/G carrying subject was derived from subtype A and B libraries and was not previously associated with host class I alleles A*23/*23, B*15/B*49, Cw*02/Cw*07.

HXB2 Location p24 (156–164)
Author Location Gag
Epitope `GPKEPFRDY`
Epitope name Gag1164
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Previously published epitope GPKEPFRDY elicits IFN-gamma ELISpot responses in 5/7 subjects; and bound HLA-B7 with low affinity in cell-based assays.

HXB2 Location p24 (156–173)
Author Location Gag
Epitope `GPKEPFRDYVDRFYKTLR`
Epitope name GAG-40
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, GPKEPFRDYVDRFyKTLR differs from the consensus C sequence GPKEPFRDYVDRFfKTLR at 1 amino acid position, i.e. by 5.6%.

HXB2 Location p24 (156–173)
Author Location p24
Epitope `GPKEPFRDYVDRFYKTLR`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, GPKEPFRDYVDRFYKTLR, had an overall frequency of recognition of 16.7% - 18.6% AA, 11.5% C, 15.9% H, 14.3% WI. This peptide is included in a 43 aa Gag-p24 highly reactive region to be used for vaccine design.

HXB2 Location p24 (157–178)
Author Location p24 (290–309)
Epitope PKEPFRDYVDRFYKTLRAEQAS
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Musey *et al.* 1997

- Cervical and peripheral blood derived CTL clones from an HIV-infected woman recognized this epitope.

HXB2 Location p24 (159–168)
Author Location Gag
Epitope EPFRDYVDRF
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human (A*0201, A2)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA A2-restricted epitope EPFRDYVDRF is from a subtype B peptide library, and is reactive in subtype B-carrying subjects. The HLA A*0201-restricted epitope is from a subtype B peptide library, and is reactive in subtype D-carrying subjects. The epitope is part of reacting peptides EPFRDYVDRFYKTLR and RQGPKEPFRDYVDRF.

HXB2 Location p24 (159–168)
Author Location Gag (291–300)
Epitope EPFRDYVDRF
Immunogen vaccine
Vector/Type: DNA, DNA with protein boost *Strain:* B clade LAI *HIV component:* Gag, Nef, Tat *Adjuvant:* IL-18
Species (MHC) mouse (H-2^{d})
Keywords Th1
References Billaut-Mulot *et al.* 2001

- DNA vaccinated BALB/c mice primed and boosted with the multiepitopic vaccine with IL18 showed lymphoproliferative responses 7 weeks post immunization.
- Strong but non-lasting HIV-specific CTL responses were detected by a Cr-release assay and DNA prime/DNA boost was more effective than DNA prime protein boost.
- Immunization with either the multiepitopic DNA or with the mixed DNA vaccine induced HIV-1 specific Th1 cytokines (IL-2 and IFN-gamma)
- Co-administration of IL18 increased T-cell responses but decreased anti-HIV antibody levels.

HXB2 Location p24 (159–168)
Author Location p24
Epitope EPFRDYVDRF
Epitope name E10F
Immunogen vaccine
Vector/Type: DNA *HIV component:* Gag
Species (MHC) mouse (H-2^{d})
Assay type Chromium-release assay
References Bojak *et al.* 2002b

- Codon-optimized gag gene DNA vaccines were compared to wild type by vaccination of BALB/c mice. Codon optimized DNA gave a Th1 polarized Th response, a strong antibody response that persisted from more than 20 weeks, and CTL responses, while wild-type DNA induced weak and inconsistent immune respones.

HXB2 Location p24 (159–168)
Author Location
Epitope EPFRDYVDRF
Epitope name E10F
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), polyepitope *HIV component:* Gag, p24 Gag, V3
Species (MHC) mouse (H-2L^{d})
Assay type Cytokine production, Chromium-release assay
Keywords epitope processing, vaccine-specific epitope characteristics, immunodominance
References Wild *et al.* 2004

- A codon optimized gag DNA vaccine was compared to a myristylation defective gag and p24 alone, both of which lack signals for secretion from transfected cells. Gag-derived immunogens that were secreted as VLPs and those that remained intracellular (p24) each produced strong CTL responses, and neither the size of antigen nor cellular trafficking and localization significantly influenced the strength of humoral and cellular immune activation. The formation and release of VLPs was not essential for eliciting strong CTL. BALB/c mice were given the DNA vaccine by i.m. administration of plasmid DNA for the prime and boost.
- Minigenes were made incorporating just 1 epitope, minitopes, carrying 1 of 3 murine class I epitopes linked to the Ad2-E3 protein-derived signal peptide to allow access of the epitope to the ER. Weak induction of cellular immune responses was observed, in contrast to the complex polyprotein. The E10F minigene did not produce a detectable CTL response.

HXB2 Location p24 (159–168)
Author Location p24 (287–309)
Epitope EPFRDYVDRF
Immunogen vaccine
Vector/Type: peptide *HIV component:* p24 Gag
Species (MHC) mouse
References Nakamura *et al.* 1997

- Mice immunized with this synthetic peptide generated specific CTLs, a proliferative response, and antibodies.
- The amino acids shown in the epitope field were based on the numbering provided by Nakamura *et al.*, and may not be correct.
- The CTL epitope was located in position 291-300.

HXB2 Location p24 (159–168)
Author Location p24 (159–168)

CTL CD8+

Epitope EPFRDYVDRF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope EPFRDYVDRF was highly conserved across all clades at >80%, and predicted to be restricted by HLA-A*0201 using 2 different peptides.

HXB2 Location p24 (159–168)
Author Location Gag (291–300)
Epitope EPFRDYVDRF
Subtype B
Immunogen HIV-1 infection, peptide-HLA interaction
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance
References Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, EPFRDYVDRF, is similar to human protein COPINE 5, sequence vPFRDYVDR.

HXB2 Location p24 (159–169)
Author Location Gag (292–301)
Epitope EPFRDYVDRFF
Subtype A, C, D
Immunogen HIV-1 infection
Species (MHC) human (B81)
Country Tanzania
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, immunodominance
References Geldmacher *et al.* 2007a

- 56 ART-naive subjects were studied to assess whether T-cell responses to Gag and Nef are biased towards infecting subtype recognition, in a setting of epidemic consisting of subtypes A,C and D and their recombinant forms. The infecting subtype was determined by multi-region hybridization assay. Overlapping 15-mer isolate-based Gag and Nef peptide sets representative of local subtypes were used. The best recognized epitope variant in terms of magnitude and breadth corresponded to infecting subtype, in this case usually type-C. Hot spots of CTL recognition in Gag were in p24, p17 and p15; hotspots against Nef were in its central, conserved region.
- Epitope variants EPFRDYVDRFf and EPFRDYVDRFy were studied as peptide sequences PK-EPFRDYVDRFf-KT (subtypes C and A) and PK-EPFRDYVDRFy-KT (subtype D) with 12.5% responders. Subtypes C and A were best recognized. Associated HLA frequently expressed within the studied cohort is listed in the study as B81.

HXB2 Location p24 (159–178)
Author Location Gag (96ZM651.8)
Epitope EPFRDYVDRFFKTLRAEQAT
Immunogen
Species (MHC) human (B*440301)
Keywords subtype comparisons, immunodominance
References Novitsky *et al.* 2001

- This study is provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort.
- 16 of 46 (34.8%) had CTL responses to one or more peptides within the second immunodominant region region of Gag (peptides SILDIKQGPKEPFRDYVDRF, EPFRDYVDRFFKTLRAEQAT, and FKTLRAEQATQEVKNWMTDT) with ELISPOT results median and range 500 (100 to 1,250) SFC/10^6 PBMC
- 3 of 6 (50%) carriers of HLA-B*44031 showed CTL responses to the peptide EPFRDYVDRFFKTLRAEQAT.

HXB2 Location p24 (159–178)
Author Location Gag (291–310)
Epitope EPFRDYVDRFFKTLRAEQAT
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 8 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location p24 (160–169)
Author Location p24
Epitope PFRDYVDRFF
Epitope name PF-10
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords subtype comparisons, epitope processing, immunodominance, cross-presentation by different HLA
References Masemola *et al.* 2004b

- Highly targeted regions in Gag for CD8+ T-cells were defined for individuals with C clade infections in South Africa. 9 specific epitopes within the most reactive regions were characterized. This is 1 of 5 novel epitopes that were found among subtype C HIV-1 from African patients who hadn't previously been identified in B clade infections. Some epitopes were shown to be promiscuous, presented by multiple class I restricting alleles. The HLA restricting element for this optimal epitope was not determined due to limited material.

HXB2 Location p24 (161–169)
Author Location
Epitope FRDYVDRFF
Immunogen
Species (MHC) human (Cw*18)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an Cw18 epitope.

HXB2 Location p24 (161–169)
Author Location (C consensus)
Epitope FRDYVDRFF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*1801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p24 (161–169)
Author Location (C consensus)
Epitope FRDYVDRFF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*1801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- FRDYVDRFF is an optimal epitope.

HXB2 Location p24 (161–169)
Author Location p24 (161–169)
Epitope FRDYVDRFF
Immunogen peptide-HLA interaction
Species (MHC) human (Cw*1801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords optimal epitope
References Honeyborne *et al.* 2006

- Novel epitopes are defined for four HLA-alleles common in South African Zulu/Xhosa populations: B*3910, B*4201, B*8101 and Cw*1801, by motif inference. HLA-A*2902 was found to overlap those of A1 and A24 supertypes.
- FRDYVDRFF was the optimal epitope for HLA-Cw*1801 with variants FRDYVDRF, RDYVDRFF, FRDYVDRFFk, pFRDYVDRFF having been tested.

HXB2 Location p24 (161–170)
Author Location p24 (subtype B, D)
Epitope FRDYVDRFYK
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human (B*1801)
References Ogg *et al.* 1998a

- Noted in Brander 1999, this database, to be B*1801, FRDYVDRFY.

HXB2 Location p24 (161–170)
Author Location p24 (subtype B, D)
Epitope FRDYVDRFYK
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human (B*1801)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*1801 epitope.

HXB2 Location p24 (161–170)
Author Location p24 (161–170 HXB2)
Epitope FRDYVDRFYK
Epitope name FK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1801)

CTL CD8+

Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.

HXB2 Location p24 (161–170)
Author Location p24 (161–170)
Epitope FRDYVDRFYK
Immunogen HIV-1 infection
Species (MHC) human (B18)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (161–170)
Author Location p24 (293–302)
Epitope FRDYVDRFYK
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B18)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- Variants FRDYVDRF(Y/F)K are specific for the B,D/A,C clades.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B18 women, 3/4 HEPS and 1/9 HIV-1 infected women recognized this epitope, likelihood ratio 5.3, p value 0.04, and HEPS women tended to respond to FRDYVDRFY/FK, while infected women tended to respond to YPLTFGWCY/F.
- The dominant response to this HLA allele was to this epitope for all 3/4 HEPS cases and for the single HIV-1 infected women that responded to this epitope.
- Four epitopes were considered to be "resistant epitopes", as they were preferentially reactive in HEPS women and so may confer resistance, and these were found in three different proteins: A2 ILK(D/E)PVHGV in RT, A*6802 DTVLEDINL in Protease, B14 DLNM/TLN(I/V)V in p24 and B18 FRDYVDRF(Y/F)K also in p24.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.

HXB2 Location p24 (161–170)
Author Location p24
Epitope FRDYVDRFYK
Subtype B, D
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human, macaque (B18)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location p24 (161–170)
Author Location p24
Epitope FRDYVDRFYK
Epitope name FK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B18)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.

- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- 95 days after first testing, epitope FRDYVDRFYK showed no variation in a treated patient. Previously published HLA-restriction for FK10 is HLA-B18.

HXB2 Location p24 (161–170)
Author Location p24
Epitope FRDYVDRFYK
Epitope name B18-FK10(p24)
Immunogen HIV-1 infection
Species (MHC) human (B27)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (161–170)
Author Location
Epitope FRDYVDRFFK
Immunogen HIV-1 infection
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 1/22 HEPS sex worker controls, ML1732.

HXB2 Location p24 (161–172)
Author Location Gag
Epitope FRDYVDRFFKAL
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-A3-restricted epitope FRDYVDRFFKAL is from a subtype A peptide library, and is reactive as part of EPFRDYVDRFFKALR in subtype A-carrying subjects.

HXB2 Location p24 (161–174)
Author Location p24 (161–174 HXB2)
Epitope FRDYVDRFYKTLRA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- Responses to this peptide were detected in 16% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location p24 (161–175)
Author Location
Epitope FRDYVDRFYKTLRAE
Immunogen HIV-1 infection
Species (MHC) human (B44)
Donor MHC A2, A32, B44, B7; A11, A2, B44, B60; A2, A31, B27, B44
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

CTL CD8+

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 74 (NIH ARRP Cat# 7945), FRDYVDRFYKTLRAE, contains an epitope restricted by HLA-B44 in different patients and elicited the following CTL responses: (1) 22+ years in a living non-progressor (2) for 12+ years in a former non-progressor who succumbed to a non-AIDS death (3) up to 15+ years in a former non-progressor who succumbed to loss of viremic control.

HXB2 Location p24 (161–175)
Author Location p24 (161–170)
Epitope FRDYVDRFYKTLRAE
Subtype A, D
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101, A*7401, B*5801
Country Uganda
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References Barugahare *et al.* 2005

- T-cell immune responses were examined in HIV-1 infected Ugandans. Similar levels of cross-clade responses for Gag, Env and Nef were observed. Higher frequencies of responses in conserved regions were found for Gag within a single clade, while areas with higher viral sequence variation had fewer detectable responses. Differential interclade sequence homologies between the Gag regions did not affect the respective level of cross-clade recognition.
- The sequence contains a known epitope (FRDYVDRFYKTL), but the subject recognizing it does not carry HLAs of the previously-defined restriction. The isolated viral sequence was frdyvdrfykVlrae, from the patient that could recognize the peptide.

HXB2 Location p24 (161–175)
Author Location Gag (293–307)
Epitope FRDYVDRFYKTLRAE
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the ES and the Progressor.

HXB2 Location p24 (161–180)
Author Location p24 (293–312 SF2)
Epitope FRDYVDRFYKTLRAEQASQD
Immunogen HIV-1 infection
Species (MHC) human (B71)
References McAdam *et al.* 1998

HXB2 Location p24 (161–180)
Author Location p24 (293–312 SF2)
Epitope FRDYVDRFYKTLRAEQASQD
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A2, A3, B8, B62.

HXB2 Location p24 (161–180)
Author Location p24 (293–312 SF2)
Epitope FRDYVDRFYKTLRAEQASQD
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

HXB2 Location p24 (162–172)
Author Location p24 (296–306 subtype A)
Epitope RDYVDRFFKTL
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Keywords subtype comparisons
References Dorrell *et al.* 1999

- CTL responses in three individuals with non-clade B infections were studied, 2 with subtype A infections, 1 with subtype C – their infections all originated in East Africa.
- This epitope is similar to the A24 DYVDRYFKT epitope found for B subtype, but CTL from this A subtype infection required the additional Arg – the B clade sequence change from F to Y diminished CTL reactivity.
- C. Brander notes that this is an A*2402 epitope in the 1999 database.

CTL CD8+

HXB2 Location p24 (162–172)
Author Location p24 (296–306 subtype A)
Epitope RDYVDRFFKTL
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*2402 epitope.

HXB2 Location p24 (162–172)
Author Location p24 (296–306)
Epitope RDYVDRFFKTL
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A24)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-A24 women, 0/4 HEPS and 6/10 HIV-1 infected women recognized this epitope, likelihood ratio 7.2, p value 0.03, and (R)YL(R/K)DQQLL tended to be reactive in HEPS and infected women, RDYVDRFFKTL in infected women only.
- The dominant response to this HLA allele was to this epitope in all of the 6/10 HIV-1 infected women.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.
- Subject ML 1707 started with a CTL response to A*6802 DTVLEDINL prior to seroconversion, and switched to A*6802 ETAYFILKL and A24 RDYVDRFFKTL post-seroconversion.

HXB2 Location p24 (162–172)
Author Location p24
Epitope RDYVDRFFKTL
Epitope name A24-RL11(p24)
Immunogen HIV-1 infection
Species (MHC) human (A24)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (162–172)
Author Location p24 (293–312 LAI)
Epitope RDYVDRFYKTL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*4402)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*4402 epitope.

HXB2 Location p24 (162–172)
Author Location p24 (162–172)
Epitope RDYVDRFYKTL
Immunogen HIV-1 infection
Species (MHC) human (B44)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (162–172)
Author Location p24 (162–172)
Epitope RDYVDRFYKTL
Immunogen HIV-1 infection
Species (MHC) human (B44)
References Day *et al.* 2001

HXB2 Location p24 (162–172)
Author Location p24
Epitope RDYVDRFYKTL
Subtype B, D
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human, macaque (B44)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

CTL CD8+

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location p24 (162–172)
Author Location Gag (B con)
Epitope RDYVDRFYKTL
Epitope name RL11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B44)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Draenert *et al.* 2004c

- CD8+ T-cell responses that persisted in individuals with advanced disease were studied; most of the optimal epitopes defined were recognized with intermediate to high avidity. On average 13 (range, 2-39) epitopic regions were targeted in an average of 6 proteins (range, 1-8). HAART resulted in decrease in antigen and reduction in gamma IFN EliSpot responses, suggesting active responses to autologous virus. The lack of mutations within most viral epitopes suggest that persistent CTL through late disease do not exert strong immune selection pressure, yet the Elispot assays show robust responses, suggesting to the authors that gamma IFN-based screening methods may not reveal functional CD8+ T-cell impairment in patients with AIDS.
- 1 subject recognized this epitope with low functional avidity. The autologous sequence matched the B consensus.

HXB2 Location p24 (162–172)
Author Location p24
Epitope RDYVDRFYKTL
Epitope name B44-RL11(p24)
Immunogen HIV-1 infection
Species (MHC) human (B44)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (162–172)
Author Location p24 (293–312 LAI)
Epitope RDYVDRFYKTL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A26, B44, B70)
References Ogg *et al.* 1998a

HXB2 Location p24 (162–172)
Author Location p24
Epitope RDYVDRFYKTL
Epitope name RL11(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope RDYVDRFYKTL elicited an immune response as part of peptide GPKEPFRDYVDRFYKTLR. In HLA-A24, -A26 and -B44 carriers, this epitope differs from the previously described epitope , RDYVDRFFKTL, at 1 residue, RDYVDRFyKTL.
- 5 of the 30 HLA-A24 carriers responded to RDYVDRFyKTL-containing peptide with average magnitude of CTL response of 182 SFC/million PBMC; 3 of the 8 HLA-A26 carriers responded with an average magnitude of CTL response of 333 SFC/million PBMC; 1 of the 6 HLA-B44 carriers responded with a magnitude of CTL response of 80 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p24 (163–171)
Author Location Gag (295–303 SUMA)

Epitope DYVDRFYKT
Epitope name Gag DT9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Donor MHC A*1103, A*2402, B*1402, B*1501, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, acute/early infection, characterizing CD8+ T cells
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape muations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

HXB2 Location p24 (163–172)
Author Location p24 (163–172)
Epitope DYVDRFYKTL
Immunogen HIV-1 infection
Species (MHC) human (A24)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (163–172)
Author Location Gag
Epitope DYVDRFFKTL
Immunogen HIV-1 infection, HIV-1 or HIV-2 infection
Species (MHC) human (A24)
Country Belgium, Senegal
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords subtype comparisons, variant cross-recognition or cross-neutralization, HIV-2
References Jennes *et al.* 2008

- To compare HIV-1 and HIV-2 CTL responses to Gag as far as homologous levels of response and cross-reactivity, 12 consecutive Gag OLP pools were used with cells from 17 HIV-1 and 17 HIV-2 patients in enhanced IFN-gamma ELISpot assays. Gag-specific homologous CTL responses were significantly higher in HIV-2 patients, but cross-reactivity in HIV-1-infected patients was broader and stronger.
- Cross-reactivity correlated with sequence similarity in HIV-2 patients, but not HIV-1 patients. CD4+ T-cell counts of HIV-2-infected patients correlated directly with homologous responses and inversely with cross-reactive responses; this was not true of HIV-1-infected subjects.
- The authors favor a model in which high HIV-2-specific CTL responses control its replication, containing immune evasion and thus limiting the possibility of cross-reaction to HIV-1 homologous epitopes.
- HIV-1 Gag epitope DYVDRFFKTL is probably cross-recognized with its homologous HIV-2 epitope, SYVDRFYKSL.

HXB2 Location p24 (163–172)
Author Location Gag
Epitope SYVDRFYKSL
Immunogen HIV-2 infection, HIV-1 or HIV-2 infection
Species (MHC) human (A24)
Country Belgium, Senegal
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords subtype comparisons, variant cross-recognition or cross-neutralization, HIV-2
References Jennes *et al.* 2008

- To compare HIV-1 and HIV-2 CTL responses to Gag as far as homologous levels of response and cross-reactivity, 12 consecutive Gag OLP pools were used with cells from 17 HIV-1 and 17 HIV-2 patients in enhanced IFN-gamma ELISpot assays. Gag-specific homologous CTL responses were significantly higher in HIV-2 patients, but cross-reactivity in HIV-1-infected patients was broader and stronger.
- Cross-reactivity correlated with sequence similarity in HIV-2 patients, but not HIV-1 patients. CD4+ T-cell counts of HIV-2-infected patients correlated directly with homologous responses and inversely with cross-reactive responses; this was not true of HIV-1-infected subjects.
- The authors favor a model in which high HIV-2-specific CTL responses control its replication, containing immune evasion and thus limiting the possibility of cross-reaction to HIV-1 homologous epitopes.
- HIV-2 Gag epitope SYVDRFYKSL is probably cross-recognized with its homologous HIV-1 epitope, DYVDRFFKTL.

HXB2 Location p24 (163–173)
Author Location Gag (297–307 SF2)
Epitope DYVDRFYKTLR
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (A*3303)
Assay type Chromium-release assay
Keywords binding affinity, computational epitope prediction
References Hossain *et al.* 2003

- HLA-A*3303 is a common HLA allele in east and southeast Asia. Pol, Gag and Nef SF2 proteins were scanned for potential A*3303 epitopes. 99 potential epitopes were synthesized, and 52/99 bound to A*3303. Six of these served as peptide-targets for lysis by PBMC from infected individual, and clones derived from 4 of these 6 could lyse HIV-vaccinia infected target cells, indicating proper processing.
- This epitope is one of the 2/6 peptides that could induce CTL responses in the PBMC of infected individuals, but was not properly processed in a vaccinia-HIV infected target cell.

HXB2 Location p24 (164–172)
Author Location p24 (164–172)
Epitope YVDRFYKTL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, YVDRFYKTL, was detected within overlapping peptides SILDIRQGPKEPFRDYV and GPKEPFRDYVDRFYKTLR.

HXB2 Location p24 (164–172)
Author Location Gag (296–304)
Epitope YVDRFYKTL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0207)
Donor MHC A*0207
Keywords subtype comparisons
References Currier *et al.* 2002a

- Cross-reactive responses were found in PBMC isolated from individuals infected with either B or CRF01_AE clade viruses, as determined by Elispot assays of target cells expressing recombinant vaccinia viruses expressing HIV-1 gag, env, nef and pol from many clades.
- The Thai subject VAIP-4 demonstrated broad CTL cross-reactivity towards gag constructs derived from subtypes A, B, C, D, F, G, H, and CRF-01_AE. Sequence alignments of this epitope showed conservation for clades B and D, and Y->F substitutions at position 6 for subtypes A, C, CDR01-AE, F, G, and H. YVDRFYKTL and the variant epitope YVDRFFKTL are recognized equally well.

HXB2 Location p24 (164–172)
Author Location p24 (164–172)
Epitope YVDRFYKTL
Immunogen HIV-1 infection
Species (MHC) human (A*0207)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location p24 (164–172)
Author Location p24 (164–172)
Epitope YVDRFFKTL
Immunogen HIV-1 infection
Species (MHC) human (A*2601)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope YVDRFFKTL was predicted to be restricted by HLA A*0203, A*0204, A*0207, A*2601 and B*3801.

HXB2 Location p24 (164–172)
Author Location p24
Epitope YVDRFYKTL
Epitope name A2-YL9(p24)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).

- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (164–172)
Author Location p24 (298–306 subtype A)
Epitope YVDRFFKTL
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (A26, B70)
Keywords subtype comparisons
References Dorrell *et al.* 1999

- CTL responses in three individuals with non-clade B infections were studied, 2 with subtype A infections, 1 with subtype C – their infections all originated in East Africa.
- This CTL epitope is conserved in A and C subtype, and B clade sequences tend to have a change from F to Y, YVDRFYKTL – both variants showed strong CTL reactivity.
- CTL reacted with targets presenting either in the context A26 or B70 – the epitope has the HLA-26 motif of Val at position 2 and Leu at the carboxy terminus, and the B70 anchor residue motif is unknown.

HXB2 Location p24 (164–172)
Author Location Gag (298–306 subtype A)
Epitope YVDRFFKTL
Subtype A
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human (A26, B70)
Keywords subtype comparisons
References Dorrell *et al.* 2001

- In vitro restimulation of CTL specific for dominant epitopes from infected individuals is possible using recombinant modified vaccinia virus Ankara (MVA) carrying A or D subtype HIV-1 Gag proteins.

HXB2 Location p24 (164–172)
Author Location p24
Epitope YVDRFFKTL
Epitope name YL-9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords subtype comparisons, epitope processing, immunodominance, cross-presentation by different HLA
References Masemola *et al.* 2004b

- Highly targeted regions in Gag for CD8+ T-cells were defined for individuals with C clade infections in South Africa. 9 specific epitopes within the most reactive regions were characterized.
- YVDRFFKTL was presented by B*15, which is more common in Zulus than Caucasians (0.153 versus 0.079). This epitope had previously identified in B clade infections.

HXB2 Location p24 (164–172)
Author Location
Epitope YVDRFFKTL
Immunogen
Species (MHC) human (B*1503)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B*1503 epitope.

HXB2 Location p24 (164–172)
Author Location Gag (296–304)
Epitope YVDRFFKTL
Subtype A, C, D
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Country Tanzania
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, immunodominance
References Geldmacher *et al.* 2007a

- 56 ART-naive subjects were studied to assess whether T-cell responses to Gag and Nef are biased towards infecting subtype recognition, in a setting of epidemic consisting of subtypes A,C and D and their recombinant forms. The infecting subtype was determined by multi-region hybridization assay. Overlapping 15-mer isolate-based Gag and Nef peptide sets representative of local subtypes were used. The best recognized epitope variant in terms of magnitude and breadth corresponded to infecting subtype, in this case usually type-C. Hot spots of CTL recognition in Gag were in p24, p17 and p15; hotspots against Nef were in its central, conserved region.
- Epitope variants YVDRFfKTL and YVDRFyKTL (HLA-B*1503) were studied as peptide sequences FRD-YVDRFfKTL-RAE (subtypes C and A) and FRD-YVDRFyKTL-RAE (subtype D), with 30% responders. Subtypes C and A sequences were recognized best. Associated HLA frequently expressed within the studied cohort is listed in the study as B*1510.

HXB2 Location p24 (164–172)
Author Location Gag
Epitope YVDRFFKTL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, viral fitness and reversion
References Chopera *et al.* 2008

- Transmission of HIV-1-escape variants from individuals with protective HLA-B*57/-B*5801 alleles to those without these alleles was studied to determine if infection with such replication-deficient mutants offered any advantage to the new host. Dependency between slower rate of disease progression in the newly infected subject and protective genotype of the infecting individual was suggested.

CTL CD8+

- 2 Gag polymorphisms in epitopes ISW9 and TW10 associated with low viral loads and high CD4+ counts during acute and chronic infection were followed in HLA-B*57 and HLA-B*5801 negative subjects for minimum 12 months. A correlation was suggested between rate of disease progression and genotype of the individual from whom virus was contracted.
- HLA-B*1510-restricted epitope YVDRFFKTL, within peptide GPKEPFRDYVDRFFKTLRAEQATQDVKNWMTDTL was able to elicit CTL response in a wild type virus-carrying subject.

HXB2 Location p24 (164–172)
Author Location Gag (296–304 96ZM651.8)
Epitope YVDRFFKRL
Immunogen
Species (MHC) human (B*1510, B70)
Keywords subtype comparisons
References Novitsky *et al.* 2001

- This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort.
- 4 subjects who responsed to the CTL epitope YVDRFFKTL – all were HLA-B*1510 and also shared HLA-Cw03, suggesting linkage disequilibrium.
- An HIV-1 B variant of the epitope YVDRFYKTL has been described, and was recognized by CTL from an HIV-1 subtype A-infected patient, and the HLA restriction of the epitope was suggested to be A26 or B70 – HLA-B*1510 is equivalent to the serological specificity HLA B70.

HXB2 Location p24 (164–172)
Author Location p24
Epitope YVDRFFKTL
Epitope name B15-YL9(p24)
Immunogen HIV-1 infection
Species (MHC) human (B15)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (164–172)
Author Location Gag
Epitope YVDRFFKAL
Subtype A, AE
Immunogen HIV-1 infection
Species (MHC) human (B15, Cw*0303)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA B15-restricted epitope YVDRFFKAL is from a subtype A peptide library (peptide EPFRDYVDRFFKALR), and was reactive in a subtype A-carrying subject. The HLA Cw*0303-restricted epitope is from a subtype A peptide library (peptide YVDRFFKALRAEQAT), and was reactive in a subtype AE-carrying subject.

HXB2 Location p24 (164–172)
Author Location p24 (164–172)
Epitope YVDRFYKTL
Immunogen HIV-1 infection
Species (MHC) human (B70)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (164–172)
Author Location p24 (164–172)
Epitope YVDRFFKTL
Immunogen
Species (MHC) human (Cw*0303)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location p24 (164–172)
Author Location
Epitope YVDRFFKTL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0303)
Donor MHC A*6802, B*1510, Cw*03
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- Known epitope YVDRFFKTL is HLA-Cw*0303-restricted. Response to a peptide containing this epitope was detected in a rapid progressor 12 weeks post-infection.

HXB2 Location p24 (164–172)
Author Location p24 (164–172)
Epitope YVDRFFKTL
Immunogen
Species (MHC) human (Cw*0304)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location p24 (164–172)
Author Location (C consensus)
Epitope YVDRFFKTL
Epitope name YL9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0304)
Donor MHC A*3402, B*0801, B*4403, Cw*0304, Cw*0401
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was one of two used to illustrate how specific epitopes were characterized with regard to defining the optimal epitope and the HLA restricting element. HLA allelic associations in the population with peptide recognition was highly predictive of the epitope within the 15 mer.

HXB2 Location p24 (164–172)
Author Location (C consensus)
Epitope YVDRFFKTL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0304)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the T8 residue of YVDRFFKTL are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location p24 (164–172)
Author Location p24
Epitope YVDRFFKTL
Epitope name YL9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0304)
Country South Africa
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization
Keywords rate of progression
References Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naive patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer Cw*0304 YL9 was used to test 24 patients and gave a median ex vivo tetramer frequency of 2.26.

HXB2 Location p24 (164–172)
Author Location p24
Epitope YVDRFFKTL
Epitope name YL9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0304)
Country South Africa
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization
Keywords rate of progression
References Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naive patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer Cw*0304 YL9 was used to test 24 patients and gave a median ex vivo tetramer frequency of 2.26.

HXB2 Location p24 (164–172)
Author Location Gag
Epitope YVDRFFKTL
Immunogen HIV-1 infection
Species (MHC) human (Cw*0304)
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons, cross-presentation by different HLA, variant cross-recognition or cross-neutralization
References Currier *et al.* 2006

- The pattern of immunodominance and epitope clustering within Gag and Nef proteins in subtype A infected individuals was similar to that seen in subtype B and C infections. An immunodominant HLA-C restricted epitope, YVDRFFKTL (YL9 from Gag protein) was observed and restricted to Cw0304.
- This immunodominant sequence FRDYVDRFFKTLRAE is associated with HLA-Cw*0304 and contains the minimal epitope YVDRFFKTL.

HXB2 Location p24 (164–172)
Author Location
Epitope YVDRFFKTL?
Epitope name YL9
Immunogen HIV-1 infection
Species (MHC) human (Cw*0304)
Country United States, South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords memory cells
References Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

HXB2 Location p24 (164–172)
Author Location
Epitope YVDRFFKTL
Epitope name YL9
Immunogen HIV-1 infection
Species (MHC) human (Cw*0304)
Country South Africa
Assay type proliferation, Tetramer binding, Intracellular cytokine staining
References Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

HXB2 Location p24 (164–172)
Author Location p24
Epitope YVDRFYKTL
Epitope name YL9(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described epitope YVDRFYKTL elicited an immune response as part of peptide YVDRFYKTLRAEQASQEV as well as peptides GPKEPFRDYVDRFYKTLR and YYVDRFYKTLRAEQASQEV. This epitope differs from the previously described HLA-A2 and B15-restricted epitope, YVDRFFKTL, at 1 residue, YVDRFyKTL.
- 18 of the 55 HLA-A2 carriers responded to a YVDRFyKTL-containing peptide with average magnitude of CTL response of 334 SFC/million PBMC; 9 of the 21 HLA-B15 carriers responded to a YVDRFyKTL-containing peptide with average magnitude of CTL response of 542 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p24 (164–181)
Author Location Gag
Epitope YVDRFYKTLRAEQASQEV
Epitope name GAG-41
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, YVDRFyKTLRAEQAsQeV differs from the consensus C sequence YVDRFfKTLRAEQAtQdV at 3 amino acid positions, i.e. by 16.7%.

HXB2 Location p24 (164–181)
Author Location p24
Epitope YVDRFYKTLRAEQASQEV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance

References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, YVDRFYKTLRAEQASQEV, had an overall frequency of recognition of 25.3% - 22% AA, 30.8% C, 31.8% H, 14.3% WI. This peptide is included in a 43 aa Gag-p24 highly reactive region to be used for vaccine design.

HXB2 Location p24 (164–181)
Author Location Gag (298–315)
Epitope `YVDRFYKSLRAEQTDPAV`
Subtype HIV-2
Immunogen HIV-2 infection
Species (MHC) human
Country Guinea-Bissau
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords rate of progression, optimal epitope, HIV-2
References Leligdowicz *et al.* 2007

- To find the factors involved in attenuated disease course and long term non-progression, HIV-2 and immune control were studied. HIV-2 viral load was used as a predictor of patient survival. HIV-2 viral load correlated inversely with magnitude of IFN-gamma response, relative dominance of Gag-specific peptides' responses over other proteins' responses, and the breadth of different peptide-specific immune responses. The most frequently recognized peptides were in Gag protein, followed by Env and Pol, while Nef and accessory proteins (Vif, Vpx, Vpr, Tat and Rev) rarely elicited responses. The 6 most recognized peptides were clustered in a highly conserved region of Gag.
- This peptide, YVDRFYKSLRAEQTDPAV, was most frequently recognized at 20 out of 65 different subjects. Its responses can be both CD8 and CD4 T cell restricted.

HXB2 Location p24 (165–178)
Author Location p24 (165–177 HXB2)
Epitope `VDRFYKTLRAEQAS`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 19% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location p24 (165–178)
Author Location p24 (165–178)
Epitope `VDRFYKLTRAEQAS`
Epitope name VS14
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, subtype comparisons, acute/early infection
References Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (ANC) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.

- Epitope sequences for this eptiope, VS14 are invariant between CON B, COT B, ANC B and M-group. Cross-recognition is seen to both A- and C-clade variants. An anchor residue is at position 9; while both A- and C- variants contain a change at position 14 to VDRFYKLTRAEQAt.
- Probable HLA restriction for this epitope was suggested to be HLA A33 based on the subject possessing the appropriate HLA class I allele.

HXB2 Location p24 (165–179)
Author Location Gag (297–311)
Epitope VDRFYKTLRAEQASQ
Epitope name VQ15
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- One subject responded to peptide VQ15, a non-B*57-restricted peptide.

HXB2 Location p24 (165–179)
Author Location
Epitope VDRFYKTLRAEQASQ
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A3, A32; B38, B64
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was recognized by a placebo patient after infection.

HXB2 Location p24 (166–174)
Author Location p24 (398–306)
Epitope DRFYKTLRA
Epitope name DA9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*14)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*14-associated substitutions within optimally defined epitope DRFYKTLRA are at positions K5 and T6, DRFYktLRA.

HXB2 Location p24 (166–174)
Author Location (C consensus)
Epitope DRFFKTLRA
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1401)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- DRFFKTLRA is an optimal epitope.

HXB2 Location p24 (166–174)
Author Location p24
Epitope DRFFKTLRA
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1401)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- DRFFKTLRA is a previously described HLA-B*1401-restricted epitope (part of Gag reacting peptide PFRDYVDRFFkTLRAEQATQD) that contains a B*1401-associated reversion at residue D (DRFFkTLRA).

HXB2 Location p24 (166–174)

Author Location p24 (298–306 LAI)
Epitope DRFYKTLRA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1402)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*1402 epitope.

HXB2 Location p24 (166–174)
Author Location (167–175)
Epitope DRFFKTLRA
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1402)
Assay type Other
Keywords HLA associated polymorphism
References Boutwell & Essex 2007

- Publicly available HIV-1 subtype C sequences from South Africa and Botswana were analyzed, and 94 HLA-associated amino acid polymorphisms were found. Many polymorphisms were associated with multiple HLA allele classes. 12% associations were negative: association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles accounted for 50% of associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes.
- DRFFKTLRA was a previously defined B*1402 presented epitope that encompassed a B*14/B*1401 associated polymorphism, DRFFkTLRA,in the fifth position. This epitope is embedded in a previoulsy determined CTL immunodominant region.

HXB2 Location p24 (166–174)
Author Location p24 (166–174)
Epitope DRFFKTLRA
Immunogen HIV-1 infection
Species (MHC) human (B*1402)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope DRFFKTLRA was predicted to be restricted by HLA B*1402, B*2701, B*2702, B*2703, B*2704, B*2705 and B*2709.

HXB2 Location p24 (166–174)
Author Location p24
Epitope DRFFKTLRA
Epitope name DA-9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1403)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords subtype comparisons, epitope processing, immunodominance, cross-presentation by different HLA
References Masemola *et al.* 2004b

- Highly targeted regions in Gag for CD8+ T-cells were defined for individuals with C clade infections in South Africa. 9 specific epitopes within the most reactive regions were characterized.
- DRFFKTLRA was presented by B*14, which is more common in Zulus than Caucasians (0.066 versus 0.038). This epitope had previously identified in B clade infections.

HXB2 Location p24 (166–174)
Author Location p24 (298–306 IIIB)
Epitope DRFYKTLRA
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords responses in children, mother-to-infant transmission
References Wilson *et al.* 1996

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.
- DRFYKILRA, a naturally occurring variant, was found in mother, and is recognized although less reactive.
- DQFYKTLRA, a naturally occurring variant, was found in infant and is not recognized.

HXB2 Location p24 (166–174)
Author Location p24 (298–306 IIIB)
Epitope DRFYKTLRA
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Cao *et al.* 1997a

- The consensus peptide for clades B and D is DRFYKTLRA.
- The consensus peptide for clades A and C is DRFFKTLRA and it is equally reactive.

HXB2 Location p24 (166–174)
Author Location p24 (298–306 HXB2)
Epitope DRFYKTLRA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords kinetics
References Yang *et al.* 1997b

CTL CD8+

- A chimeric universal T cell receptor was created by linking CD4 or an HIV-specific anti-gp41 Ig sequence to the signaling domain of the T cell receptor chain ζ, and transducing into CD8+ cells.
- The response using universal-receptor-bearing CD8+ cells to lyse infected cells *in vitro* was comparable to the natural occurring responses of CTL-clones from HIV+ individuals in terms of kinetics and efficiency.
- A CTL clone specific for this epitope was used for the comparison.

HXB2 Location p24 (166–174)
Author Location p24
Epitope DRFWKTLRA
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B14)
Keywords subtype comparisons, HIV exposed persistently seronegative (HEPS)
References Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The D subtype consensus is identical to the B clade epitope.
- The A subtype consensus is drFfKtLRA.

HXB2 Location p24 (166–174)
Author Location p24 (298–306 LAI)
Epitope DRFYKTLRA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Harrer *et al.* 1996b

HXB2 Location p24 (166–174)
Author Location p24 (298–306)
Epitope DRFYKTLRA
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Yang *et al.* 1996

- CD4+ cell lines acutely infected with HIV were studied to determine their susceptibility to lysis by CTL.
- Clones specific for RT lysed HIV-1 infected cells at lower levels than Env or Gag specific clones.
- The distinction was thought to be due to lower expression of RT relative to Env and Gag.
- CTL can lyse infected cells early after infection, possibly prior to viral production.

HXB2 Location p24 (166–174)
Author Location p24 (298–306)
Epitope DRFYKTLRA
Immunogen HIV-1 infection
Species (MHC) human (B14)
Assay type CTL suppression of replication
References Yang *et al.* 1997a

- CTL inhibit HIV-1 replication at effector cell concentrations comparable to those found *in vivo*.
- CTL produced HIV-1-suppressive soluble factors – MIP-1α, MIP-1β, RANTES, after antigen-specific activation.
- CTL suppress HIV replication more efficiently in HLA-matched cells.

HXB2 Location p24 (166–174)
Author Location p24 (298–306)
Epitope DRFYKTLRA
Immunogen in vitro stimulation or selection
Species (MHC) human (B14)
Keywords dendritic cells
References Zarling *et al.* 1999

- This study compares the ability of macrophages and dendritic cells to stimulate primary responses in CD8+ lymphocytes isolated from HLA-appropriate HIV-uninfected donors using peptide-pulsed APC – the dendritic cells performed better as APC for the stimulation of primary responses.
- Strong CTL responses were elicited by the epitopes DRFYKTLRA and GEIYKRWII when presented by either immature or mature dendritic cells – macrophages were not able to prime a CTL response against DRFYKTLRA.
- A weak response to KLTPLCVSL was stimulated using macrophages as the APC.
- No detectable response was observed for the following previously-defined HIV epitopes: KIRLRPGGK, ILKEPVHGV, IRLRPGGK, GPKVKQWPL.

HXB2 Location p24 (166–174)
Author Location p24
Epitope DRFYKLTRA
Immunogen
Species (MHC) human (B14)
References Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective.
- HIV-2 sequence: DRFYKSLRA is cross-reactive, Harrer *et al.* [1993]

HXB2 Location p24 (166–174)
Author Location p24 (298–306 IIIB)
Epitope DRFYKTLRA
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords responses in children, mother-to-infant transmission, escape
References Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- DRFYKILRA and DQFYKTLRA were escape mutants.

HXB2 Location p24 (166–174)
Author Location p24 (SF2)
Epitope DRFYKTLRA

Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in 2/5 HIV+ individuals who were HLA B14 living in Boston – this epitope did not fall within the three most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa.

HXB2 Location p24 (166–174)
Author Location p24 (SF2)
Epitope DRFYKTLRA
Epitope name DA9
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords acute/early infection
References Goulder *et al.* 2001a

- Data from patient AC13 suggest a role for this epitope in initial control of viremia in acute infection, as it is one of several subdominant CTL epitopes recognized during the initial decline in viremia.
- A CTL response to SL9, SLYNTVATL, was not evident until 18 months post-presentation.

HXB2 Location p24 (166–174)
Author Location p24 (166–174)
Epitope DRFYKTLRA
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (166–174)
Author Location p24 (298–306 SF2)
Epitope DRFYKTLRA
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B14+ individuals that had a CTL response to this epitope broken down by group: 3/3 group 1, 1/2 group 2, and 0/0 group 3.

HXB2 Location p24 (166–174)
Author Location p24 (298–306)
Epitope DRFFKTLRA
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B14)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- Variants DRF(F/W)KTLRA are specific for clades A/B.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B14 women, 0/4 HEPS and 6/7 HIV-1 infected women recognized this epitope, likelihood ratio 14.4, p value 0.004 and HEPS women tended to respond to DLNMMLNIV/DLNTMLNVV, while infected women tended to respond to DRF(F/W)KTLRA.
- The dominant response to this HLA allele was to this epitope for all of the 6/7 HIV-1 infected women.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.

HXB2 Location p24 (166–174)
Author Location p24 (SF2)
Epitope DRFYKTLRA
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.

HXB2 Location p24 (166–174)
Author Location p24
Epitope DRFYKTLRA

CTL CD8+

Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords epitope processing
References Cao *et al.* 2002

- AC13 is a B14 restricted CTL clone that recognizes DRFYKTLRA.
- CTL could be activated by a fusion protein of an HIV protein and anthrax lethal factor (LFn-HIV) that promotes antigen presenting cell uptake of exogenous protein and allows processing through the MHC class I pathway. This strategy for CTL detection could allow antigen presentation without generation of cells by the standard methods of using live viral vectors carrying a protein, or by loading the cells with peptides and by-passing processing.

HXB2 Location p24 (166–174)
Author Location p24
Epitope DRFWKTLRA
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2002

- Neisseria gonorrhea cervititis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
- Ghonorrhea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

HXB2 Location p24 (166–174)
Author Location p24
Epitope DRFYKTLRA
Subtype B, D
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human (B14)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location p24 (166–174)
Author Location p24 (166–174)
Epitope DRFYKTLRA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Donor MHC A1, A3, B14, B7, Cw*0702, Cw*0802; A1A1, B14, B8, Cw7, Cw8
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- This epitope was recognized in two subjects early in infection, presented by B14 in each case.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

HXB2 Location p24 (166–174)
Author Location p24 (166–174)
Epitope DRFYKTLRA
Epitope name Gag/p24-DA9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Assay type Chromium-release assay
Keywords binding affinity, TCR usage, characterizing CD8+ T cells
References Yang *et al.* 2003b

CTL CD8+

- Killing efficiency of CTLs and their ability to suppress viral replication is shown to depend more on epitope specificity than to antigenic avidity. Different clones recognizing the same epitope had similar killing efficiency despite their variation in avidity. Nef specific CTL clones tended to be most inhibitory, followed by Gag, then by RT specific clones, regardless of avidity.
- 1/14 CTL T-cell clones tested were specific for Gag/p24-DA9. Under conditions of excess peptide (100ug/ml), there was no difference in their lytic potential; all possessed similar effector capacity. Avidity was measured as the sensitizing dose of peptide required for 50% of maximal killing (SD50), which varied from 20 pg/ml to 100 ng/ml, over four orders of magnitude for all 14 epitopes. The SD50 value for Gag/p24-DA9 was 100,000 pg/ml, it had the lowest avidity of the 14 tested.

HXB2 Location p24 (166–174)
Author Location (C consensus)
Epitope DRFFKTLRA
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B14)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p24 (166–174)
Author Location (B consensus)
Epitope DRFYKTLRA
Epitope name DA9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Donor MHC A28, A29, B14, B44, Cw8; A25, A32, B08, B14, Cw7, Cw8; A03, B14, B60, Cw3, Cw7
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 3/9 individuals recognized this epitope, presented by HLA-B14.

HXB2 Location p24 (166–174)
Author Location Gag (298–306)
Epitope DRFYKTLRA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location p24 (166–174)
Author Location Gag (298–306)
Epitope DRFYKTLRA
Epitope name DA9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Donor MHC A*02, A*68, B*14, B*52, Cw*08, Cw*12
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords escape, optimal epitope
References Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- A form of this epitope that elicited a diminished Elispot response, DRFYrTLRA, dominated the viral sequence for several years, and then reverted back to the B consensus form, DRFYKTLRA.

HXB2 Location p24 (166–174)
Author Location p24
Epitope DRFYKTLRA
Epitope name DA9
Immunogen
Species (MHC) (B14)

CTL CD8+

Keywords review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion
References Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

HXB2 Location p24 (166–174)
Author Location p24
Epitope DRFYKTLRA
Epitope name B14-DA9(p24)
Immunogen HIV-1 infection
Species (MHC) human (B14)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (166–174)
Author Location p24 (166–174)
Epitope DRFYKLTRA
Epitope name DA9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, subtype comparisons, acute/early infection
References Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (ANC) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- Epitope sequences for this eptiope, DA9 are invariant between CON B, COT B, ANC B and M-group. Cross-recognition is seen to both A- and C-clade variants. An anchor residue is at position 2; while both A- and C- variants contain a change at position 4 to DRFfKLTRA. HLA-B14 restriction was inferred based on 2 subjects possessing appropriate HLA class I allele and prior publication.

HXB2 Location p24 (166–174)
Author Location
Epitope DRFYKTLRA
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (B14)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location p24 (166–174)
Author Location p24 (subtype B)
Epitope DRFYKTLRA
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B*1402, B14)
Keywords subtype comparisons
References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among B and D clade viruses.
- The Clade A version of the epitope, DRFFKLTRA, was preferentially recognized by CTL.
- This epitope was recognized by two different exposed and uninfected prostitutes.

HXB2 Location p24 (166–175)
Author Location p24 (298–306 HX10)
Epitope DRFYKTLRAE
Immunogen HIV-1 infection

Species (MHC) human (B14)
Keywords immunodominance
References Wagner *et al.* 1999

- The immunodominant CTL response in a long-term survivor was to this highly conserved and functionally relevant epitope.
- By testing mutations in an HXB2 background, it was found that all mutations within the epitope that abrogated CTL recognition also abolished viral infectivity.
- The epitope in this study overlaps the major homology region for which highly conserved residues exist in all known lenti- and onco-viruses and yeast transposons.
- Patient was part of the study in Harrer *et al.* [1996a]

HXB2 Location p24 (166–175)
Author Location Gag (298–307)
Epitope DRFYKTRAE
Immunogen HIV-1 infection
Species (MHC) human (B14)
Donor MHC A24, A33, B14, B27
Assay type Chromium-release assay
Keywords TCR usage, genital and mucosal immunity
References Musey *et al.* 2003

- CTL clones from blood, semen, cervix and rectum samples from 12 individuals were compared. CTL clones derived from blood and mucosal samples had similar high lysis efficiency, primarily perforin dependent, and TCRβ VDJ region sequencing revealed cases of expansion of the same clone in different compartments.
- CD8+ T cell clones directed at this epitope were derived from blood and cervix.

HXB2 Location p24 (166–176)
Author Location Gag (295–305 BORI)
Epitope DRFYKTLRAEQ
Epitope name Gag DQ11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1402)
Donor MHC A*2902, B*1402, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, immunodominance, acute/early infection, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient BORI had high viral loads and rapid CD4 decline. BORI mounted 8 detected responses. BORI did not control viral replication well, and escape mutations occurred early and in most epitopes, 6/7 that were precisely identified.
- DRFYKTLRAEQ didn't vary. There was no response in acute infection to this epitope, but the response was detectable by early infection.

HXB2 Location p24 (166–176)
Author Location Gag
Epitope DRFYKTLRAEQ
Subtype A, B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-B14-restricted epitope DRFYKTLRAEQ is from subtype A and B peptide libraries, and is reactive as part of peptide YVDRFYKTLRAEQAS in a subtype B-carrying subject.

HXB2 Location p24 (169–183)
Author Location Gag (301–315 SF2)
Epitope YKTLRAEQASQEVKN
Epitope name Peptide 76
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF2 *HIV component:* Gag, Tat *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse (H-2^d)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, optimal epitope
References Cellini *et al.* 2008

- In order to increase the known number of epitopes in Gag protein so that they can be assayed for reactivity in vaccine studies, BALB/c mice were inoculated with Gag or Gag+Tat. OLPs were used to elicit T-cell immune responses from mouse splenocytes, tested for by cytotoxicity or ELISpot assays. 5 novel predicted optimal CTL epitopes, 2 novel predicted CD4 epitopes and 2 immune response eliciting peptides were found.
- Reactive peptide YKTLRAEQASQEVKN was previously known to have a potential (still unidentified) epitope, but here it was characterized for the first time.

HXB2 Location p24 (169–183)
Author Location Gag (301–315)
Epitope YKTLRAEQASQEVKN
Immunogen vaccine

CTL CD8+

Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized both by mice co-immunized with Gag and Tat, and by mice immunized with Gag alone.

HXB2 Location p24 (169–183)
Author Location Gag (301–315)
Epitope `YKTLRAEQASQEVKN`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the ES.

HXB2 Location p24 (169–185)
Author Location p24 (169–184 HXB2)
Epitope `YKTLRAEQASQDVKNWN`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- Responses to this peptide were detected in 17% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location p24 (169–188)
Author Location Gag (301–320)
Epitope `YKTLRAEQASQEVKNWMTET`
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A1, A66, B52, B57
Assay type Chromium-release assay
Keywords TCR usage, genital and mucosal immunity
References Musey *et al.* 2003

- CTL clones from blood, semen, cervix and rectum samples from 12 individuals were compared. CTL clones derived from blood and mucosal samples had similar high lysis efficiency, primarily perforin dependent, and TCRβ VDJ region sequencing revealed cases of expansion of the same clone in different compartments.
- CD8+ T cell clones directed at this epitope were derived from blood and rectum.

HXB2 Location p24 (169–188)
Author Location Gag (301–320)
Epitope `FKTLRAEQATQDVKNWMTDT`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 8 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location p24 (171–180)
Author Location p24
Epitope `TLRAEQATQD`
Epitope name TD-10
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0304)
Country South Africa

Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords subtype comparisons, epitope processing, immunodominance, cross-presentation by different HLA
References Masemola *et al.* 2004b

- Highly targeted regions in Gag for CD8+ T-cells were defined for individuals with C clade infections in South Africa. 9 specific epitopes within the most reactive regions were characterized. This is 1 of 5 novel epitopes that were found among subtype C HIV-1 from African patients who hadn't previously been identified in B clade infections. Some epitopes were shown to be promiscuous, presented by multiple class I restricting alleles.
- TLRAEQATQD was presented by Cw*03 and newly identified in this study; Cw*03 is more common in Zulus than Caucasians (0.157 versus 0.101).

HXB2 Location p24 (172–189)
Author Location Gag
Epitope `LRAEQASQEVKNWMTETL`
Epitope name GAG-42
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, LRAEQAsQeVKNWMTeTL differs from the consensus C sequence LRAEQAtQdVKNWMTdTL at 3 amino acid positions, i.e. by 16.7%.

HXB2 Location p24 (172–189)
Author Location p24
Epitope `LRAEQASQEVKNWMTETL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, LRAEQASQEVKNWMTETL, had an overall frequency of recognition of 22.7% - 20.3% AA, 46.2% C, 18.2% H, 9.5% WI. This peptide is included in a 43 aa Gag-p24 highly reactive region to be used for vaccine design.

HXB2 Location p24 (172–189)
Author Location Gag (306–323)
Epitope `LRAEQTDPAVKNWMTQTL`
Subtype HIV-2
Immunogen HIV-2 infection
Species (MHC) human
Country Guinea-Bissau
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords rate of progression, optimal epitope, HIV-2
References Leligdowicz *et al.* 2007

- To find the factors involved in attenuated disease course and long term non-progression, HIV-2 and immune control were studied. HIV-2 viral load was used as a predictor of patient survival. HIV-2 viral load correlated inversely with magnitude of IFN-gamma response, relative dominance of Gag-specific peptides' responses over other proteins' responses, and the breadth of different peptide-specific immune responses. The most frequently recognized peptides were in Gag protein, followed by Env and Pol, while Nef and accessory proteins (Vif,

CTL CD8+

Vpx, Vpr, Tat and Rev) rarely elicited responses. The 6 most recognized peptides were clustered in a highly conserved region of Gag.
- This peptide, LRAEQTDPAVKNWMTQTL, was recognized by 11 out of 65 subjects. It is found in the 149 amino-acid long HIV-2 proteome region of Gag 175-323.

HXB2 Location p24 (173–181)
Author Location Gag (305–313 SUMA)
Epitope RAEQASQEV
Epitope name Gag RV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*0802)
Donor MHC A*1103, A*2402, B*1402, B*1501, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, acute/early infection, characterizing CD8+ T cells
References Jones *et al.* 2004
- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape muations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

HXB2 Location p24 (173–181)
Author Location
Epitope RAEQASQEV
Immunogen HIV-1 infection
Species (MHC) human (Cw08)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006
- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope RAEQASQEV elicited a magnitude of response of 220 SFC with a functional avidity of 0.01nM.

HXB2 Location p24 (173–181)
Author Location p24 (305–313)
Epitope RAEQASQEV
Immunogen HIV-1 infection
Species (MHC) human (Cw8)
References Johnson *et al.* 1991
- Originally reported as HLA-B14 restricted, but subsequently found not to be presented by cells transfected with B14.
- Thought to be HLA-Cw8 restricted (C. Brander and B. Walker)

HXB2 Location p24 (173–181)
Author Location p24
Epitope RAEQASQEV
Immunogen HIV-1 exposed seronegative
Species (MHC) human (Cw8)
Keywords subtype comparisons, HIV exposed persistently seronegative (HEPS)
References Rowland-Jones *et al.* 1998a
- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A subtype consensus is RAeQAtQEV.
- The D subtype consensus is RAEQsQdV.
- Thought to be HLA-Cw8 restricted, not B14 as originally reported (C. Brander, B. Walker, and S. Rowland-Jones, personal communication)

HXB2 Location p24 (173–181)
Author Location p24 (305–313)
Epitope RAEQASQEV
Immunogen HIV-1 infection
Species (MHC) human (Cw8)
References Price *et al.* 1995
- Study of cytokines released by HIV-1 specific activated CTL.
- Thought to be HLA-Cw8 restricted, not B14 as originally reported (C. Brander, B. Walker, and S. Rowland-Jones, personal communication)

HXB2 Location p24 (173–181)
Author Location p24 (305–313)
Epitope RAEQASQEV
Immunogen HIV-1 infection
Species (MHC) human (Cw8)
References Lubaki *et al.* 1997
- Eighty two HIV-1-specific CTL clones from 5 long-term non-progressors were isolated and analyzed for breadth of response.

- A sustained Gag, Env and Nef response was observed, and clones were restricted by multiple HLA epitopes, indicating a polyclonal response.
- Despite this being a well defined conserved epitope, and thought to be presented by B14, none of the 11 gag-specific clones from a B-14 positive subject could recognize either it or p24 PQDLNTMLN.
- Thought to be HLA-Cw8 restricted, not B14 as originally reported (C. Brander, B. Walker, and S. Rowland-Jones, personal communication)

HXB2 Location p24 (173–181)
Author Location p24 (305–313)
Epitope RAEQASQEV
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (Cw8)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location p24 (173–181)
Author Location Gag (305–313)
Epitope RAEQASQEV
Epitope name RV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw8)
Donor MHC A*02, A*68, B*14, B*52, Cw*08, Cw*12
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords escape, optimal epitope
References Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- Elispot responses to the consensus form of this epitope, RAEQASQEV, were much more intense than to the most common variants of the epitope found over time in this individual, RAEQAStEV and RAEQASQdV. There was a diminished response to RAEQAStEV and no response to RAEQASQdV, so these appear to be escape variants. The strong response to the consensus form persisted, despite the fact it was not observed among the autologous sequences until it surfaced as a minor variant (5/13 sequences) after 6 years of chronic infection.

HXB2 Location p24 (173–181)
Author Location p24
Epitope RAEQASQEV
Epitope name Cw8-RV9(p24)
Immunogen HIV-1 infection
Species (MHC) human (Cw8)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (173–181)
Author Location
Epitope RAEQASQEV
Immunogen HIV-1 infection
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 1/22 HEPS sex worker controls ML1792.

HXB2 Location p24 (173–182)
Author Location Gag (Henan isolate)
Epitope RAEQASQEVK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p24 (173–183)
Author Location Gag (308–318)
Epitope RAEQATQDVKN
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p24 (173–187)
Author Location
Epitope RAEQASQEVKNWMTE
Immunogen HIV-1 infection
Species (MHC) human (B44)
Donor MHC A2, A32, B44, B7; A11, A2, B44, B60
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 77 (NIH ARRP Cat# 7948), RAEQASQEVKNWMTE, contains an epitope restricted by HLA-B44 in different patients. It elicited the following CTL responses: (1) 78 sfc/million PBMC for up to 22+ years in a living non-progressor (2) 2144 sfc/million PBMC for up to 12 years in a former non-progressor who succumbed to non-AIDS death.

HXB2 Location p24 (173–187)
Author Location Gag
Epitope RAEQATQEVKNWMTE
Subtype A, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 3 subjects responded to peptide RAEQATQEVKNWMTE from subtypes CRF01_AE and CRF02_AG; 1 of the 3 subjects also responded to peptide RAEQATQdVKNWMTd from subtype A.

HXB2 Location p24 (173–187)
Author Location Gag
Epitope RAEQATQDVKNWMTD
Subtype A
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide RAEQATQDVKNWMTD from subtype A.

HXB2 Location p24 (174–184)
Author Location Gag
Epitope AEQASQDVKNW
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*44)
Country Canada, South Africa
Keywords escape
References Carlson *et al.* 2008

- A statistical model, the phylogenetic dependency network (PDN), was developed to differentiate the confounding effects of codon variation, linkage disequilibrium of HLA alleles and HIV phylogeny from HLA-associated evolution including HIV selection by HLA-pressure and codon evolution.
- This approach was applied to 2 cohorts of 1144 Gag sequences from HIV-infected individuals, generating associations between HIV codons themselves and codons with HLA alleles. Results generated predicted escapes that confirmed that escape kinetics and compensating mutations are consistent across clades. General patterns of covariation and CTL adaptation were determined. Some clade-based differences were identified.

- HLA-B*44-restricted optimal epitope AEQASQDVKNW has a mutant, resistant form, AEQASQeVKNW, found primarily in clade B. The optimal epitope form is found mostly in clade C sequences.

HXB2 Location p24 (174–184)
Author Location p24 (306–316)
Epitope `AEQASQDVKNW`
Epitope name AW11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*44)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*44-associated substitutions within optimally defined epitope AEQASQDVKNW are at positions S5 and D7, AEQAsQdVKNW.

HXB2 Location p24 (174–184)
Author Location p24 (306–316 LAI)
Epitope `AEQASQDVKNW`
Subtype B
Immunogen
Species (MHC) human (B*4402)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*4402 epitope.

HXB2 Location p24 (174–184)
Author Location p24 (306–316 LAI)
Epitope `AEQASQDVKNW`
Subtype B
Immunogen
Species (MHC) human (B*4402, B44)
References Brander & Walker 1997

- Pers. comm. from D. Lewinsohn to C. Brander and B. Walker, C Brander *et al.*, this database, 1999.

HXB2 Location p24 (174–184)
Author Location p24
Epitope `AEQATQDVKNW`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4403)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- AEQATQDVKNW is a previously described HLA-B*4403-restricted epitope (part of Gag reacting peptide KTLRAEQATQdVKNWMTDTLL) that contains a B*4403-associated reversion at residue D (AEQATQdVKNW).

HXB2 Location p24 (174–184)
Author Location Gag (306–316)
Epitope `AEQASQEVKNW`
Immunogen HIV-1 infection
Species (MHC) human (B44)
References Brodie *et al.* 1999

- The ability of CTL effector cells was studied by expanding autologous HIV-1 Gag-specific CTL *in vitro*, and adoptively transferring them.
- The transferred CTLs migrated to the lymph nodes and transiently reduced circulating productively infected CD4+ T cells, showing that CTL move to appropriate target sites and mediate anti-viral effects.

HXB2 Location p24 (174–184)
Author Location p24 (306–316)
Epitope `AEQASQEVKNW`
Immunogen HIV-1 infection
Species (MHC) human (B44)
References Brodie *et al.* 2000

- Study tracks and quantifies *in vivo* migration of neo-marked CD8 HIV-specific CTL.
- Adoptively transferred gene-marked HIV-specific CTL homed to specific lymph node sites, colocalizing within the parafollicular regions of the lymph node adjacent to cells expressing HIV tat-fusion transcripts, indicative of viral replication.
- The CTL clones expressed CCR5 and localized among HIV-1 infected cells expressing MIP-1alpha and MIP-1beta, CC-chemokines produced at sites of viral replication, suggesting a possible homing mechanism.
- This study provides a methodology for tracking and studying antigen specific CTL *in vivo*

HXB2 Location p24 (174–184)
Author Location p24 (306–316 LAI)
Epitope `AEQASQDVKNW`
Epitope name G3
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B44)
Keywords HAART, ART
References Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNgamma production to measure responses.

- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

HXB2 Location p24 (174–184)
Author Location p24 (174–184)
Epitope `AEQASQDVKNW`
Immunogen HIV-1 infection
Species (MHC) human (B44)
References Day *et al.* 2001

- B44-restricted CTL response was strongest to this epitope in one individual.

HXB2 Location p24 (174–184)
Author Location p24
Epitope `AEQASQDVKNW`
Epitope name B44-AW11(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B44)
Donor MHC A32, B44
Keywords HAART, ART, supervised treatment interruptions (STI)
References Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (`http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html`) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient B displayed the greatest response to epitope B44-AW11(p24) and also responded to A32-PW10(RT) in both PB and LN samples, while a third response against epitope A32-RW10(gp120) was only detected in the LN sample.

HXB2 Location p24 (174–184)
Author Location Gag (B con)
Epitope `AEQASQEVKNW`
Epitope name AW11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B44)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Draenert *et al.* 2004c

- CD8+ T-cell responses that persisted in individuals with advanced disease were studied; most of the optimal epitopes defined were recognized with intermediate to high avidity. On average 13 (range, 2-39) epitopic regions were targeted in an average of 6 proteins (range, 1-8). HAART resulted in decrease in antigen and reduction in gamma IFN EliSpot responses, suggesting active responses to autologous virus. The lack of mutations within most viral epitopes suggest that persistent CTL through late disease do not exert strong immune selection pressure, yet the Elispot assays show robust responses, suggesting to the authors that gamma IFN-based screening methods may not reveal functional CD8+ T-cell impairment in patients with AIDS.
- 1 subject recognized this epitope with low functional avidity. The autologous sequence matched the B consensus.

HXB2 Location p24 (174–184)
Author Location (B consensus)
Epitope `AEQASQDVKNW`
Epitope name AW11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B44)
Donor MHC A02, A11, B18, B44, Cw12, Cw5; A28, A29, B14, B44, Cw8
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 2/9 individuals recognized this epitope, presented by HLA-B44.

HXB2 Location p24 (174–184)
Author Location Gag (306–316)
Epitope `AEQASQDVKNW`
Epitope name AW11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B44)
Donor MHC A11, A2, B18, B44, Cw12, Cw5

Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords optimal epitope
References Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- This epitope did not vary.

HXB2 Location p24 (174–184)
Author Location Gag (306–316)
Epitope AEQASQDVKNW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B44)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location p24 (174–184)
Author Location Gag (306–316)
Epitope AEQASADVKNW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B44)
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location p24 (174–184)
Author Location p24
Epitope AEQASQDVKNW
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human (B44)
Donor MHC A23, A34, B44, B53, Cw4, Cw6
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence had an D7E change, AEQASQeVKNW.

HXB2 Location p24 (174–184)
Author Location p24
Epitope AEQASQDVKNW
Epitope name B44-AW11(p24)
Immunogen HIV-1 infection
Species (MHC) human (B44)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (174–184)
Author Location
Epitope AEQASQDVKNW
Immunogen HIV-1 infection
Species (MHC) human (B44)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

CTL CD8+

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope AEQASQDVKNW elicited a magnitude of response of 525 SFC with a functional avidity of 0.5nM.

HXB2 Location p24 (174–184)
Author Location
Epitope AEQASQDVKNW
Immunogen HIV-1 infection
Species (MHC) human (B44)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B44), an additional HLA (B45) was statistically predicted to be associated with this epitope.

HXB2 Location p24 (174–184)
Author Location p24
Epitope AEQASQDVKNW
Epitope name AW11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B44)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- No variation was found in epitope AEQASQDVKNW in an untreated patient. Previously published HLA-restriction for AW11 is HLA-B44.

HXB2 Location p24 (174–184)
Author Location p24
Epitope AEQASQEVKNW
Epitope name AW11(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B44)
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope AEQASQEVKNW elicited an immune response in Chinese HIV-1 positive subjects as part of peptide LRAEQASQEVKNWMTETL. This epitope differs from the previously described HLA-B44-restricted epitope, AEQASQDVKNW, at 1 residue, AEQASQeVKNW.
- 2 of the 6 HLA-B44 carriers responded to AEQASQeVKNW-containing peptide with average magnitude of CTL response of 190 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p24 (174–185)
Author Location p24 (174–185)
Epitope AEQASQEVKNWM
Immunogen
Species (MHC) human (Cw5)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location p24 (175–186)
Author Location p24 (307–318)
Epitope EQASQEVKNWMT
Immunogen HIV-1 infection
Species (MHC) human (B44)
References Quayle *et al.* 1998

- HIV is found in semen both as cell-associated and cell-free forms, and HIV-specific CTL could be found in the semen of 5/5 men with CD4 greater than 500 – 3 of the men were analyzed in detail and had broad CTL to gag, env and pol.
- Two CTL lines from one donor recognized this epitope.
- Isolation of CTLs specific to HIV in both male and female urinal tracts provide evidence that virus-specific lymphocytes come from the urogenital mucosa, and the authors speculate that CTL in mucosal tissues may be correlated with lower viral load in semen and reduced transmission.

HXB2 Location p24 (176–184)
Author Location p24 (308–316 LAI)
Epitope QASQEVKNW
Subtype B
Immunogen HIV-1 infection

Species (MHC) human (B*5301)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*5301 epitope.

HXB2 Location p24 (176–184)
Author Location (C consensus)
Epitope QATQDVKNW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- QATQDVKNW is an optimal epitope.

HXB2 Location p24 (176–184)
Author Location
Epitope QASQEVKNW
Epitope name Gag-QW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5301, B57)
Donor MHC 01RCH59: A*0201, A*3201, B*4002, B*5301, Cw*0202, Cw*0401
Keywords HAART, ART
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Subject 01RCH59 was Hispanic, was not on HAART, viral load 5100, CD4 count 349, and she also recognized PIQKETWETW, RT(392-401), A*3201.
- Among HIV+ individuals who carried HLA B*5301, 11/15 (73%) recognized this epitope.
- Among HIV+ individuals who carried HLA B57, 3/6 (60%) recognized this epitope.

HXB2 Location p24 (176–184)
Author Location Gag
Epitope QASQEVKNW
Epitope name QW9
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B*57-restricted optimal epitope QASQEVKNW was tested for immune response.

HXB2 Location p24 (176–184)
Author Location p24 (176–184)
Epitope QASQEVKNW
Epitope name QW10
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country United Kingdom, Kenya
Assay type CD8 T-cell Elispot - IFNγ
Keywords TCR usage, structure, characterizing CD8+ T cells
References Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B*57-peptide complexes were studied.
- In addition, immunodominancy of the previously mapped B*57 epitopes during chronic infection was assessed. KGFNPEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

HXB2 Location p24 (176–184)
Author Location p24 (308–316)
Epitope QASQEVKNW
Epitope name QW9
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country Kenya
References Peters *et al.* 2008a

- Gag sequences from 468 HIV-1 positive sex workers from the Kenyan Pumwani cohort were analyzed to bioinformatically identify positively selected residues that could be related to antigen processing. Mutation effects on disease progression were followed by mean CD4 counts. This method is also one way of identifying potential CTL epitopes and classifying them.
- A Gag positive selection map was generated and sites were classified as beneficial or harmful to HIV. They were correlated to antigen processing (proteasomal cleavage), antigen presentation (TAP transport efficiency) and T-cell receptor binding.
- p17 and p24's structural constraints limited their diversity, while p7-p1-p6 showed a higher average entropy.
- This HLA-B*57-restricted immunodominant epitope, QASQEVKNW, is located in the p24 region.

HXB2 Location p24 (176–184)
Author Location p24 (309–317 LAI)
Epitope QASQEVKNW
Subtype B

CTL CD8+

Immunogen HIV-1 infection
Species (MHC) human (B*5701)
References Goulder *et al.* 1996b

- Recognition of this peptide by two long-term non-progressors.
- Peptide defined on the basis of B*5801 binding motif, yet not cross-restricted except at high concentrations.
- Described as B*5701 in C. Brander *et al.*, this database, 1999.

HXB2 Location p24 (176–184)
Author Location p24 (311–319 LAI)
Epitope QASQEVKNW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*5701 epitope.

HXB2 Location p24 (176–184)
Author Location
Epitope QASQEVKNW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords rate of progression, immunodominance
References Migueles & Connors 2001

- HLA B*5701 was found in a very high frequency in HIV-1 infected non-progressors, 11/13 (85%) versus 19/200 (9.5%) of progressors. Non-progressors tended to have an immune response that was highly focused on four p24 epitopes that were presented by B*5701, ISPRTLNAW, KAFSPEVIPMF, TSTLQEQIGW, and QASQEVKNW.
- Only QASQEVKNW was recognized in all of the LTNP's tested.

HXB2 Location p24 (176–184)
Author Location
Epitope QASQEVKNW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords rate of progression, immunodominance
References Migueles & Connors 2001

- CTL activity was monitored in 27 individuals, including 10 LTNP with an over-expression of HLA B*5701 – these individuals have viral loads below the threshold of infection without therapy, and their CD8+ T-cell response tends to be focused on peptides that contain B*5701 epitopes ISPRTLNAW, KAFSPEVIPMF, TSTLQEQIGW, or QASQEVKNW.
- CTL responses are broader in B*5701+ individuals with progressive viremia than those that control viremia.
- The HLA-A*0201 SLYNTVATL epitope response was not as strong individuals that carried both A2, B57.

HXB2 Location p24 (176–184)
Author Location Gag (308–316)
Epitope QASQEVKNW
Epitope name QW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Assay type Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Migueles *et al.* 2003

- cDNA Gag sequences from a set of 17 HLA-B*5701+ progressors and 10 LTNPs were obtained, and the variation in four p24 B*5701 epitopes examined. Sequence variants were more common ($p < 0.01$) in the epitopes in the progressors (median 3, range 1-7) than LTNPs (median 2, range 0-4).
- In general use of the autologous protein in a target cell did not diminish the overall CD8+ T-cell responses.
- The substituion E312D (qasqDvknw) was common in progressors (8/17) and rare in LTNP (1/8) ($p = 0.06$). qasqDvknw and qasqEvknw peptides were made; this mutation does not affect binding to B*57. 2/4 progressors that carried only the D variant could not recognize the D variant peptide, but could recognize the E variant peptide, demonstrating immune escape.

HXB2 Location p24 (176–184)
Author Location p24 (176–184)
Epitope QASQEVKNW
Epitope name QAS
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells
References Turnbull *et al.* 2006

- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.
- This epitope, B57-QAS, that is very strongly associated with delayed progression to AIDS, and its alanine-substituted variants are weakly cross-recognized.

HXB2 Location p24 (176–184)
Author Location (C consensus)
Epitope QATQDVKNW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

CTL CD8+

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p24 (176–184)
Author Location p24
Epitope QATQDVKNW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- QATQDVKNW is a previously described HLA-B*5801-restricted epitope (part of Gag reacting peptide FFKTLRAEQAtQDVKNWMTDT) that contains a B*5801-associated reversion at residue T (QAtQDVKNW).

HXB2 Location p24 (176–184)
Author Location Gag (308–316)
Epitope QASQEVKNW
Epitope name QAS
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B53)
Country Gambia
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords cross-presentation by different HLA, characterizing CD8+ T cells, HIV-2
References Gillespie *et al.* 2005

- CD8 T-cell responses were evaluated and compared in HIV-1 and HIV-2 infected individuals. A significantly greater magnitude and breadth of Gag-specific responses were found in HIV-1 infected individuals, possibly because undetectable viral load in HIV-2 infected individuals. This study suggests that responses in HIV-2 infection reflect antigen load in plasma, as is the case in HIV-1 infection. No correlation was found between immune control of HIV-2 and the frequency of perforin-expressing virus-specific CD8 T-cells.
- QASQEVKNW is a HIV-1 epitope cross-presented by B53 and B*5801. It was recognized in 4/4 B*5801+ HIV-1 infected individuals, and 7/7 B53+ HIV-1 infected individuals. HIV-2 infected individuals preferentially recognized the B58 HIV-2 epitope TSTVEEQIQW, and B53 epitope TPYDINQML.

HXB2 Location p24 (176–184)
Author Location p24 (308–316 LAI)
Epitope QASQEVKNW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B53)
References Buseyne *et al.* 1997

- Minimal sequence determined through epitope mapping.
- This is a relatively conserved epitope.
- HLA-Cw*0401 was defined as the restricting element, but cells that carry Cw*0401 varied in their ability to present this epitope – this could be the result of diminished cell-surface expression of Cw*0401 in some cells.
- The HLA presenting molecule for this epitope was originally described as Cw*0401, but subsequent experiments with an HLA B53+ C4- cell line and with C1R cells transfected with HLA-B53 have shown that the HLA restricting element is HLA-B53 (F. Buseyne, pers. comm. 2000)

HXB2 Location p24 (176–184)
Author Location p24 (NL43)
Epitope QASQEVKNW
Epitope name QW9
Immunogen in vitro stimulation or selection
Species (MHC) human (B53)
Keywords epitope processing, dendritic cells
References Buseyne *et al.* 2001

- Exogenous presentation or cross-presentation of epitopes by antigen presenting cells (APC) without protein synthesis is an alternative pathway for CTL epitope processing that may be important in the initial generation of viral specific CTL.
- Dendritic cells treated with AZT to inhibit protein synthesis were able to elicit a strong specific CTL response in QASQEVKNW specific CTL clone 141 without protein synthesis, while macrophages demonstrated a decreased presentation efficiency.
- Exogenous Gag epitope presentation was Env-dependent and required receptor-dependent fusion.

HXB2 Location p24 (176–184)
Author Location p24 (308–316)
Epitope QATQEVKNW
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B53)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.

CTL CD8+

- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B53 women, 1/2 HEPS and 7/9 HIV-1 infected women recognized this epitope.

HXB2 Location p24 (176–184)
Author Location p24 (308–316 subtype A consensus)
Epitope QATQEVKNM
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (B53)
Keywords binding affinity, subtype comparisons
References Dorrell *et al.* 2001

- In clade A infected Gambians, three HLA-B53 epitopes were defined in Gag p24 using ELISPOT, tetramer, and cytotoxicity assays.
- Two of the new epitopes lacked the predicted P2 anchors, DTINEEAAEW and QATQEVKNM, and bound to B53 with high affinity, thus extending the anchor residue motif for B53 and the related B35.
- While S, T, and P could all fit into the HLA-B35 or HLA-B53 B pocket and form a hydrogen bond, A would not form a bond, so the authors propose compensatory interactions account for the high affinity of QATQEVKNM for B53.
- QATQEVKNM was recognized in 6/7 HLA-B53 subjects.
- Cross-recognition of QATQEVKNM was not studied here, but it was noted that both the A, QATQEVKNM, and B, QASQDVKNW, subtype version of this epitope, are also presented by HLA-B57 and B58, common HLA alleles in Africans.

HXB2 Location p24 (176–184)
Author Location p24
Epitope QASQEVKNW
Epitope name B53-QW9(p24)
Immunogen HIV-1 infection
Species (MHC) human (B53)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (176–184)
Author Location
Epitope QATQEVKNW
Immunogen HIV-1 infection
Species (MHC) human (B53)
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining
Keywords responses in children, rate of progression
References Chakraborty *et al.* 2005

- A study of long-term surviving children in Kenya revealed CD8 T-cell responses in all progression groups. The most striking atttribute of long term surviving children was strong CD4 T-cell responses, which may be significant in delaying disease progression.
- Response detected in 2 LTNP children.

HXB2 Location p24 (176–184)
Author Location
Epitope QASQEVKNW
Immunogen HIV-1 infection
Species (MHC) human (B53, B57, Cw04)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope QASQEVKNW when restricted by HLA-B53, elicited a magnitude of response of 595 SFC with a functional avidity of 0.1nM and binding affinity of 9.7nM. When restricted by HLA-B57, it elicited a magnitude of response of 350 SFC with a functional avidity of 10nM and binding affinity of 157nM. When restricted by HLA-Cw04, it elicited a magnitude of response of 755 SFC with a functional avidity of 0.05nM.

HXB2 Location p24 (176–184)
Author Location
Epitope QASQEVKNW
Immunogen HIV-1 infection
Species (MHC) human (B53, B57, Cw04)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental

methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA associations (B53, B57, Cw04), an additional HLA (B58) was statistically predicted to be associated with this epitope.

HXB2 Location p24 (176–184)
Author Location Gag (304–321 B con)
Epitope QASQEVKNW
Epitope name QW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B53, B58)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Draenert *et al.* 2004c
- CD8+ T-cell responses that persisted in individuals with advanced disease were studied; most of the optimal epitopes defined were recognized with intermediate to high avidity. On average 13 (range, 2-39) epitopic regions were targeted in an average of 6 proteins (range, 1-8). HAART resulted in decrease in antigen and reduction in gamma IFN EliSpot responses, suggesting active responses to autologous virus. The lack of mutations within most viral epitopes suggest that persistent CTL through late disease do not exert strong immune selection pressure, yet the Elispot assays show robust responses, suggesting to the authors that gamma IFN-based screening methods may not reveal functional CD8+ T-cell impairment in patients with AIDS.
- 2 subjects recognized this epitope with high functional avidity. Autologous sequence revealed no substitutions in this epitope compared to the B consensus.

HXB2 Location p24 (176–184)
Author Location Gag (SF2)
Epitope QASQEVKNW
Epitope name QW9
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords acute/early infection
References Goulder *et al.* 2001a
- This peptide elicited a weak CTL response during acute infection of patient PI004.
- Three CTL responses, to epitopes TSTLQEQIGW, ISPRTLNAW, and KAFSPEVIPMF, were evident early after infection; CTL responses to SLYNTVATL, QASQEVKNW, EIYKRWII, and FLKEKGGL were detectable at 5 months post-infection and beyond.

HXB2 Location p24 (176–184)
Author Location p24 (176–184)
Epitope QASQEVKNW
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004
- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 6/7 patients recognized this epitope.

HXB2 Location p24 (176–184)
Author Location Gag
Epitope QASQEVKNW
Epitope name QW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a
- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 5, qasqDvknw, was found in the most polymorphic residue in the epitope. This was shared between clades B and C. The most common substitution in people carrying B57 was in position 3, qaTqevknw.

HXB2 Location p24 (176–184)
Author Location p24 (308–316)
Epitope QATQDVKNW
Epitope name QW9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Ethiopia
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance, escape, variant cross-recognition or cross-neutralization
References Currier *et al.* 2005
- Epitope sequence variation and CD8 T-cell responses were analyzed in C subtype infected HLA-B57-positive individuals from Ethiopia. KF11 was the immunodominant response.
- QATQDVKNW had a single variant, D5E (QATQEVKNW) in 1 subject; there was no apparent immune selection in this epitope. The QW9 peptide was tested in 2 B57-positive subjects; neither responded.

HXB2 Location p24 (176–184)
Author Location
Epitope QASQEVKNW
Immunogen HIV-1 infection, vaccine

CTL CD8+

Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location p24 (176–184)
Author Location Gag
Epitope QASQEVKNW
Epitope name QW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- QW9, QASQEVKNW, is a known HLA-B57-restricted epitope used as a positive control for eliciting CTL IFN-gamma response.

HXB2 Location p24 (176–184)
Author Location
Epitope QASQEVKNW
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords responses in children, mother-to-infant transmission
References Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.

HXB2 Location p24 (176–184)
Author Location (LAI)
Epitope QASQEVKNW
Subtype B
Immunogen
Species (MHC) human (Cw4)
References Buseyne 1999

HXB2 Location p24 (176–184)
Author Location p24 (176–184)
Epitope QASGEVKNW
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (Cw4)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location p24 (176–184)
Author Location p24
Epitope QASQEVKNW
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human (B53, Cw4)
Donor MHC A23, A24, B35, B58, Cw4, Cw7; A23, A34, B44, B53, Cw4, Cw6
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from two infected people carrying subtype D Gag. The epitope sequence in one person matched the peptide, in the other had an E5D change, QASQdVKNW.

HXB2 Location p24 (176–184)
Author Location Gag

Epitope QASQEVKNW
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, epitope processing, characterizing CD8+ T cells
References Beattie *et al.* 2004

- This study compared CD8+ T cell EliSpot reponses to 58 Gag peptides that were optimal epitopes, with responses to overlapping 15 mers that spanned Gag. When screening for HIV-1-specific CD8 T-cell responses from 49 HIV+ people, overlapping 15-mer peptide pools revealed several novel responses that would have been missed using predefined CD8 epitopes. However, the 15-mer pools often missed low-level responses to predefined epitopes, especially when the epitope was located centrally in the 15-mer peptide, and the overall level of response to the 15 mers was generally lower(mean 1.4 fivel fold dilutions lower, range 0-3).
- In one individual, a response to QASQEVKNW could be detected at a concentration of 0.2 ug/ml, while a response to RAEQASQEVKNWMTE required 25 ug/ml for detection.

HXB2 Location p24 (176–185)
Author Location p24 (311–319 SF2)
Epitope QASKEVKNWV
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B57+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/0 group 2, and 1/2 group 3.

HXB2 Location p24 (176–185)
Author Location Gag
Epitope QTDPAVKNWM
Immunogen HIV-2 infection, HIV-1 or HIV-2 infection
Species (MHC) human
Country Belgium, Senegal
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords subtype comparisons, HIV-2
References Jennes *et al.* 2008

- To compare HIV-1 and HIV-2 CTL responses to Gag as far as homologous levels of response and cross-reactivity, 12 consecutive Gag OLP pools were used with cells from 17 HIV-1 and 17 HIV-2 patients in enhanced IFN-gamma ELISpot assays. Gag-specific homologous CTL responses were significantly higher in HIV-2 patients, but cross-reactivity in HIV-1-infected patients was broader and stronger.
- Cross-reactivity correlated with sequence similarity in HIV-2 patients, but not HIV-1 patients. CD4+ T-cell counts of HIV-2-infected patients correlated directly with homologous responses and inversely with cross-reactive responses; this was not true of HIV-1-infected subjects.
- The authors favor a model in which high HIV-2-specific CTL responses control its replication, containing immune evasion and thus limiting the possibility of cross-reaction to HIV-1 homologous epitopes.
- Novel HIV-2 Gag epitope QTDPAVKNWM (HLA-B53-restriction suggested by comparison with variant QATQDVKNWM) is not cross-recognized with its homologous and previously described HIV-1 epitope, QATQDVKNWM.

HXB2 Location p24 (177–185)
Author Location p24 (177–185)
Epitope ATQEVKNWM
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B53)
Keywords HIV exposed persistently seronegative (HEPS), immunodominance
References Kaul *et al.* 2001a

- Variants A(T/S)QEVKNWM are specific for the A/B clades.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B53 women, 1/2 HEPS and 5/9 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in the 1/2 HEPS case and in only one of the 5/9 HIV-1 infected women.

HXB2 Location p24 (179–189)
Author Location Gag (312–322 SIV)
Epitope AAVKNWMTQTL
Epitope name AL11
Immunogen vaccine
Vector/Type: DNA, DNA prime with virus-like particle (VLP) boost *Strain:* SIV *HIV component:* Gag
Species (MHC) mouse (H-2D^b)
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining

CTL CD8+

Keywords vaccine-induced epitopes, immunodominance, vaccine antigen design, SIV
References Liu *et al.* 2006a
- An SIV Gag DNA vaccine was studied in mice in order to enhance subdominant immune responses to the KV9 epitope, without compromising its immunodominant response to the Gag AL11 epitope. Both epitopes share a common MHC restricting allele. Novel vaccine strategies including anatomic separation and heterologous prime-boost were investigated to expand vaccine-elicited CTL responses. This was the first study of its kind using DNA gene-based vaccines.
- This immunodominant epitope, AAVKNWMTQTL (AL11), was omitted from the initial vaccination administered, rendering the mouse incapable of recognizing it or the mutated peptide AAVKaWMTQTL, and allowing instead a dramatic, sustained response to the subdominant epitope studied.
- The immunodomination of AL11 over the subdominant epitope (KV9) was found to be a local rather than systemic mechanism, depending on anatomic the site of vaccine administration.

HXB2 Location p24 (179–189)
Author Location Gag (312–322 SIV)
Epitope `AAVKNWMTQTL`
Epitope name AL11
Immunogen
Species (MHC) (H2-Db)
Donor MHC A*0101, A*0201, B*0801, B*50, Cw*0602, Cw*0701
References

HXB2 Location p24 (180–189)
Author Location p24 (313–322)
Epitope `EVKNWMTETL`
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B53)
Keywords HIV exposed persistently seronegative (HEPS), immunodominance
References Kaul *et al.* 2001a
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location p24 (180–190)
Author Location p24 (397–411)
Epitope `EVKNWMTETLL`
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008
- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.
- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.
- CTL immune response to consensus sequence EVKNWMTETLL was elicited in subject 00016. Consensus epitope of subject 0015 was the same as Clade B consensus and of subject 0016 was dVKNWMTETLL.

HXB2 Location p24 (181–190)
Author Location p24 (181–190)
Epitope `VKNWMTETLL`
Epitope name VL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*08)
Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords rate of progression, immune evasion
References Kemal *et al.* 2008
- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-B*08-restricted autologous epitope VKNWMTETLL only elicited a CTL response at the first time point. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location p24 (181–190)
Author Location p24 (313–322 LAI)
Epitope `VKNWMTETLL`
Subtype B
Immunogen
Species (MHC) human (B8)
References Brander & Walker 1996
- P. Johnson, pers. comm.

HXB2 Location p24 (181–191)
Author Location p24 (181–191)
Epitope VKNWMTETLLV
Epitope name VV11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, subtype comparisons, acute/early infection
References Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (ANC) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- Epitope sequences for this eptiope, VV11 are invariant between CON B, COT B, ANC B and M-group. Cross-recognition is seen only to the A-clade variant. Anchor residues are at positions 2, 9 and 10; while the C-clade variant contains a semi-conservative change at position 7 to VKNWMTdTLLV.
- This epitope was suggested to be preented by HLA-B27, based on the subject possessing the appropriate HLA class I allele.

HXB2 Location p24 (185–199)
Author Location Gag (301–315 SF2)
Epitope MTETLLVQNANPDCK
Epitope name Peptide 80
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF2 *HIV component:* Gag, Tat *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse (H-2^d)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes
References Cellini *et al.* 2008

- In order to increase the known number of epitopes in Gag protein so that they can be assayed for reactivity in vaccine studies, BALB/c mice were inoculated with Gag or Gag+Tat. OLPs were used to elicit T-cell immune responses from mouse splenocytes, tested for by cytotoxicity or ELISpot assays. 5 novel predicted optimal CTL epitopes, 2 novel predicted CD4 epitopes and 2 immune response eliciting peptides were found.
- Reactive peptide MTETLLVQNANPDCK is now predicted to have a potential CTL epitope.

HXB2 Location p24 (185–199)
Author Location Gag (317–331)
Epitope MTETLLVQNANPDCK
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized by mice co-immunized with Gag and Tat, but not by mice immunized with Gag alone.

HXB2 Location p24 (185–202)
Author Location (C consensus)
Epitope MTDTLLVQNANPDCKTIL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location p24 (190–199)
Author Location Gag (Henan isolate)
Epitope LVQNSNPDCK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p24 (191–199)
Author Location p24 (323–331 Henan isolate)
Epitope VQNSNPDCK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- Newly identified HLA-A11-restricted epitope.
- VQNSNPDCK was 1 of 2 most frequently recognized peptides restricted by HLA-A11 (54%).

HXB2 Location p24 (191–199)
Author Location p24 (323–331 SF2, HXBc2/Bal R5)
Epitope VQNANPDCK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A24, A3, B7, B8, Cw7
Country United States
Assay type Cytokine production, Flow cytometric T-cell cytokine assay, Degranulation, CD107a and b cell surface mobilization
Keywords supervised treatment interruptions (STI), immunodominance, characterizing CD8+ T cells, drug resistance
References Daucher *et al.* 2008

- A detailed analysis of 6 chronically infected patients' CTL responses to autologous virus was performed after ART and SIT (structured interruption of therapy). Qualitative responses including degranulation and production of IFN-gamma, MIP-1beta, TNF-alpha, IL-2, but not memory CD27, CD45RO and CD57 T cells correlated with extended low plasma viremia. Frequency and breadth of CTL response as well as immune escape did not influence virological outcome.
- One patient exhibited drug resistance mutations K170R (to NNRTI efavirenz) and D76N, K70R (to NRTIs).
- Autologous epitopes were preferentially recognized over optimal, consensus sequences.
- Patients with favorable virological outcomes demonstrated CTL recognition within multiple, conserved regions of Gag and Nef.
- Patients with poor virological outcomes recognized optimal epitopes with much lower frequencies, though this was not significant.
- HLA-A3-restricted epitope, VQNANPDCK, elicited a response in 1 patient and is found in Gag immunodominant region LVQNANPDCKTILKALG.

HXB2 Location p24 (191–205)
Author Location p24 (191–205)
Epitope VQNANPDCKTILKAL
Immunogen HIV-1 infection
Species (MHC) human (B51)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (191–205)
Author Location p24 (323–337)
Epitope VQNANPDCKTILKAL
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Nixon & McMichael 1991

- Two CTL epitopes defined (see also p17(21-35))

HXB2 Location p24 (191–205)
Author Location p24 (325–339 SF2)
Epitope VQNANPDCKTILKAL
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords review, immunodominance, escape
References Goulder *et al.* 1997a; Phillips *et al.* 1991

- Longitudinal study of CTL escape mutants in people with the appropriate HLA types – little variation was observed in the immunodominant B27 epitope, relative to the B8 epitopes, which varied over time.
- Goulder *et al.* [1997a] is a review of immune escape that points out that there may be a protective effect associated with B27, and that HLA-B8 individuals tend to progress more rapidly than HLA B27 patients.

HXB2 Location p24 (191–205)
Author Location Gag (320–328 BH10, LAI)
Epitope VQNANPDCKTILKAL
Immunogen HIV-1 infection
Species (MHC) human
References Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is TLLVQNANP) has similarity with growth differentiation factor 11, fragment THLVQQANP.

HXB2 Location p24 (191–210)
Author Location p24 (323–342 SF2)
Epitope VQNANPDCKTILKALGPAAT

Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- Three of these 12 had CTL response to this peptide.
- The responding subjects were HLA-A3, A24, B8, B55; HLA-A1, A11, B8, B27.

HXB2 Location p24 (191–210)
Author Location p24 (323–342 SF2)
Epitope VQNANPDCKTILKALGPAAT
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

HXB2 Location p24 (193–201)
Author Location Gag (327–335 SF2)
Epitope NANPDCKTI
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Keywords subtype comparisons, rate of progression
References Tomiyama *et al.* 1999

- HLA-B27, -B51, and -B57 are associated with slow progression to AIDS, while HLA-B35, -B8, -B24 are associated with a rapid progression to AIDS (Nat. Med. 2:405, 1996;Lancet 22:1187, 1986;Hum Immunol 22:73, 1988;Hum Immunol 44:156, 1995)
- 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%
- Of the 172 HIV-1 peptides with HLA-B*5101 anchor residues, 33 bound to HLA-B*5101, seven of these peptides were reactive with CTL from 3 B*5101 positive individuals, and six were properly processed.
- Four of the six epitopes were highly conserved among B subtype sequences, NANPDCKTI is conserved.

HXB2 Location p24 (193–201)
Author Location p24 (193–201)
Epitope NANPDCKTI
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Donor MHC A*0201, A*31, B*27, B*5101, Cw*02; A*2402, A*26, B*07, B*5101, Cw*07
Country Japan
Assay type Chromium-release assay
Keywords epitope processing, escape
References Yokomaku *et al.* 2004

- Epitope variants escaped from being killed by CTLs in an endogenous expression system although they were recognized when corresponding synthetic peptides were exogenously loaded onto the cells. Escape is thus probably due to changes that occur during the processing and the presentation of epitopes in infected cells.
- Epitope variant nSnpdckNi was not recognized when added exogenously or when processed endogenously, but the mutations were in anchor residues and presumably inhibited binding to B*5101.

HXB2 Location p24 (193–201)
Author Location p24 (325–333)
Epitope NANPDCKTI?
Immunogen HIV-1 infection
Species (MHC) human (B51)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 3/11 of the HLA A2+ individuals were HLA B51 and two of these responded to this epitope as well as to other epitopes.

HXB2 Location p24 (193–201)
Author Location p24 (324–335 IIIB)
Epitope NANPDCKTI
Immunogen HIV-1 infection
Species (MHC) human (B51)
Keywords responses in children, mother-to-infant transmission, escape
References Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- No variants of this epitope were found in a non-transmitting mother that had a CTL response to this epitope.

HXB2 Location p24 (193–201)
Author Location p24 (323–333)
Epitope NANPDCKTI
Epitope name NAN
Immunogen HIV-1 infection
Species (MHC) human (B51)
Keywords HAART, ART, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- None of the 8 study subjects recognized this epitope but none were HLA B51+

HXB2 Location p24 (193–201)
Author Location p24 (193–201)
Epitope NANPDCKTI
Immunogen HIV-1 infection
Species (MHC) human (B51)

Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these eptiopes, but this increased over time.

HXB2 Location p24 (193–201)
Author Location p24 (193–201)
Epitope NANPDSKTI
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A*3101, A68, B*4403, B51
Keywords supervised treatment interruptions (STI)
References Arnedo-Valero *et al.* 2004

- T cell immune responses following STI were monitored in two chronically HIV-1 infected partners (A and B) who had contracted HIV-1 in 1992. STI induced strong transitory CD4+ and CD8+ T cell responses in both patients. Patient A displayed broad CD8+ T cell responses directed against Env, Pol, Gag, and Nef HIV-1 antigens. CTL responses in patient B were directed against two epitopes: Gag(p24)NANPDSKTI and Pol(RT)EELRQHLLRW.

HXB2 Location p24 (193–201)
Author Location p24
Epitope NANPDCKTI
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A01, A32, B*1410, B15; A*3101, A68, B*4403, B51
Country Spain
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, supervised treatment interruptions (STI)
References Arnedo-Valero *et al.* 2004

- T cell immune responses following STI were monitored in two chronically HIV-1 infected partners (A and B) who had contracted HIV-1 during 1992. STI induced strong transitory CD4+ and CD8+ T cell responses in both patients. The viruses remained very closely related over 10 years, despite the two individuals having different HLA types; the authors suggest the maintained similarity does not support a strong role for HLA driven HIV diversity as has been claimed in Moore et al. (Science 2002).
- During the second treatment stop, patient A developed a strong proliferative response to p24, and multiple strong CD8+ T cell repsonses to Env, Pol, Gag and Nef. This patient was able to control viral load for two years follow up without therapy. Patient B developed a very weak CD4+ T cell response against p24 during breaks in therapy, and had CD8+ responses to two epitopes. Patient A: A01, A32, B*1410, B15; Patient B: A*3101, A68, B*4403, B51.

HXB2 Location p24 (193–201)
Author Location p24 (191–205)
Epitope NANPDCKTI
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (193–202)
Author Location p24 (193–201)
Epitope NSNPDCKTIL
Epitope name NL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*51)
Donor MHC A*01, A*6801, B*08, B*51, Cw*07, Cw*15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-B51-restricted autologous epitope NSNPDCKTIL was able to elicit CTL response only by the last time point.
- HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location p24 (193–205)
Author Location p24
Epitope NANPDCKTILRAL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*3910)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ

Keywords HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- NANPDCKTILRAL is a previously described HLA-B*3910-restricted epitope (part of Gag reacting peptide LVNAN-PDCKtILRALGPGT) that contains a B*3910-associated sequence polymorphism at residue T (NANPDCKtILRAL).

HXB2 Location p24 (193–207)
Author Location
Epitope NANPDCKTILKALGP
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A2, A32, B44, B7
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 82 (NIH ARRP Cat# 7953), NANPDCKTILKALGP, contains an epitope restricted by HLA-B7 and elicited a CTL response in a living non-progressor for 22+ years at >100 sfc/million PBMC.

HXB2 Location p24 (194–202)
Author Location p24 (194–202)
Epitope ANPDCKTIL
Epitope name ANP
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A2, A68.1, B*07, B*3503, Cw*0401, Cw*0702, DQ2, DQ6, DR15, DR17, DR51, DR52
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ
Keywords rate of progression, escape
References Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses,and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relatively efficiency of the variant eptiopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- This was one of 8 reactive epitopes found not to vary over time.

HXB2 Location p24 (194–202)
Author Location Gag
Epitope ANPDCKTIL
Subtype B, C, AE
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-B7-restricted epitope ANPDCKTIL is from subtype B and C peptide libraries, and is reactive as part of peptide LLVQNANPDCKTILK in a subtype AE-carrying subject.

HXB2 Location p24 (195–202)
Author Location (C consensus)
Epitope NPDCKTIL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the T6 residue of NPDCKTIL are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location p24 (195–202)
Author Location p24 (323–342)
Epitope NPDCKTIL
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Bernard *et al.* 1998

- This study focuses on six rare long-term survivor HIV-infected people who were infected for many years without exhibiting immune dysregulation – such immunologically normal HIV-infected (INHI) cases occur at a frequency between 0.1 and 1% in the infected population.

CTL CD8+

- No direct CTL were found in any of the six INHIs, but above background CTLp activity was founded in 3/6 INHIs.
- Epitope sequences were deduced from larger reactive peptides based on HLA binding motifs – XPXXXXXL is a B35 binding motif.

HXB2 Location p24 (195–202)
Author Location
Epitope NPDCKTIL
Epitope name Gag-NL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B35, 3/17 (18%) recognized this epitope.

HXB2 Location p24 (195–202)
Author Location Gag
Epitope NPDCKTIL
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA B35-restricted epitope NPDCKTIL is from subtype B and C peptide libraries, and is reactive as part of peptide LLVQNANPDCKTILK in a subtype B-carrying subject.

HXB2 Location p24 (195–202)
Author Location p24 (327–334 SF2, HXBc2/Bal R5)
Epitope NPDCKTIL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A24, A3, B7, B8, Cw7
Country United States
Assay type Cytokine production, Flow cytometric T-cell cytokine assay, Degranulation, CD107a and b cell surface mobilization
Keywords supervised treatment interruptions (STI), immunodominance, characterizing CD8+ T cells, drug resistance
References Daucher *et al.* 2008

- A detailed analysis of 6 chronically infected patients' CTL responses to autologous virus was performed after ART and SIT (structured interruption of therapy). Qualitative responses including degranulation and production of IFN-gamma, MIP-1beta, TNF-alpha, IL-2, but not memory CD27, CD45RO and CD57 T cells correlated with extended low plasma viremia. Frequency and breadth of CTL response as well as immune escape did not influence virological outcome.
- One patient exhibited drug resistance mutations K170R (to NNRTI efavirenz) and D76N, K70R (to NRTIs).
- Autologous epitopes were preferentially recognized over optimal, consensus sequences.
- Patients with favorable virological outcomes demonstrated CTL recognition within multiple, conserved regions of Gag and Nef.
- Patients with poor virological outcomes recognized optimal epitopes with much lower frequencies, though this was not significant.
- HLA-B8-restricted epitope, NPDCKTIL, elicited a response in 1 patient and is found in Gag immunodominant region LVQNANPDCKTILKALG.

HXB2 Location p24 (195–205)
Author Location (C consensus)
Epitope NPDCKTILRAL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*3910)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- NPDCKTILRAL is an optimal epitope.

HXB2 Location p24 (196–204)
Author Location Gag (328–336)
Epitope PDCKTILKA
Subtype B
Immunogen HIV-1 infection, peptide-HLA interaction
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance
References Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, PDCKTILKA, is similar to human protein Deltex 4 homolog, sequence HPDCKTI.

HXB2 Location p24 (197–205)

Author Location p24 (329–337)
Epitope DCKTILKAL
Epitope name DL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*08)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*08-associated substitution within optimally defined epitope DCKTILKAL is at positions K3, DCkTILKAL. DL9 has a very low recognition frequency and does not escape.

HXB2 Location p24 (197–205)
Author Location p24 (329–337 LAI)
Epitope DCKTILKAL
Subtype B
Immunogen
Species (MHC) human (B*0801)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*0801 epitope.

HXB2 Location p24 (197–205)
Author Location p24 (329–337 LAI)
Epitope DCKTILKAL
Subtype B
Immunogen
Species (MHC) human (B8)
References Sutton *et al.* 1993

- Predicted epitope based on B8-binding motifs, from larger peptide VQNANPDCKTILKAL.

HXB2 Location p24 (197–205)
Author Location p24 (329–337)
Epitope DCKTILKAL
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords escape
References Nowak *et al.* 1995

- In a longitudinal study of CTL response and immune escape – the variant DCRTILKAL was also found, binds to B8, but is not recognized.

HXB2 Location p24 (197–205)
Author Location p24 (329–337)
Epitope DCKTILKAL
Immunogen
Species (MHC) human (B8)
References McAdam *et al.* 1995

- Defined as minimal epitope by titration and binding studies.

HXB2 Location p24 (197–205)
Author Location p24 (197–205)
Epitope DCKTILKAL
Immunogen
Species (MHC) human (B8)
References Goulder *et al.* 1997g

- Included in a study of the B8 binding motif.

HXB2 Location p24 (197–205)
Author Location p24 (329–337)
Epitope DCKTILKAL
Epitope name DCK
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART, supervised treatment interruptions (STI), immunodominance, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- This epitope was recognized at a low level by only 1 of the 7/8 study subjects that were HLA B8.
- Patient SC12(HLA A1, B8/39, Cw0701/0702, DR2/3, DR51/52, DQ2/6) had sustained therapy started during acute infection and maintained an immunodominant response to FLKEKGGL throughout and minor responses to GEIYKRWII, DCKTILKAL, GGKKKYKLK – GEIYKRWII and GGKKKYKLK responses were stimulated by a brief period off therapy.

HXB2 Location p24 (197–205)
Author Location p24 (197–205)
Epitope DCKTILKAL
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (197–205)
Author Location p24 (197–205)
Epitope DCKTILKAL
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Day *et al.* 2001

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual.

HXB2 Location p24 (197–205)

Author Location p24
Epitope DCKTILKAL
Epitope name DCK
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART, supervised treatment interruptions (STI)
References Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFNgamma Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

HXB2 Location p24 (197–205)
Author Location Gag (329–337)
Epitope DCKTILKAL
Immunogen HIV-1 infection
Species (MHC) humanized rabbit (B8)
Donor MHC A03, A28, B07, B08
Country Canada
Assay type proliferation, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, memory cells, immune dysfunction
References Gamberg *et al.* 2004a

- HAART restores HIV specific immunity after advanced infection by increase of CD4+ and CD8+ T cell numbers after supression of viral replication. However, HIV specific CTLs emerged only with detectable viral replication breakthroughs and were short-lived while CD4+ T-cell responses remained compromised, suggesting failure of generating stable CD8+ memory T-cells in the absence of HIV-specific T-helper responses.

HXB2 Location p24 (197–205)
Author Location (B consensus)
Epitope DCKTILKAL
Epitope name DL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A01, A03, B08, B14, Cw7, Cw8
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location p24 (197–205)
Author Location p24
Epitope DCKTILKAL
Epitope name B8-DL9(p24)
Immunogen HIV-1 infection
Species (MHC) human (B8)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (197–205)
Author Location
Epitope DCKTILKAL
Immunogen
Species (MHC) (B8)
Keywords review, immunodominance, escape, vaccine antigen design
References Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection.

HXB2 Location p24 (197–211)
Author Location Gag (329–343)
Epitope DCKTILKALGPAATL
Epitope name DL15
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.

- One subject responded to peptide DL15, a non-B*57-restricted peptide.

HXB2 Location p24 (197–211)
Author Location Gag (329–343)
Epitope DCKTILKALGPAATL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the ES.

HXB2 Location p24 (199–213)
Author Location Gag
Epitope KSILRGLGAGATLEE
Subtype A
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0308, A*24, B*15, B*18, Cw, DPA1*0103, DPB1, DQB1*03, DQB1*06, DRB1*12, DRB1*15, DRB3, DRB5
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- Epitope-containing peptide KSILRGLGAGATLEE, seen in a subtype-A carrying subject was derived from a subtype A library and was not previously associated with host class I alleles A*24/*0308; B*15/*18; Cw.

HXB2 Location p24 (199–218)
Author Location Gag (331–350)
Epitope KTILRALGPGATLEEMMTAC
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location p24 (201–215)
Author Location Gag
Epitope ILRALGPGATLEEMM
Subtype CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 2 subjects responded to peptide ILRALGPGATLEEMM from subtype CRF02_AG.

HXB2 Location p24 (203–211)
Author Location p24 (335–343 SF2, HXBc2/Bal R5)
Epitope KALGPAATL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B15, Cw3)
Donor MHC A2, A3, B15, B7, Cw3, Cw6
Country United States
Assay type Cytokine production, Flow cytometric T-cell cytokine assay, Degranulation, CD107a and b cell surface mobilization
Keywords supervised treatment interruptions (STI), immunodominance, characterizing CD8+ T cells, drug resistance
References Daucher *et al.* 2008

- A detailed analysis of 6 chronically infected patients' CTL responses to autologous virus was performed after ART and SIT (structured interruption of therapy). Qualitative responses including degranulation and production of IFN-gamma, MIP-1beta, TNF-alpha, IL-2, but not memory CD27, CD45RO and CD57 T cells correlated with extended low plasma viremia. Frequency and breadth of CTL response as well as immune escape did not influence virological outcome.
- One patient exhibited drug resistance mutations K170R (to NNRTI efavirenz) and D76N, K70R (to NRTIs).
- Autologous epitopes were preferentially recognized over optimal, consensus sequences.
- Patients with favorable virological outcomes demonstrated CTL recognition within multiple, conserved regions of Gag and Nef.

- Patients with poor virological outcomes recognized optimal epitopes with much lower frequencies, though this was not significant.
- HLA-B15 and -Cw3-restricted epitope, KALGPAATL, elicited a response in 1 patient and is found in Gag immunodominant region DCKTILKALGPAATLE.

HXB2 Location p24 (203–211)
Author Location Gag
Epitope RALGPGATL
Subtype B, C, D, A1
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- RALGPGATL was predicted to be supertype B7-restricted. It was recognized by at least 4 patients with restricting HLA supertype who were infected with several different HIV subtypes.

HXB2 Location p24 (203–211)
Author Location Gag (335–343 SUMA)
Epitope KALGPAATL
Epitope name Gag KL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*1103, A*2402, B*1402, B*1501, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, acute/early infection, characterizing CD8+ T cells
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape muations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

HXB2 Location p24 (203–211)
Author Location Gag
Epitope RALGPGATL/M
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords HLA associated polymorphism
References Rousseau *et al.* 2008

- 3 phylogenetic correction methods—MLL (maximum likelihood character state analysis followed by likelihood ratio test), MLF (maximum likelihood character state analysis followed by Fisher test), and parsimony character state analysis were used to identify points in the HIV-1 subtype C proteome that conferred susceptibility or resistance to CTLs. Associations of HLA-epitope combinations that were inferred to be susceptible or resistant were organized into immunological sets that would help identify the best residues and genes as candidates for vaccines. While all proteins were interrogated, Gag, Pol, Env and Nef were focused upon. Amino acid changes were evaluated for association with plasma viral load.
- Proteome maps may be seen at `http://www.hiv.lanl.gov/content/immunology/hlatem/study5/index.html` with information showing single or multiple sites involving escape and reversion.
- HLA-B and -C alleles associated more with aa changes than HLA-A, suggesting that the former 2 are more important in driving viral evolution.
- The ratio of susceptible to resistant residues in HIV proteins was in descending order, Vpr>Gag>Rev>Pol>Nef>Vif>Tat>Env>Vpu, showing that epitopes from the earlier proteins are more conserved owing to viral fitness cost upon mutation.
- This Gag p24 HLA C*08-restricted epitope, RALGPGATL/M was susceptible at P5. Variants RALGaGATL/M, RALGqGATL/M, RALGsGATL/M, RALGtGATL/M and RALGvGATL/M were resistant to CTL response, but associated with lower viral loads. This epitope is 1 of 7 that suggest a fitness cost to immune escape.

HXB2 Location p24 (204–214)
Author Location Gag (343–353)
Epitope ALGPGASLEEM
Subtype C

Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p24 (205–219)
Author Location
Epitope `LGPAATLEEMMTACQ`
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, A32, B44, B7; A2, A24, B15, B40
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 85 (NIH ARRP Cat# 7956), LGPAATLEEMMTACQ, contains an epitope restricted by HLA-A2 in different patients and elicited the following CTL immune responses: (1) $\sim$50 sfc/million PBMC for 22+ years in a living non-progressor (2) for 22+ years in another living non-progressor.

HXB2 Location p24 (206–214)
Author Location Gag (338–346)
Epitope `GPGATLEEM`
Subtype A, C, D
Immunogen HIV-1 infection
Species (MHC) human
Country Tanzania
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords rate of progression, immunodominance
References Geldmacher *et al.* 2007b

- The objectives of this study were to find antiviral epitopic determinants of Gag HIV-specific CTL response and to find 'host HLA-CTL response' correlations. By studying 56 ART-naive subjects including low viral load (LVL) responders, the authors show that subjects expressing the "protective" HLA-B*0702, -B*5801, and -B*8101 have broader Gag epitope recognition which may be abrogated if co-expressed with HLA-B alleles associated with rapid AIDS progression. Also, a negative linear relation was seen between Gag epitope numbers and plasma viral load while a positive relationship was seen with CD4 T-cell count. Finally, LVL subjects recognized specific Gag regions at the N- and C-termini of the protein more often than peptides in the middle of the protein.
- Epitope GPGATLEEM, whose presentation by HLA-B*8101 is inferred, is strongly associated with LVL. However, the second position GpGATLEEM is highly variable.

HXB2 Location p24 (208–226)
Author Location Gag
Epitope `AATLEEMMTACQGVGGPSH`
Epitope name GAG-47
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, aAtLEEMMTACQGVGGPSH differs from the consensus C sequence gAsLEEMMTACQGVGGPSH at 2 amino acid positions, i.e. by 10.5%.

HXB2 Location p24 (209–217)
Author Location Gag
Epitope `ATLEEMMTA`
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A*0206)
Country Thailand
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords optimal epitope

References Kantakamalakul *et al.* 2006

- T cell responses in CRF01_AE infected individuals from Thailand were studied. Fine mapping of the peptides containing potentially novel epitopes revealed novel restriction of a previously identified epitope in this population.
- A novel restriction allele for this epitope (ATLEEMMTA) was found, HLA-A*0206.

HXB2 Location p24 (209–217)
Author Location Gag (341–)
Epitope ATLEEMMTA
Epitope name Gag341
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* p24 Gag *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder that did not induce CTL and CD8+ T-cell IFN gamma responses in mice, although responses were detected in 2/17 HIV+ HLA-A2 subjects.

HXB2 Location p24 (209–217)
Author Location
Epitope ATLEEMMTA
Epitope name Gag 341
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Gag 341 ATLEEMMTA epitope was highly conserved and found in all 11 patients but only 2 had CTL immune responses to it.

HXB2 Location p24 (209–217)
Author Location Gag
Epitope ATLEEMMTA
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-A2-restricted epitope ATLEEMMTA is from a subtype B peptide library, and is reactive as part of peptide ATLEEMMTACQGVGG in a subtype D-carrying subject.

HXB2 Location p24 (209–217)
Author Location Gag (341–)
Epitope ATLEEMMTA
Epitope name Gag341
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Gag epitope ATLEEMMTA, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients.

HXB2 Location p24 (209–223)
Author Location
Epitope ATLEEMMTACQGVGG
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, A32, B44, B7; A2, A24, B15, B40
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 86 (NIH ARRP Cat# 7957), ATLEEMMTACQGVGG, contains an epitope restricted by HLA-A2 in different patients and elicited the following CTL immune responses: (1) ∼50 sfc/million PBMC for 22+ years in a living non-progressor (2) for 22+ years in another living non-progressor.

HXB2 Location p24 (211–230)
Author Location p24 (343–362 SF2)
Epitope LEEMMTACQGVGGPGHKARV
Immunogen HIV-1 infection
Species (MHC) human (B7)
References McAdam *et al.* 1998

HXB2 Location p24 (211–230)
Author Location p24 (345–364 SF2)
Epitope LEEMMTACQGVGGPGHKARV
Immunogen HIV-1 infection
Species (MHC) human
References van Baalen *et al.* 1993

- Gag CTL epitope precursor frequencies estimated, peptide mapping.

HXB2 Location p24 (211–231)
Author Location p24 (343–362 SF2)
Epitope LEEMMTACQGVGGPGHKARVL
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A1, A2, B50, B57.

HXB2 Location p24 (212–222)
Author Location Gag (347–357)
Epitope EEMMTACQGVG
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p24 (213–221)
Author Location Gag
Epitope EMMTACQGV
Epitope name E9V
Immunogen vaccine
Vector/Type: measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140ΔV3
Species (MHC) transgenic mouse (A*0201)
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells
References Lorin *et al.* 2005a

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

HXB2 Location p24 (213–221)
Author Location Gag (345–)
Epitope EMMTACQGV
Epitope name Gag345
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* p24 Gag *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced a response in 1/6 transgenic mice. Responses were detected in 1/17 HIV+ HLA-A2 subjects.

HXB2 Location p24 (213–221)
Author Location

CTL CD8+

Epitope EMMTACQGV
Epitope name Gag 345
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Gag 345 EMMTACQGV epitope was highly conserved, being found in all 11 patients but none had immune responses to it. Only 1 of 17 patients had CTL recall response to it.

HXB2 Location p24 (213–227)
Author Location
Epitope EMMTACQGVGGPGHK
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A2, B60, B7; A11, A2, B44, B60
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 87 (NIH ARRP Cat# 7958), EMMTACQGVGGPGHK, contains an epitope restricted by HLA-A11 in different patients and elicited the following CTL responses: (1) 844 sfc/million PBMC for 11.3 years in a living non-progressor (2) 318 sfc/million PBMC for 12 years in a former non-progressor who succumbed to a non-AIDS death.

HXB2 Location p24 (217–227)
Author Location p24 (349–359)
Epitope ACQGVGGPGHK
Epitope name AK11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*11)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-A*11-associated substitution within optimally defined epitope ACQGVGGPGHK is at positions G9, ACQGVGGPgHK. Recognition frequency of AK11 was > 30% and escapes were seen 22 months post-infection.

HXB2 Location p24 (217–227)
Author Location p24 (349–359 IIIB)
Epitope ACQGVGGPGHK
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*1101 epitope.

HXB2 Location p24 (217–227)
Author Location Gag (349–359)
Epitope ACQGVGGPGHK
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Keywords subtype comparisons, TCR usage
References Fukada *et al.* 2002

- Counterparts for eight known clade B HLA A*1101 epitopes were generated for clade E (CRF01). Three epitopes, identical among clade A-E, were cross-reactive and recognized by clade E infected individuals. The clade E and B analogs to three more HLA A*1101 epitopes was recognized in a clade specific manner. Two other HLA A*1101 clade B defined epitopes were found not to have stimulated a response in clade E infected individuals.
- ACQGVGGPGHK was found to elicit clade-specific responses in clade B (ACQGVGGPGHK is most common in clades A and B) and clade E (acqgvggpShk is most common and is also common in clades C and D). ACQGVGGPGHK was recognized by CTL from 4/5 B clade infected Japanese subjects, and acqgvggpShk from 3/7 E clade infected Thai subjects.
- The binding of the two variants to HLA A*1101 was almost identical, but bulk CTL generated from individuals did not cross-react with the cross-clade peptides, indicating the lack of cross-reactivity was due to TCR specificity.

HXB2 Location p24 (217–227)
Author Location Gag (349–359 SUMA)
Epitope ACQGVGGPGHK
Epitope name Gag AK11

Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*1103)
Donor MHC A*1103, A*2402, B*1402, B*1501, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, acute/early infection, characterizing CD8+ T cells
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape muations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

HXB2 Location p24 (217–227)
Author Location p24 (349–359 IIIB)
Epitope ACQGVGGPGHK
Immunogen HIV-1 infection
Species (MHC) human (A11)
References Sipsas *et al.* 1997

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by three lab workers accidentally infected with HIV-1 IIIB.
- ACQGVGGPSHK, a variant found in HIV RF, was also recognized.

HXB2 Location p24 (217–227)
Author Location p24 (SF2)
Epitope ACQGVGGPGHK
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a HIV+ Caucasian living in Boston – this epitope did not fall within the three most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa.

HXB2 Location p24 (217–227)
Author Location p24 (349–359)
Epitope ACQGVGGPGHK
Epitope name ACQ
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC SC19: A*11, A*29, B*08, B*44, Cw*06, Cw*0701, DQ2, DQ8, DR3, DR52, DR53, DR7; SC18: A*02, A*11, B*50, B*58, Bw4, Bw6, Cw*0401, Cw10, DQ2, DQ8, DR3, DR4, DR52, DR53
Keywords HAART, ART, supervised treatment interruptions (STI), immunodominance, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- Both of the 2/8 HLA-A11 study subjects recognized this CTL epitope.
- Patient SC19(HLA A11/12, B8/44, Cw06/0701, DR3/7, DR52/53, DQ 2/8) had a CTL response to epitopes FLKEKGGL, GEIYKRWII, ACQGVGGPGHK, AVDLSHFLK, and FNCGGEFFY that declined during therapy initiated at day 197.
- Patient SC18(HLA A2/11, B8/44, Cw06/0701, DR3/7, DR52/53, DQ2) recognizes the epitopes ACQGVGGPGHK, QVPLRPMTYK, AVDLSHFLK, and one called QIY but not fully described – he had brief therapy upon seroconversion and has had low viral load during 600 days of follow up.

HXB2 Location p24 (217–227)
Author Location p24 (216–226)
Epitope ACQGVGGPGHK
Immunogen HIV-1 infection
Species (MHC) human (A11)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location p24 (217–227)
Author Location p24 (349–359 SF2)
Epitope ACQGVGGPGHK
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A11+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 0/0 group 2, and 2/2 group 3.

HXB2 Location p24 (217–227)
Author Location p24
Epitope ACQGVGGPGHK
Epitope name ACQ
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords HAART, ART, supervised treatment interruptions (STI)
References Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFNgamma Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

HXB2 Location p24 (217–227)
Author Location (B consensus)
Epitope ACQGVGGPGHK
Epitope name AK11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A29, B08, B44, Cw4, Cw7
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location p24 (217–227)
Author Location Gag (349–359)
Epitope ACQGVGGPGHK
Epitope name AK11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords escape, TCR usage, variant cross-recognition or cross-neutralization, optimal epitope
References Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wild type, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wild type.
- A novel CD8 T-cell response was generated against the escape variant acqgvggpShk.
- Additional analyses showed that the majority of individuals expressing HLA-A11 targeted the acqgvggpShk variant sequence while the wild-type sequence was less frequently recognized.

HXB2 Location p24 (217–227)
Author Location Gag
Epitope ACQGVGGPGHK
Epitope name AK11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 9, acqgvggpShk, was found in the most polymorphic residues in the epitope. These were shared between clades B and C.

HXB2 Location p24 (217–227)
Author Location p24
Epitope ACQGVGGPGHK
Epitope name A11-AK11(p24)
Immunogen HIV-1 infection
Species (MHC) human (A11)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins

References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (217–227)
Author Location p24 (217–227)
Epitope ACQGVGGPGHK
Epitope name AK11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, subtype comparisons, acute/early infection
References Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (ANC) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- Epitope sequences for this eptiope, AK11 are invariant between CON B, COT B, ANC B and M-group. Cross-recognition is seen only to the A-clade variant. An anchor residue is at position 11; while the C-clade variant contains a semi-conservative change at position 9 to ACQGVGGPsHK. HLA-A11 restriction was inferred based on the subject possessing the appropriate HLA class I allele and prior publication.

HXB2 Location p24 (217–227)
Author Location p24
Epitope ACQGVGGPSHK
Epitope name AK11(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope ACQGVGGPSHK elicited an immune response in Chinese HIV-1 positive subjects as part of peptide ACQGVGGPSHKARVLAEA. This epitope differs from the previously described HLA-A11-restricted epitope sequence, ACQGVGGPGHK, at 1 residue, ACQGVGGPsHK.
- 3 of the 28 HLA-A11 carriers responded to ACQGVGGPsHK-containing peptide with average magnitude of CTL response of 145 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p24 (217–231)
Author Location
Epitope ACQGVGGPGHKARVL
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A2, B60, B7; A11, A2, B44, B60
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 88 (NIH ARRP Cat# 7959), ACQGVG-GPGHKARVL, contains an epitope restricted by HLA-A11 in different patients and elicited the following CTL responses: (1) 663 sfc/million PBMC for 11.3 years in a living non-progressor (2) 447 sfc/million PBMC for 12 years in a former non-progressor who succumbed to a non-AIDS death.

HXB2 Location p24 (217–231)
Author Location Gag
Epitope ACQGVGGPSHKARIL
Subtype A, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other

CTL CD8+

Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide ACQGVGGPSHKARIL from subtype A and to peptide ACQGVGGPSHKARvL from subtype CRF01_AE.

HXB2 Location p24 (218–227)
Author Location Gag (350–359 Henan isolate)
Epitope CQGVGGPGHK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- CQGVGGPGHK was 1 of 2 most frequently recognized peptides restricted by HLA-A11 (59%).

HXB2 Location p24 (219–231)
Author Location Gag
Epitope QGVGGPGHKARVL
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*02, A*33, B*14, B*35, Cw*07, Cw*1214, DPA1*01, DPA1*0201, DPB1*0201, DPB1*1001, DQB1*05, DRB1*01, DRB1*11
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- Epitope-containing peptide QGVGGPGHKARVL, seen in a subtype-B carrying subject was derived from subtype B and C libraries and was not previously associated with host class I alleles A*02/*33; B*14/*35, Cw*04/*1214.

HXB2 Location p24 (220–227)
Author Location p24
Epitope GVGGPGHK
Epitope name A11-GK8(p24)
Immunogen HIV-1 infection
Species (MHC) human (A11)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (220–227)
Author Location p24
Epitope GVGGPSHK
Epitope name GK8(p24)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope GVGGPSHK elicited an immune response in Chinese HIV-1 positive subjects as part of peptide AATLEEMMTACQGVGGPSH. This epitope differs from the previously described HLA-A11-restricted epitope, GVGGPSGK, at 1 residue, GVGGPsHK.
- 6 of the 28 HLA-A11 carriers responded to GVGGPsHK-containing peptide with average magnitude of CTL response of 345 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p24 (220–229)
Author Location Gag (Henan isolate)
Epitope GVGGPGHKAR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p24 (220–229)
Author Location Gag
Epitope GVGGPGHKAR
Subtype B, F
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country Argentina
Keywords dynamics, escape, HLA associated polymorphism
References Dilernia *et al.* 2008

- Dynamics of CTL escape mutations was studied theoretically by analyzing plasma samples from 302 subjects (collected over 20 years). HLA associated polymorphisms accumulated in a subtype-specific manner.
- Epitope GVGGPGHKAR with anchor residues at GVGGPGHKA(R) mutates to GVGGPsHKAR which is moderately supported as escape by phylogenetic correction.

HXB2 Location p24 (221–231)
Author Location p24 (353–363 LAI)
Epitope VGGPGHKARVL
Epitope name G1
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords HAART, ART
References Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNgamma production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

HXB2 Location p24 (221–231)
Author Location Gag
Epitope VGGPGHKARVL
Subtype C, AE
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Gudmundsdotter *et al.* 2008

- By studying Gag p24 in different subtypes of subjects, previously discovered and new epitopes were identified. New T cell epitopes, both CD8 and CD4, related to the patients' HLA are described.
- T cells cross-reacted to peptides from different patient subtypes, and this cross-reactivity was distributed along the entire p24 protein.
- HLA-B7-restricted epitope VGGPGHKARVL is from a subtype C peptide library, and is reactive as part of peptide QGVGGPGHKARVL in a subtype AE-carrying subject.

HXB2 Location p24 (223–231)
Author Location Gag
Epitope GPGHKARVL
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*07)
Country Canada, South Africa
References Carlson *et al.* 2008

- A statistical model, the phylogenetic dependency network (PDN), was developed to differentiate the confounding effects of codon variation, linkage disequilibrium of HLA alleles and HIV phylogeny from HLA-associated evolution including HIV selection by HLA-pressure and codon evolution.
- This approach was applied to 2 cohorts of 1144 Gag sequences from HIV-infected individuals, generating associations between HIV codons themselves and codons with HLA alleles. Results generated predicted escapes that confirmed that escape kinetics and compensating mutations are consistent across clades. General patterns of covariation and CTL adaptation were determined. Some clade-based differences were identified.
- Clades B and C, HLA-B*07-restricted optimal epitope GPGHKARVL has a susceptible form, GPsHKARVL.

HXB2 Location p24 (223–231)
Author Location p24 (355–363)
Epitope GPGHKARVL
Epitope name GL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*07)
Country Australia, Canada, Germany, United States
Keywords escape, HLA associated polymorphism
References Brumme *et al.* 2008a

CTL CD8+

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*07-associated substitution within optimally defined epitope GPGHKARVL is at positions G3, GPgHKARVL. With a low recognition frequency of ∼20%, GL9 also has a low rate of escape.

HXB2 Location p24 (223–231)
Author Location (LAI)
Epitope GPGHKARVL
Subtype B
Immunogen
Species (MHC) human (B*0702)
Keywords optimal epitope
References Goulder 1999; Llano *et al.* 2009

- C. Brander notes this is a B*0702 epitope.

HXB2 Location p24 (223–231)
Author Location p24 (223–231 SF2)
Epitope GPGHKARVL
Epitope name GL9
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
References Altfeld *et al.* 2001a

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- The response to GPGHKARVL was dominant.

HXB2 Location p24 (223–231)
Author Location (C consensus)
Epitope GPSHKARVL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p24 (223–231)
Author Location (C consensus)
Epitope GPGHKARVL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the G3 residue of GPGHKARVL are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location p24 (223–231)
Author Location (C consensus)
Epitope GPSHKARVL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- GPSHKARVL is an optimal epitope.

HXB2 Location p24 (223–231)
Author Location (224–232)
Epitope GPSHKARVL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Assay type Other
Keywords HLA associated polymorphism
References Boutwell & Essex 2007

- Publicly available HIV-1 subtype C sequences from South Africa and Botswana were analyzed, and 94 HLA-associated amino acid polymorphisms were found. Many polymorphisms were associated with multiple HLA allele classes. 12% associations were negative: association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles accounted for 50% of associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes.

- GPSHKARVL was a previously defined B*0702 presented epitope that encompassed a B*07- associated polymorphism, GPsHKARVL,in the third position.

HXB2 Location p24 (223–231)
Author Location p24 (1858–)
Epitope GPGHKARVL
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Country Australia
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, HLA associated polymorphism
References Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore et al., Science 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- The third position of this epitope GPgHKARVL has a mutational pattern that is correlated HLA B*0702. This epitope was experimentally tested using IFN-gamma Elispot and functional avidity studies.

HXB2 Location p24 (223–231)
Author Location p24
Epitope GPGHKARVL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- GPGHKARVL is a previously described HLA-B*0702-restricted epitope (part of Gag reacting peptide MTACQGVG-GPgHKARVL) that contains a B*0702-associated sequence polymorphism at residue G (GPgHKARVL).

HXB2 Location p24 (223–231)
Author Location
Epitope GPGHKARVL
Immunogen HIV-1 infection
Species (MHC) human (B07)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B07), an additional HLA (B40) was statistically predicted to be associated with this epitope.

HXB2 Location p24 (223–231)
Author Location Gag (355–363)
Epitope GPSHKARVL
Subtype A, C, D
Immunogen HIV-1 infection
Species (MHC) human (B07, B42, B81)
Country Tanzania
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, immunodominance
References Geldmacher *et al.* 2007a

- 56 ART-naive subjects were studied to assess whether T-cell responses to Gag and Nef are biased towards infecting subtype recognition, in a setting of epidemic consisting of subtypes A,C and D and their recombinant forms. The infecting subtype was determined by multi-region hybridization assay. Overlapping 15-mer isolate-based Gag and Nef peptide sets representative of local subtypes were used. The best recognized epitope variant in terms of magnitude and breadth corresponded to infecting subtype, in this case usually type-C. Hot spots of CTL recognition in Gag were in p24, p17 and p15; hotspots against Nef were in its central, conserved region.
- Epitope variants GPsHKARVL and GPgHKARVL were studied as peptide sequences ACQGVG-GPsHKARVL (subtypes C and D) and ACQGVG-GPgHKARVL (subtype A) with 12.5% responders. Subtypes C and D were best recognized. Associated HLAs frequently expressed within the studied cohort are listed in the study as B07, B42 and B81.

HXB2 Location p24 (223–231)
Author Location p17
Epitope GPGHKARVL
Subtype D
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC A23, A24, B35, B58, Cw4, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of

CTL CD8+

the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

HXB2 Location p24 (223–231)
Author Location p24 (355–363 LAI)
Epitope GPGHKARVL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords review, escape
References Goulder *et al.* 1997e; Goulder *et al.* 1997a
- HLA-identical sibling hemophiliac brothers were both infected with the same batch of factor VIII.
- One had a strong response to this peptide, the other a weak response. They were tested 6-8 years after infection.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

HXB2 Location p24 (223–231)
Author Location p24 (SF2)
Epitope GPSHKARVL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a
- The CTL-dominant response was focused on this epitope in a HIV+ Caucasian living in Boston – this epitope did not fall within the three most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa.

HXB2 Location p24 (223–231)
Author Location p24 (SF2)
Epitope GPSHKARVL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a
- The CTL-dominant response was focused on this epitope in a HIV+ Caucasian living in Boston – this epitope did not fall within the three most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
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HXB2 Location p24 (223–231)
Author Location p24 (223–231 SF2)
Epitope GPGHKARVL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b
- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 1/4 group 1, 2/3 group 2, and 0/1 group 3.

HXB2 Location p24 (223–231)
Author Location p24 (223–231)
Epitope GPGHKARVL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001
- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes.
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

HXB2 Location p24 (223–231)
Author Location p24 (223–231)
Epitope GPGHKARVL
Epitope name B7-GL9

Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), immunodominance, acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- Only two epitopes were detected during acute infection in patient AC-06, B7 restricted gp41 epitope IPRRIRQGL and Gag GPGHKARVL. GPGHKARVL was the first targeted peptide, and remained immunodominant through the 34 month study period.
- 3/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 1/4 individuals had detectable responses to this epitope after STI.

HXB2 Location p24 (223–231)
Author Location p24 (223–231)
Epitope `GPGHKARVL`
Epitope name B7-GL9 Gag
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), escape, early treatment, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the intial CTL response.
- In the earliest sample at day18 the sequence for this epitope was gpShkarvl. gpghkarvl dominated at day 606; both were equally well recognized.
- This was an immunodominant epitope, and was present in both viruses, the original strain and the superinfecting strain.

HXB2 Location p24 (223–231)
Author Location p24 (223–231)
Epitope `GPGHKARVL`
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 4/7 patients recognized this epitope.

HXB2 Location p24 (223–231)
Author Location (B consensus)
Epitope `GPGHKARVL`
Epitope name GL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A03, B07, Cw7
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location p24 (223–231)
Author Location Gag (355–363)
Epitope `GPGHKARVL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location p24 (223–231)
Author Location p24
Epitope `GPGHKARVL`
Epitope name B7-GL9(p24)
Immunogen HIV-1 infection
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ

CTL CD8+

Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24 (223–231)
Author Location Gag
Epitope GPGHKARVL
Epitope name B7-GL9 Gag (353-363)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A1, A24, B27, B7
Country France
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, immunodominance, characterizing CD8+ T cells
References Almeida *et al.* 2007

- Since it is suggested that a single response to B27-KK10 epitope may be responsible for the association of HLA-B*2705 patients with AIDS-free survival, B27-KK10-specific CTLs were compared to other HLA-specific CTLs in phenotype, function, clonal diversity, and antigen sensitivity in 47 treatment-naive infected slow or nonprogressing patients.
- cVL, the cell-associated viral load (number of infected cells harboring HIV DNA) correlated inversely with Gag-specific CTLs. This was most significant in HLA-B27 donors, and KK10 was identified as the peptide generating strongest CTL responses.
- GPGHKARVL was a dominant epitope found in non-B27-KK10 CTL responses. TCR sequences were studied in 6 patients.

HXB2 Location p24 (223–231)
Author Location Gag
Epitope GPGHKARVL
Subtype B, F
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Argentina
Keywords dynamics, escape
References Dilernia *et al.* 2008

- Dynamics of CTL escape mutations was studied theoretically by analyzing plasma samples from 302 subjects (collected over 20 years). HLA associated polymorphisms accumulated in a subtype-specific manner.
- Epitope GPGHKARVL with anchor residues at G(P)GHKARV(L) mutates to GPsHKARVL which is moderately supported as escape by phylogenetic correction.

HXB2 Location p24 (223–231)
Author Location Gag
Epitope GPSHKARVL
Epitope name Gag1150
Subtype C
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Epitope GPSHKARVL elicits IFN-gamma ELISpot responses in 5/7 subjects; and bound HLA-B7 with high affinities in soluble and cell-based assays. Previously published HLA restriction of this epitope includes HLA-B (LANL database).

HXB2 Location p24 (223–231)
Author Location Gag (355–363)
Epitope GPGHKARVL
Epitope name GL9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Other
Keywords supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism
References Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alelles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- A strong negative association between B*0702 and conservation of sequence is observed.
- Statistically significant associations between numbers of HLA-B0702 and -B4201 expressing subjects and epitope GPGHKARVL were found.

HXB2 Location p24 (223–231)
Author Location p24
Epitope GPSHKARVL
Epitope name GL9(p24)

Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope GPSHKARVL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide ACQGVGGPSHKARVLAEA. This epitope differs from the previously described HLA-B7-restricted epitope, GPGHKARVL, at 1 residue, GPsHKARVL.
- 1 of the 9 HLA-B7 carriers responded to GPsHKARVL-containing peptide with average magnitude of CTL response of 870 SFC/million PBMC (author communication and Fig.1).

II-B-4 Gag p24-p2p7p1p6 CTL/CD8+ epitopes

HXB2 Location p24-p2p7p1p6 (221–4)
Author Location
Epitope `VGGPGHKARVLAEAM`
Immunogen HIV-1 infection
Species (MHC) human (A2, B7)
Donor MHC A11, A2, B60, B7; A2, A32, B44, B7
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 89 (NIH ARRP Cat# 7960), VGGPGHKARVLAEAM, which contains epitopes restricted by HLA-A2 and -B7 in different patients, elicited the following CTL responses: (1) at 11.3 years in a living non-progressor (2) 56 sfc/million PBMC in another living non-progressor for 22+ years.

HXB2 Location p24-p2p7p1p6 (221–4)
Author Location Gag
Epitope `VGGPSHKARILAEAM`
Subtype A, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide VGGPSHKARILAEAM from subtype A and to peptide VGGPSHKARvLAEAM from subtype CRF01_AE.

HXB2 Location p24-p2p7p1p6 (223–1)
Author Location Gag
Epitope `GPGHKARVLA`
Immunogen
Species (MHC) human (B7)
References De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conservered regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFNγ production in an ELISPOT assay.
- GPGHKARVLA was confirmed as an HLA-B7 epitope in this study, and had been previously published.

HXB2 Location p24-p2p7p1p6 (223–1)
Author Location Gag
Epitope `GPGHKARVLA`
Epitope name 1291
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A03, A24, B07, B38, Cw07, Cw12/13; A01, A03, B07, B08, Cw03, Cw07
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.

CTL CD8+

- Estimated binding probability for GPGHKARVLA: 28%

HXB2 Location p24-p2p7p1p6 (225–8)
Author Location
Epitope GHKARVLAEAMSQVT
Immunogen HIV-1 infection
Species (MHC) human (A2, B7)
Donor MHC A11, A2, B60, B7; A2, A32, B44, B7
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 90 (NIH ARRP Cat# 7961), GHKARVLAEAMSQVT, which contains epitopes restricted by HLA-A2 and -B7 in different patients, elicited the following CTL responses: (1) at 11.3 years in a living non-progressor (2) 56 sfc/million PBMC in another living non-progressor for 22+ years (3) for 12 years in a former non-progressor who succumbed to non-AIDS death.

HXB2 Location p24-p2p7p1p6 (225–8)
Author Location Gag (357–372 LAI)
Epitope GHKARVLAEATLSQVN
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Buseyne *et al.* 1993a

- Vertical transmission of HIV ranges from 13% to 39%.
- Primary assays showed that cytotoxic activity against at least one HIV protein was detected in 70% of infected children.
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
- Patient EM28 (CDC P2A) had a CTL response to four epitopes in Gag.

HXB2 Location p24-p2p7p1p6 (229–7)
Author Location Gag (361–370)
Epitope RVLAEAMSQV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- RVLAEAMSQV was seen in 69% HLA-A2-positive individuals.

HXB2 Location p24-p2p7p1p6 (229–12)
Author Location
Epitope RVLAEAMSQVTNSAT
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A11, A2, B60, B7; A2, A24, B15, B40; A2, A31, B27, B44
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 91 (NIH ARRP Cat# 7962), RVLAEAMSQVTNSAT, contains an epitope restricted by HLA-A2 in different patients and elicited the following CTL immune responses: (1) for 19+ years in a living non-progressor (2) for 22+ years in another living non-progressor (3) for 22+ years in a former non-progressor who succumbed to loss of viremic control.

HXB2 Location p24-p2p7p1p6 (230–7)
Author Location Gag (363–370)
Epitope VLAEAMSQV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

HXB2 Location p24-p2p7p1p6 (230–7)
Author Location Gag (386–)
Epitope VLAEAMSQV
Epitope name Gag-386
Immunogen
Species (MHC) human (A*0201)
Keywords binding affinity, subtype comparisons, supertype, computational epitope prediction, immunodominance
References Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- VLAEAMSQV binds to all five HLA-A2 supertype alleles tested: A*0201, A*0202, A*0203, A*0206 and A*6802 (highest affinity)
- 4/22 individuals with chronic HIV-1 infection recognized this epitope, and it was immunodominant in 3/4 by ELISPOT.
- 0/12 acutely infected individuals recognized this epitope.

HXB2 Location p24-p2p7p1p6 (230–7)
Author Location Gag
Epitope VLAEAMSQV
Epitope name Gag 386
Subtype M
Immunogen vaccine, in vitro stimulation or selection, computer prediction
Vector/Type: DNA, peptide *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, mouse, humanized mouse (A*0201)
Assay type Cytokine production, T-cell Elispot
Keywords subtype comparisons, computational epitope prediction, escape, TCR usage, variant cross-recognition or cross-neutralization
References McKinney *et al.* 2004

- This study examined variant recognition of epitopes presented by A*0201 and A*1101. Numerous amino acid substitutions can be introduced into epitopes without disrupting their recognition by CTLs, although epitopes with multiple substitutions were less recognized. An algorithm was constructed for prediction of epitopes capable of inducing responses to a great number of variant epitopes.
- A total of 20 variant forms of Gag 386 were identified. More than 95% of the variant epitopes were recognized by CTLs from mice immunized with the parental form.
- Gag 386 epitope (parent or variant form) was present in 97% of HIV sequences of many M group subtypes.

HXB2 Location p24-p2p7p1p6 (230–7)
Author Location Gag (386–)
Epitope VLAEAMSQV
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (A*0201)
Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008

- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location p24-p2p7p1p6 (230–7)
Author Location
Epitope VLAEAMSQV
Epitope name Gag-VV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A02, 3/29 (10%) recognized this epitope.

HXB2 Location p24-p2p7p1p6 (230–7)
Author Location Gag (362–)
Epitope VLAEAMSQV
Epitope name Gag362(9L)
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type T-cell Elispot, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

CTL CD8+

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder that induced CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 1/17 HIV+ HLA-A2 subjects.
- The variant vlaeamsqA was also immunogenic in A2 transgenic mice, eliciting a CD8+ T-cell response, as was recognized in 3/17 HIV+ people, including the person that recognized the vlaeamsqV variant.

HXB2 Location p24-p2p7p1p6 (230–7)
Author Location p24 (230–238)
Epitope VLAEAMSQV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords acute/early infection, optimal epitope
References Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized during chronic infection.

HXB2 Location p24-p2p7p1p6 (230–7)
Author Location p24-p2p7p1p6 (362–370)
Epitope VLAEAMSQV
Epitope name VV9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A*02, A*32, B*07, B*40, Cw*03, Cw*07
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, acute/early infection, viral fitness and reversion
References Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- The mother was A02+ and carried a variant form of the epitope, VLAEAMShV, which she passed to her A02- child. This form persisted in her child for 15 months.

HXB2 Location p24-p2p7p1p6 (230–7)
Author Location p24
Epitope VLAEAMSQV
Epitope name A2-VV9(gp24)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p24-p2p7p1p6 (230–7)
Author Location p2p7p1p6 (362–370 Henan isolate)
Epitope VLAEAMSQV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- While VLAEAMSQV was described previously to have strong CTL response in HLA-A2 individuals, in this study 8 of 13 (61%) A2-positive individuals demonstrated moderate response to this peptide.

HXB2 Location p24-p2p7p1p6 (230–7)
Author Location
Epitope CLAEAMSQV
Epitope name Gag 362(9V)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords variant cross-recognition or cross-neutralization
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Gag 362(9V) CLAEAMSQV epitope was found in 8 patients but only 1 had a CTL immune response to it.
- A variant, 9A (CLAEAMSQa) involving the C-terminal anchor binding position was cross-recognized by CTLs to this epitope.

HXB2 Location p24-p2p7p1p6 (230–7)
Author Location Gag (362–)
Epitope `VLAEAMSQV`
Epitope name Gag362(9V)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Gag epitope VLAEAMSQV, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients. A variant of this epitope, VLAEAMSQa, was seen in DK1.

HXB2 Location p24-p2p7p1p6 (230–7)
Author Location Gag (362–)
Epitope `VLAEAMSQA`
Epitope name Gag362(9A)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Gag epitope VLAEAMSQA, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients.

HXB2 Location p24-p2p7p1p6 (230–7)
Author Location Gag
Epitope `VLAEAMSQV`
Epitope name Gag386
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- VLAEAMSQV is a Gag epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location p24-p2p7p1p6 (230–7)
Author Location Gag (397–405)
Epitope `VLAEAMSQV`
Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.

CTL CD8+

- This epitope can bind all five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802)

HXB2 Location p24-p2p7p1p6 (230–7)
Author Location Gag
Epitope VLAEAMSQV
Epitope name Gag386
Subtype A, B, C, D
Immunogen HIV-1 infection
Species (MHC) human, mouse (A2 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope VLAEAMSQV of the HLA-A2 supertype bound most strongly to HLA-A*0203, -A*0201, -A*0202 and -A*0206, but also to -A*6802. It was conserved 100% in subtype A, 74% in B, 13% in C and 25% in subtype D. 2/22 HLA-A2 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Gag386.

HXB2 Location p24-p2p7p1p6 (230–8)
Author Location p2p7p1p6 (362–371 Henan isolate)
Epitope VLAEAMSQVT
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- VLAEAMSQVT was among 5 most recognized peptides (69%).

II-B-5 Gag p2p7p1p6 CTL/CD8 + epitopes

HXB2 Location p2p7p1p6 (1–10)
Author Location p2p7p1p6 (1903–)
Epitope AEAMSQVTNS
Epitope name A*3101 KR9
Immunogen HIV-1 infection
Species (MHC) human (B*4002)
Country Australia
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, HLA associated polymorphism
References Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore et al., Science 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- Mutational patterns in the ninth position, AEAMSQVTnS, in this epitope are correlated with the host carrying HLA B*4002.

HXB2 Location p2p7p1p6 (1–10)
Author Location p2p7p1p6 (1–10)
Epitope AEAMSQVTNS
Immunogen
Species (MHC) human (B*4501)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location p2p7p1p6 (2–16)
Author Location
Epitope EAMSQVTNSATIMMQ
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A11, A2, B60, B7; A2, A24, B15, B40; A2, A31, B27, B44; A2, A32, B44, B7
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.

- Peptide 92 (NIH ARRP Cat# 7963), EAMSQVTNSATIMMQ, contains an epitope restricted by HLA-A2 in different patients and elicited the following CTL immune responses: (1) for 19+ years in a living non-progressor (2) for 22+ years in another living non-progressor (3) for 22+ years in a former non-progressor who succumbed to loss of viremic control (4) for 19+ years in yet another living non-progressor.

HXB2 Location p2p7p1p6 (5–13)
Author Location p15 (5–13)
Epitope SQVTNSATI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, SQVTNSATI, was detected within overlapping peptide EAMSQVTNSATIMMQR.

HXB2 Location p2p7p1p6 (5–13)
Author Location Gag (SF2)
Epitope SQVTNPANI
Immunogen vaccine
Strain: B clade SF2 *HIV component:* Gag
Species (MHC) mouse (H-2D^b)
References Paliard *et al.* 1998

- HIV-1 (SF2)p55gag vaccination of H-2 mice activates a CTL response against this epitope.
- CTL that recognized SQVTNPANI in the context of H-2D^b cross-reacted with H-2 alloantigens H-2L^d and an unidentified self-peptide.
- A postulate: heterozygosity at the MHC level could prevent the maturation of some T cell receptor combinations for foreign peptide and self-MHC constructs because of thymic depletion and tolerance.

HXB2 Location p2p7p1p6 (8–17)
Author Location Gag
Epitope TNSANIMMQR
Epitope name TR10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 5, tnsaSimmqr, was found in the most polymorphic residues in the epitope. One escape mutation, at position 2,tTsanimmqr, was found not to correspond to the most polymorphic residues in the epitope. This is a novel partially mapped epitope.

HXB2 Location p2p7p1p6 (14–28)
Author Location
Epitope MMQRGNFRNQRKIVK
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* Other *HIV component:* gp160
Species (MHC) human
Donor MHC A3, A33; B15 (63), B27
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location p2p7p1p6 (18–37)
Author Location Gag (96ZM651.8)
Epitope SNFKGNKRMVKCFNCGKEGH
Immunogen
Species (MHC) human (A*020101)
References Novitsky *et al.* 2001

- This study is provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort.
- 4 of 8 individuals (50%) who were positive for HLA-A*02011 responded to the peptide SNFKGNKRMVKCFNCGKEGH.

HXB2 Location p2p7p1p6 (19–33)
Author Location Gag
Epitope NFRGPKRIKCFNCG
Subtype A

Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 2 subjects responded to peptide NFRGPKRIKCFNCG from subtype A.

HXB2 Location p2p7p1p6 (21–29)
Author Location Gag (C-96BW04.09)
Epitope `KGPRRIVKC`
Epitope name B1
Subtype C
Immunogen vaccine
Vector/Type: DNA, alphavirus replicon *Strain:* C clade C-96BW04.09, C clade C-96BW15C05 *HIV component:* Gag, Gag-Pol, Pol
Species (MHC) mouse (H-2^{d})
Assay type Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, vaccine antigen design
References Megede *et al.* 2006

- HIV clade C gag, pol and fusion gagpol vaccines were compared in mice. Breadth of T cell responses was improved in mice immunized with gagpol fusion genes, compared to single antigen constructs. 5 new murine CD8+ T cell epitopes were mapped.
- This is a novel epitope.

HXB2 Location p2p7p1p6 (21–29)
Author Location Gag (C-96BW15C05)
Epitope `KGPKRIIKC`
Epitope name B2
Subtype C
Immunogen vaccine
Vector/Type: DNA, alphavirus replicon *Strain:* C clade C-96BW04.09, C clade C-96BW15C05 *HIV component:* Gag, Gag-Pol, Pol
Species (MHC) mouse (H-2d)
Assay type Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, vaccine antigen design
References Megede *et al.* 2006

- HIV clade C gag, pol and fusion gagpol vaccines were compared in mice. Breadth of T cell responses was improved in mice immunized with gagpol fusion genes, compared to single antigen constructs. 5 new murine CD8+ T cell epitopes were mapped.
- This is a novel immunodominant epitope.

HXB2 Location p2p7p1p6 (23–33)
Author Location Gag (386–396)
Epitope `SKRIVKCFNCG`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p2p7p1p6 (25–34)
Author Location Gag (Henan isolate)
Epitope `KTVKCFNCGR`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p2p7p1p6 (34–48)
Author Location p7 (397–411)
Epitope `KEGHIAKNCRAPRKK`
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008

- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.

- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.
- CTL immune response to consensus sequence KEGHIAKNCRAPRKK was elicited in subject 00016. Consensus epitopes of subjects were KEGHlArNCRAPRKK.

HXB2 Location p2p7p1p6 (34–48)
Author Location Gag (397–411)
Epitope `KEGHIAKNCRAPRKK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the ES. Both the ES and the Progressor had K411R substitution.

HXB2 Location p2p7p1p6 (38–47)
Author Location p7 (401–410)
Epitope `IAKNCRAPRK`
Epitope name IAKK10
Subtype D
Immunogen HIV-1 infection
Species (MHC) human (A*03)
Country Kenya
References Peters *et al.* 2008a

- Gag sequences from 468 HIV-1 positive sex workers from the Kenyan Pumwani cohort were analyzed to bioinformatically identify positively selected residues that could be related to antigen processing. Mutation effects on disease progression were followed by mean CD4 counts. This method is also one way of identifying potential CTL epitopes and classifying them.
- A Gag positive selection map was generated and sites were classified as beneficial or harmful to HIV. They were correlated to antigen processing (proteasomal cleavage), antigen presentation (TAP transport efficiency) and T-cell receptor binding.
- p17 and p24's structural constraints limited their diversity, while p7-p1-p6 showed a higher average entropy.
- Epitope IAKNCRAPRK, is unique to this Kenyan cohort. Its optimal, published epitope is LARNCRAPRK (LARK10). HLA-A*0301-restricted mutant K403R, IArNCRAPRK, is shown to be under selection pressure. D clade adapted IAKNCRAPRK has a substantially reduced TAP binding compared with optimal LARK10

HXB2 Location p2p7p1p6 (38–47)
Author Location p7 (1996–)
Epitope `LARNCRAPRK`
Epitope name A*3101 LR9
Immunogen HIV-1 infection
Species (MHC) human (A*3101)
Country Australia
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, HLA associated polymorphism
References Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore et al., Science 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- The third position of the epitope LArNCRAPRK an HLA-A*3101 correlated amino acid, however which one of the two common forms, LArNCRAPRK or LAkNCRAPRK, was the escape or and which was the susceptible form depended on the patient tested. Testing was performed by IFN-gamma ELIspot (magnitude) and functional avidity studies.

HXB2 Location p2p7p1p6 (38–47)
Author Location Gag
Epitope `LARNCRAPRK`
Epitope name 1331
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, A23, B49, B57; A03, A24, B27, B57, Cw13, Cw18; A03, A26, B08, B52
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for LARNCRAPRK: 35%. Immunodominant epitope.

HXB2 Location p2p7p1p6 (38–48)
Author Location Gag (402–412)
Epitope IAKNCRAPRKK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p2p7p1p6 (38–52)
Author Location
Epitope TARNCRAPRKKGCWK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 101 (NIH ARRP Cat# 7972), TARNCRAPRKKGCWK, contains an epitope restricted by HLA-A3 in a living non-progressor and elicited CTL immune response of 80 sfc/million PBMC at 12.5 years, decreasing to below 50 sfc/million PBMC at 22.8 years.

HXB2 Location p2p7p1p6 (38–52)
Author Location Gag (401–415)
Epitope IAKNCRAPRKKGCWK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the ES. Both the ES and the Progressor had K411R substitution.

HXB2 Location p2p7p1p6 (42–50)
Author Location p15 (42–50 SF2)
Epitope CRAPRKKGC
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Donor MHC B14
Keywords immunodominance
References Yu *et al.* 2002b

- 26/57 HIV-1 infected subjects displayed Gag p15-specific CD8+ T-cell IFNgamma responses were measured by Elispot and intracellular staining. The immunodominant regions targeted by CD8+ T-cells were mapped to three functional domains: the zinc finger structures, the protease cleavage site p7/p1, and to the Vpr binding site in p6.
- p15 contributed on average 17% of the total Gag response (rage 0-100%).
- 3 optimal CTL epitopes were mapped within p15: KELYPLTSL, CRAPRKKGC, and FLGKIWPSYK.
- 2/6 HLA-B14+ subjects recognized this epitope. The binding motif for B14 is C-term Cys, positions 2 and 5 Arg.

HXB2 Location p2p7p1p6 (42–50)
Author Location p15 (42–50)
Epitope CRAPRKKGC
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location p2p7p1p6 (42–50)
Author Location (B consensus)
Epitope CRAPRKKGC
Epitope name CC9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Donor MHC A28, A29, B14, B44, Cw8
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope

HXB2 Location p2p7p1p6 (42–50)
Author Location Gag (405–413)
Epitope CRAPRKKGC
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location p2p7p1p6 (43–52)
Author Location Gag (Henan isolate)
Epitope KAPRKKGCWK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p2p7p1p6 (52–61)
Author Location (Henan isolate)
Epitope KCGKEGHQMK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p2p7p1p6 (55–70)
Author Location p15 (446–460 BRU)
Epitope KEGHQMKDCTERQANF
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Claverie *et al.* 1988

- One of 4 epitopes first predicted, then subsequently shown to stimulate an HLA-A2 restricted CTL line.

HXB2 Location p2p7p1p6 (55–70)
Author Location Gag (41–56)
Epitope KEGHQMKDCTERQANF
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 19 patients recognized this epitope.

HXB2 Location p2p7p1p6 (58–69)
Author Location p24
Epitope HQMKDCNERQAN
Subtype B, G
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, A36, B45, B58, Cw3, Cw6
Country Nigeria
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell

CTL CD8+

responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype G Gag. The autologous epitope sequence had 2 changes, an E8T substitution and a two amino acid insertion, QG at position 10, that could impact the anchor: HQMKDC-NtRqgQAN.

HXB2 Location p2p7p1p6 (62–72)
Author Location Gag (426–436)
Epitope DCTERQANFLG
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005
- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 3/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p2p7p1p6 (62–72)
Author Location Gag (425–435)
Epitope DCTERQANFLG
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008
- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.
- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.
- CTL immune response to consensus sequence DCTERQANFLG was elicited in subject 00016. Consensus epitope of subjects were the same as Clade B consensus.

HXB2 Location p2p7p1p6 (63–71)
Author Location p15 (63–71)
Epitope CTERQANFL
Immunogen HIV-1 infection
Species (MHC) human (B61)
Donor MHC A*0201, A11, B51, B61, Cw*14, Cw2
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003
- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

HXB2 Location p2p7p1p6 (63–71)
Author Location p15 (63–71)
Epitope CTERQANFL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B61)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, subtype comparisons, acute/early infection
References Malhotra *et al.* 2007b
- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (ANC) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- This epitope, CTERQANFL, is invariant across CON A, B, C and M-Group sequences, as well as clade B COT and ANC sequences. HLA-B61 restriction was inferred based on subject possessing appropriate HLA class I allele and prior publication.

HXB2 Location p2p7p1p6 (63–71)
Author Location
Epitope CTERQANFL
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A*0201, A*1101; B*4002, B*5101
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it both before and after infection.

HXB2 Location p2p7p1p6 (64–71)
Author Location p15 (64–71)
Epitope TERQANFL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*40)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, TERQANFL, was detected within overlapping peptides QMKDCTERQANFLGKIW and RQANFLGKIWPSHKGR.

HXB2 Location p2p7p1p6 (64–71)
Author Location p2p7p1p6 (427–434)
Epitope TERQANFL
Epitope name TL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*40)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*40-associated substitution within optimally defined epitope TERQANFL is at position T1, TERQANFL.

HXB2 Location p2p7p1p6 (64–71)
Author Location
Epitope TERQANFL
Epitope name Gag-TL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*4002)
Donor MHC A*0201, A*3201, B*4002, B*5301, Cw*0202, Cw*0401
Keywords HAART, ART
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- This epitope was newly defined in this study.
- Patient 01RCH59 was Hispanic, not on HAART, and had a viral load of 5100 and CD4 count of 349 – she also recognized AEWDRVHPV, p24(78-86), HLA-B*4002 and KEKGGLEGL, Nef(92-100), HLA-B*4002.
- Among HIV+ individuals who carried HLA B40, 3/5 (60%) recognized this epitope.

HXB2 Location p2p7p1p6 (64–71)
Author Location p15 (64–71)
Epitope TERQANFL
Immunogen
Species (MHC) human (B*4002)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location p2p7p1p6 (64–71)
Author Location p2p7p1p6
Epitope TERQANFL
Epitope name TL8(p2p7p1p6)
Subtype B
Immunogen HIV-1 infection

CTL CD8+

Species (MHC) human (B40)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B40-restricted epitope TERQANFL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide QMKDCTERQANFLGKIW.
- 5 of the 20 HLA-B40 carriers responded to TERQANFL-containing peptide with average magnitude of CTL response of 361 SFC/million PBMC (author communication and Fig.1).

CTL CD8+

HXB2 Location p2p7p1p6 (65–75)
Author Location Gag (429–439)
Epitope ERQANFLGKIW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p2p7p1p6 (66–74)
Author Location (C consensus)
Epitope RQANFLGKI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*13)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- RQANFLGKI is an optimal epitope.

HXB2 Location p2p7p1p6 (66–74)
Author Location Gag (429–437)
Epitope RQANFLGKI
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*13)
Donor MHC A*0301, A*3001, B*1301, B*1402, Cw*0602, Cw*0802
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords epitope processing, immune evasion, viral fitness and reversion, HLA associated polymorphism
References Honeyborne *et al.* 2007

- To determine whether HLA-B*13-restricted CTL responses could partially explain low viremic loads in patients, a cohort of chronic C-clade infected subjects was studied. 6 novel B*13-restricted CTL epitopes were defined from both C- and B-clade viruses, 3 of which were within Gag. B*13-restricted CTL responses correlated with lower viremia, with most immunity targeted against Gag epitopes (p15, p17, p24). Gag epitope escape variants may exact a high viral fitness cost, mutations being seen within and around the optimal epitope.
- Mutations in this epitope, RQANFLGKI, were seen at K436R i.e. to RQANFLGrI as well as at I437VLM i.e. to RQANFLGKv, RQANFLGKl and RQANFLGKm. These C-terminii variants may compromise viral fitness by interference with protease cleavage between p7 and p1.

HXB2 Location p2p7p1p6 (66–74)
Author Location p2p7p1p6 (429–437)
Epitope RQANFLGKI
Epitope name RI9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*13)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*13-associated substitution within optimally defined epitope RQANFLGKI is at positions K8 and I9, RQANFLGki.

HXB2 Location p2p7p1p6 (66–74)
Author Location
Epitope RQANFLGKI
Epitope name RI9
Immunogen
Species (MHC) human (B13)
Keywords optimal epitope

References Llano *et al.* 2009
- C. Brander notes this is a B13 epitope.

HXB2 Location p2p7p1p6 (66–74)
Author Location p2p7p1p6
Epitope RQANFLGKI
Epitope name RI9(p2p7p1p6)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B13)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008
- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B13-restricted epitope RQANFLGKI elicited an immune response in Chinese HIV-1 positive subjects as part of peptides QMKDCTERQANFLGKIW and RQANFLGKIWPSHKGR.
- 9 of the 29 HLA-B13 carriers responded to RQANFLGKI-containing peptide #59 with average magnitude of CTL response of 342 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p2p7p1p6 (66–80)
Author Location
Epitope RQANFLGKIWPSYKG
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008
- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 108 (NIH ARRP Cat# 7979), RQANFLGKIWPSYKG, contains an epitope restricted by HLA-A2 in different patients and elicited the following CTL responses: (1) for 22+ years in a living non-progressor (2) for 22+ years in another living non-progressor (3) 54 sfc/million PBMC at 21.3 years in yet another living non-progressor (4) 68 sfc/million PBMC for 12 years in a former non-progressor who succumbed to non-AIDS death (5) 319 sfc/million PBMC for 22.8 years in a former non-progressor who succumbed to loss of viremic control.

HXB2 Location p2p7p1p6 (66–80)
Author Location p15 (66–80)
Epitope RQANFLGKIWPSYKG
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003
- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- Responses to this peptide were detected in 16% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location p2p7p1p6 (66–80)
Author Location Gag (429–443)
Epitope RQANFLGKIWPSHKG
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008
- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the Progressor, who had H441Y substitution.

CTL CD8+

HXB2 Location p2p7p1p6 (66–81)
Author Location p15
Epitope RQANFLGKIWPSHKGR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, RQANFLGKIWPSHKGR, had an overall frequency of recognition of 23.3% - 18.6% AA, 30.8% C, 31.8% H, 9.5% WI. This peptide is included in a 27 aa Gag-p15 highly reactive region to be used for vaccine design.

HXB2 Location p2p7p1p6 (66–81)
Author Location p15
Epitope RQANFLGKIWPSHKGR
Immunogen
Species (MHC)
References

HXB2 Location p2p7p1p6 (70–77)
Author Location Gag (433–)
Epitope FLGKIWPS
Epitope name Gag433
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* Gag *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder that induced CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 7/17 HIV+ HLA-A2 subjects.

HXB2 Location p2p7p1p6 (70–77)
Author Location p15 (70–77)
Epitope FLGKIWPS
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, subtype comparisons, acute/early infection
References Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (ANC) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- This epitope, FLGKIWPS, is invariant across CON A, B, C and M-Group sequences, as well as clade B COT and ANC sequences. HLA-A02 restriction was inferred based on subject possessing appropriate HLA class I allele and prior publication.

HXB2 Location p2p7p1p6 (70–77)
Author Location
Epitope FLGKIWPS
Epitope name Gag 433
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords variant cross-recognition or cross-neutralization
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Gag 433 FLGKIWPS epitope was found in 9 patients and was frequently targeted as 5 had CTL immune responses to it. Non-identical patient isolates of this epitope had 1 or more amino acid differences that elicited a positive CTL response.

HXB2 Location p2p7p1p6 (70–77)
Author Location Gag (433–)
Epitope `FLGKIWPS`
Epitope name Gag433
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Gag epitope FLGKIWPS, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients.

HXB2 Location p2p7p1p6 (70–79)
Author Location Gag (433–442)
Epitope `FLGKIWPSHK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- Two patients developed responses to epitope FLGKIWPSHK during primary infection and one after primary, during early chronic infection. This was one of the epitopes targeted by broad HLA-A2-restricted CTL responses.

HXB2 Location p2p7p1p6 (70–79)
Author Location p15 (70–79)
Epitope `FLGKIWPSHK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, FLGKIWPSHK, was detected within overlapping peptides QMKDCTERQANFLGKIW, RQANFLGKIW-PSHKGR and GKIWPSHKGRPGNFLQSR.

HXB2 Location p2p7p1p6 (70–79)
Author Location p15 (70–79 SF2)
Epitope `FLGKIWPSYK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords immunodominance
References Yu *et al.* 2002b

- 26/57 HIV-1 infected subjects displayed Gag p15-specific CD8+ T-cell IFNgamma responses were measured by Elispot and intracellular staining. The immunodominant regions targeted by CD8+ T-cells were mapped to three functional domains: the zinc finger structures, the protease cleavage site p7/p1, and to the Vpr binding site in p6.
- p15 contributed on average 17% of the total Gag response (rage 0-100%).

- 3 optimal CTL epitopes were mapped within p15: KELYPLTSL, CRAPRKKGC, and FLGKIWPSYK.
- FLGKIWPSYK was embedded in a peptide recognized by 14/57 (25%) of subjects.
- 13/24 (54%) of HLA-A*0201+ subjects recognized this peptide.

HXB2 Location p2p7p1p6 (70–79)
Author Location p2p7p1p6 (1–10)
Epitope FLGKIWPSYK
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location p2p7p1p6 (70–79)
Author Location (C consensus)
Epitope FLGKIWPSHK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location p2p7p1p6 (70–79)
Author Location (C consensus)
Epitope FLGKIWPSHK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- FLGKIWPSHK is an optimal epitope.

HXB2 Location p2p7p1p6 (70–79)
Author Location (C consensus)
Epitope FLGKIWPSHK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0205)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- FLGKIWPSHK is an optimal epitope.

HXB2 Location p2p7p1p6 (70–79)
Author Location
Epitope FLGKIWPSYK
Immunogen HIV-1 infection
Species (MHC) human (A02)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope FLGKIWPSYK elicited a magnitude of response of 200 SFC with a functional avidity of 5nM and binding affinity of 40nM.

HXB2 Location p2p7p1p6 (70–79)
Author Location Gag (1–10)
Epitope FLGKIWPSYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) goat (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords acute/early infection, optimal epitope
References Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized during chronic infection, in 54% of 74 chronically infected A2+ individuals, but in no acute cases (0/14).

HXB2 Location p2p7p1p6 (70–79)
Author Location p2p7p1p6
Epitope FLGKIWPSYK
Epitope name A2-FK10(p1)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ

Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p2p7p1p6 (70–79)
Author Location Gag
Epitope FLGKIWPSHK
Subtype B, C, A1, AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- The well identified, immunogenic HLA-A2-restricted epitope FLGKIWPSHK of HIV-Gag was used in a peptide pool to stimulate PBMCs from 31 HIV-1 + subjects by ELISpot assay.

HXB2 Location p2p7p1p6 (70–79)
Author Location p15
Epitope FLGKIWPSHK
Epitope name FK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- Epitope, FLGKIWPSHK, went from 3-4 functional to monofunctional in the response it was able to elicit with no sequence change in an untreated patient. Previously published HLA-restriction for FK10 was HLA-A2.

HXB2 Location p2p7p1p6 (70–79)
Author Location p2p7p1p6
Epitope FLGKIWPSHK
Epitope name FK10(p2p7p1p6)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope FLGKIWPSHK elicited an immune response in Chinese HIV-1 positive subjects as part of peptide RQANFLGKIWPSHKGR. This epitope differs from the previously described HLA-B7-restricted epitope, FLGKIWPSYK, at 1 residue, FLGKIWPShK.
- 11 of the 55 HLA-A2 carriers responded to FLGKIWPShK-containing peptide with average magnitude of CTL response of 188 SFC/million PBMC.

HXB2 Location p2p7p1p6 (70–84)
Author Location
Epitope FLGKIWPSYKGRPGN
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that

CTL CD8+

coincided with LTNP status, but 50% did not remain non-progressors.

- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 109 (NIH ARRP Cat# 7980), FLGKIWPSYK-GRPGN, contains an epitope restricted by HLA-A2 in different patients and elicited the following CTL responses: (1) for 22+ years in a living non-progressor (2) for 22+ years in another living non-progressor (3) 72 sfc/million PBMC at 21.3 years in yet another living non-progressor (4) 68 sfc/million PBMC for 12 years in a former non-progressor who succumbed to non-AIDS death (5) 319 sfc/million PBMC for 22.8 years in a former non-progressor who succumbed to loss of viremic control.

HXB2 Location p2p7p1p6 (70–84)
Author Location Gag (433–447)
Epitope FLGKIWPSHKGRPGN
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the Progressor, who had H441Y substitution.

HXB2 Location p2p7p1p6 (73–81)
Author Location p2p7p1p6 (2113–)
Epitope KIWPSYKGR
Epitope name A*3101 KR9
Immunogen HIV-1 infection
Species (MHC) human (A*3101)
Country Australia
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, HLA associated polymorphism
References Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore et al., Science 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- The seventh position (K), KIWPSYkGR, is an HLA-A*3101 correlated amino acid. The susceptible form of this epitope is KIWPSYKGR, whilst the escape form is KIWPSYrGR, as indicated by the mutational patterns; this was validated experimentally using IFN-gamma Elispot and functional avidity studies.

HXB2 Location p2p7p1p6 (74–88)
Author Location p2p7p1p6 (437–451)
Epitope IWPSHKGRPGNFLQS
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008

- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.
- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.
- CTL immune response to consensus sequence IWPSHK-GRPGNFLQS was elicited in subject 00016.

HXB2 Location p2p7p1p6 (75–85)
Author Location p17 (124–132 LAI)
Epitope PPSGKGGNY
Subtype HIV-2
Immunogen HIV-1 or HIV-2 infection
Species (MHC) human (B35)
Country Gambia
Keywords HIV exposed persistently seronegative (HEPS), HIV-2
References Rowland-Jones *et al.* 1995

- Established by titration. HIV-1infected and HIV-2-infected B35+ subjects recognized both the HIV-1 (NSSKVSQNY) and HIV-2 forms (PPSGKGGNY).

HXB2 Location p2p7p1p6 (82–96)
Author Location
Epitope PGNFLQSRPEPTAPP

Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, A32, B44, B7
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- 13 TAHIV (transfusion acquired HIV) LTNPs were studied longitudinally for up to 27 years to find correlations and indicators of elite control versus delayed progresson to AIDS. 12 of 13 subjects had one or more host genetic factor that coincided with LTNP status, but 50% did not remain non-progressors.
- Immune factors that correlated with LTNP status were very low HIV viremia (<100 copies/ml) associated with Gag p24 proliferative CD4 response. Decline in p24-induced proliferation strongly preceded loss of non-progression to AIDS. Strong Gag-specific CTL responses in one sub-cohort were indicative of control while Pol-specific responses were effective in controlling HIV replication in the other sub-group.
- Peptide 112 (NIH ARRP Cat# 7983), PGNFLQSRPEPTAPP, contains an epitope restricted by HLA-A2 and elicited a CTL response for 19.3 years in a living non-progressor.

HXB2 Location p2p7p1p6 (83–97)
Author Location p15 (418–433 BRU)
Epitope GNFLQSRPEPTAPPF
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Claverie *et al.* 1988

- One of 4 epitopes first predicted, then subsequently shown to stimulate an HLA-A2 restricted CTL line.

HXB2 Location p2p7p1p6 (83–97)
Author Location Gag (69–83)
Epitope GNFLQSRPTAPPF
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 19 patients recognized this epitope.

HXB2 Location p2p7p1p6 (83–97)
Author Location Gag (453–462 BH10, LAI)
Epitope GNFLQSRPEPTAPPF
Immunogen HIV-1 infection
Species (MHC) human
References Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is PEPTAPPFLQ) has similarity with the T-cell surface glycoprotein CD5, fragment PEPTAPPRLQ.

HXB2 Location p2p7p1p6 (83–103)
Author Location Gag
Epitope QNRPEPRPEPTAPPAENFRES
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- A reversion at resdue T in Gag reacting peptide QNRPEPRPEPtAPPAENFRES was associated with host HLA-B*3910. No known HLA-B*39-restricted epitope was in this sequence.

HXB2 Location p2p7p1p6 (85–94)
Author Location Gag (448–457 Henan isolate)
Epitope FLQSRPEPTA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- Newly identified HLA-A2-restricted epitope.
- FLQSRPEPTA was among 5 mostly recognized peptides (77%).

HXB2 Location p2p7p1p6 (89–97)
Author Location Gag
Epitope RPEPTAPPA
Epitope name Gag1159
Subtype C
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

CTL CD8+

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Novel Gag epitope RPEPTAPPA elicits IFN-gamma ELISpot responses in 2/7 subjects; and bound HLA-B7 with low and high affinities in soluble and cell-based assays respectively.

HXB2 Location p2p7p1p6 (91–100)
Author Location p2p7p1p6
Epitope EPTAPPEESF
Subtype D
Immunogen HIV-1 infection
Species (MHC) human (B35, B58)
Donor MHC A23, A24, B35, B58, Cw4, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

HXB2 Location p2p7p1p6 (91–100)
Author Location Gag
Epitope EPTAPPAESF
Epitope name Gag1162
Subtype C
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Novel Gag epitope EPTAPPAESF elicits IFN-gamma ELISpot responses in 1/7 subjects; and bound HLA-B7 with low and medium affinities in soluble and cell-based assays respectively.

HXB2 Location p2p7p1p6 (94–102)
Author Location Gag
Epitope APPAESFRF
Epitope name Gag1147
Subtype C
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Novel Gag epitope APPAESFRF elicits IFN-gamma ELISpot responses in 2/7 subjects; and bound HLA-B7 with low and high affinities in soluble and cell-based assays respectively.

HXB2 Location p2p7p1p6 (98–112)
Author Location p6 (461–475)
Epitope ESFRFGEETTTPSQK
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008

- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.
- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.
- CTL immune response to consensus sequence ESFRFGEETTTPSQK was elicited in subject 00016. Consensus epitopes of subject 00015 was ESFRlGEETTsPSQK and of subject 00016 was ESFRFGEETTsPSQK.

HXB2 Location p2p7p1p6 (103–120)
Author Location Gag
Epitope GEETTTPSQKQEPIDKEL
Epitope name GAG-64
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, gEETTtPsqKQEPiDkEl differs from the consensus C sequence EETTPapKQEPkDrEp at 7 amino acid positions, i.e. by 38.9%.

HXB2 Location p2p7p1p6 (108–116)
Author Location p2p7p1p6
Epitope `TPSQKQEPI`
Subtype D
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC A23, A24, B35, B58, Cw4, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

HXB2 Location p2p7p1p6 (108–116)
Author Location p15
Epitope `TPSQKQEPI`
Subtype D
Immunogen HIV-1 infection
Species (MHC) human (B53)
Donor MHC A23, A34, B44, B53, Cw4, Cw6
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

HXB2 Location p2p7p1p6 (110–118)
Author Location Gag (Henan isolate)
Epitope `SQKQEQIDK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

HXB2 Location p2p7p1p6 (111–127)
Author Location Gag
Epitope `QKQGTIDKELYPLASLK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This is a novel unmapped epitope. Two changes over time in the individual that recognized this peptide: `QKQGTkDKELYP-LvSLK`

HXB2 Location p2p7p1p6 (111–127)

CTL CD8+

Author Location Gag
Epitope QKQEPIDKELYPLASLK
Epitope name GAG-65
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, qKQEPiDkElyPLaSLK differs from the consensus C sequence pKQEPkDrEPLtSLK at 6 amino acid positions, i.e. by 35.3%.

HXB2 Location p2p7p1p6 (113–121)
Author Location p15
Epitope QEPIDKELY
Subtype D
Immunogen HIV-1 infection
Species (MHC) human (B44)
Donor MHC A23, A34, B44, B53, Cw4, Cw6
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

HXB2 Location p2p7p1p6 (114–123)
Author Location (C consensus)
Epitope EPKDREPL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- EPKDREPL is an optimal epitope.

HXB2 Location p2p7p1p6 (114–123)
Author Location p2p7p1p6
Epitope EPIDKELYPL
Subtype D
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC A23, A24, B35, B58, Cw4, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

HXB2 Location p2p7p1p6 (114–123)
Author Location p15
Epitope EPIDKELYPL
Subtype D
Immunogen HIV-1 infection
Species (MHC) human (B53)
Donor MHC A23, A34, B44, B53, Cw4, Cw6
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

HXB2 Location p2p7p1p6 (114–124)
Author Location p6 (477–487)
Epitope EPIDKELYPLA
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008

- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.
- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.
- CTL immune response to consensus sequence EPIDKELYPLA was elicited in subject 00016. Consensus epitope of subject 00015 was EtIgKELYPLA and of 00016 was EaIDKELYPLA.

HXB2 Location p2p7p1p6 (118–126)
Author Location Gag (481–489)
Epitope KELYPLTSL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*40)
Donor MHC A*03, A*24, B*35, B*40
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, variant cross-recognition or cross-neutralization, superinfection
References Yang *et al.* 2005b

- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
- A response to this epitope was detected before superinfection but diminished afterward. The epitope in the infecting and superinfecting strain had the sequence: kelyplAsl. The second infecting strain had a 4-amino acid insertion proximal to the epitope, RGIDkelyplAsl.

HXB2 Location p2p7p1p6 (118–126)
Author Location p2p7p1p6 (481–489)
Epitope KELYPLTSL
Epitope name KL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*40)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*40-associated substitution within optimally defined epitope KELYPLTSL is at position E2, KeLYPLTSL.

HXB2 Location p2p7p1p6 (118–126)
Author Location p2p7p1p6 (118–126)
Epitope KELYPLTSL
Immunogen
Species (MHC) human (B*4001)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is a B*4001 epitope.

HXB2 Location p2p7p1p6 (118–126)
Author Location p6 (2233–)
Epitope KELYPLTSL
Immunogen HIV-1 infection
Species (MHC) human (B*4001)
Country Australia
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, HLA associated polymorphism
References Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore et al., Science 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- The mutational patterns in the second position in the HLA B*4001 epitope KELYPLTSL are correlated with the host carrying HLA B*4001.

HXB2 Location p2p7p1p6 (118–126)
Author Location Gag p6 (481–489)
Epitope KELYPLTSL
Epitope name KL9
Immunogen HIV-1 infection
Species (MHC) human (B40)
Donor MHC A*02, A*32, B*07, B*40, Cw*03, Cw*07
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, acute/early infection, viral fitness and reversion
References Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- A B40+ mother carried the KEmYPLaSL variant of the epitope and transmitted it to her B40- infant. The variant form continued to dominate the infant's sequences at months 3 and 15.

HXB2 Location p2p7p1p6 (118–126)
Author Location p15
Epitope KELYPLTSL
Epitope name B40-KL9(p15)
Immunogen HIV-1 infection
Species (MHC) human (B40)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location p2p7p1p6 (118–126)
Author Location p15 (118–126 SF2)
Epitope KELYPLTSL
Epitope name p15-24
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B60)
Keywords immunodominance, cross-presentation by different HLA
References Yu *et al.* 2002b

- 26/57 HIV-1 infected subjects displayed Gag p15-specific CD8+ T-cell IFNgamma responses were measured by Elispot and intracellular staining. The immunodominant regions targeted by CD8+ T cells were mapped to three functional domains: the zinc finger structures, the protease cleavage site p7/p1, and to the Vpr binding site in p6.
- p15 contributed on average 17% of the total Gag response (rage 0-100%).
- 3 optimal CTL epitopes were mapped within p15: KELYPLTSL, CRAPRKKGC, and FLGKIWPSYK.
- Four patients who were HLA-B60+ recognized KELYPLTSL.
- The binding motif for B60 is C-term Leu and 2nd position Glu.
- Four patients who did not carry HLA-B60 also recognized the 15 amino acid long peptide carrying KELYPLTSL, suggesting other epitopes in this immediate region can be presented by other HLA class I molecules.

HXB2 Location p2p7p1p6 (118–126)
Author Location p2p7p1p6
Epitope KELYPLTSL
Epitope name KL9(p2p7p1p6)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.

- Author defined epitope KELYPLASL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide as part of peptides QKQEPIDKELYPLASLK and KELYPLASLKSLFGNDPS. This epitope differs from the previously described HLA-B40-restricted epitope, KELYPLTSL, at 1 residue, KELYPLaSL.
- 5 of the 20 HLA-B40 carriers responded to KELYPLaSL-containing peptide #65 with average magnitude of CTL response of 462 SFC/million PBMC (author communication and Fig.1).

HXB2 Location p2p7p1p6 (118–135)
Author Location Gag
Epitope KELYPLASLKSLFGNDPS
Epitope name GAG-66
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, kElyPLaSLKSLFGnDPs differs from the consensus C sequence rEPLtSLKSLFGsDPl at 6 amino acid positions, i.e. by 33.3%.

HXB2 Location p2p7p1p6 (118–137)
Author Location Gag
Epitope KEMYPLASLRSLFGNDPSSQ
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Novel unmapped epitope.
- An S->L change was observed over time: KEMYPLASLRSLFGNDPlSQ

HXB2 Location p2p7p1p6 (120–129)
Author Location p2p7p1p6
Epitope LYPLASLRSL
Subtype D
Immunogen HIV-1 infection
Species (MHC) human (A24)
Donor MHC A23, A24, B35, B58, Cw4, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

HXB2 Location p2p7p1p6 (121–129)
Author Location p15
Epitope YPLASLRSL
Subtype D
Immunogen HIV-1 infection
Species (MHC) human (B53)
Donor MHC A23, A34, B44, B53, Cw4, Cw6
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.

CTL CD8+

- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

HXB2 Location p2p7p1p6 (121–129)
Author Location p2p7p1p6 (36–44)
Epitope YPLASLRSL
Epitope name B7-YL9 Gag
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), escape, early treatment, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The second infecting strain had the variant ypPlaslrsl. The CTL response was zero at all timepoints for the first variant. Insertion of a proline at position 3 (first variant) resulted in prevention of initial presentation of this region to the immune system.

HXB2 Location p2p7p1p6 (121–130)
Author Location Gag (545–)
Epitope YPLASLRSLF
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (B*0702)
Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008

- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location p2p7p1p6 (121–130)
Author Location p2p7p1p6
Epitope YPLASLRSLF
Subtype D
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC A23, A24, B35, B58, Cw4, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

HXB2 Location p2p7p1p6 (121–130)
Author Location Gag (484–493)
Epitope YPLTSLRSLF
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Jin *et al.* 2000b

- This B7 epitope is one of three subdominant CTL responses detected in a long-term non-progressor.
- A dominant B7 epitope was defined using conventional methods, and three additional sub-dominant HLA B7 epitopes were defined by first using a non-anchor based strategy, EpiMatrix, to identify 2078 possible epitopes in the autologous HIV-1, followed by B7 anchor residue prediction to narrow the set to 55 peptides for experimental testing.

HXB2 Location p2p7p1p6 (121–130)
Author Location Gag
Epitope YPLTSLRSLF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A*0301, A*2301, B*0702, B*1503
Country United States
Keywords escape, acute/early infection
References Bernardin *et al.* 2005

- Full HIV genomes from nine individuals were analyzed for mutations prior to seroconversion and 7 to 28 days later. It was found that the influence of the host's HLA type was reflected within weeks of infection; a statistically significant number of early nonsynonymous mutations were observed within previously reported CTL epitopes.
- T to A mutation was observed in position 4, and R to K in position 7.

HXB2 Location p2p7p1p6 (121–130)
Author Location Gag
Epitope YPLASLRSLF
Epitope name Gag545
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design

References Wilson *et al.* 2008
- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- YPLASLRSLF is a Gag epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location p2p7p1p6 (121–130)
Author Location Gag
Epitope YPLASLRSLF
Epitope name Gag545
Subtype B
Immunogen HIV-1 infection
Species (MHC) human, mouse (B7 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003
- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope YPLASLRSLF of the HLA-B7 supertype bound most strongly to HLA-B*5101, -B*5301 and also to -B*5301, -B*3501, -B*0702. It was conserved 32% in subtype B. 2/16 HLA-B7 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Gag545.

HXB2 Location p2p7p1p6 (122–132)
Author Location Gag (486–496)
Epitope PLTSLKSLFGS
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005
- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 3/25 patients responded to this peptide (IFN-γ CD8+ response). An IL-2 response was not detectable.

HXB2 Location p2p7p1p6 (123–130)
Author Location p2p7p1p6
Epitope LASLRSLF
Subtype D
Immunogen HIV-1 infection
Species (MHC) human (B58)
Donor MHC A23, A24, B35, B58, Cw4, Cw7
Country Democratic Republic of the Congo
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Geels *et al.* 2005
- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

II-B-6 Gag CTL/CD8+ epitopes

HXB2 Location Gag
Author Location
Epitope
Immunogen computer prediction
Species (MHC) (A*0201, B*3501)
Keywords subtype comparisons, computational epitope prediction
References Schönbach *et al.* 2002
- Computational methods (artificial neural networks, hidden Markov models, binding matrices based on HLA association rates) were used to identify HLA-A*0201 and HLA-B*3501 HIV T-cell epitope candidates from 533 Gag, Env and Pol sequences of which 374 were derived from HIV-1, 97 were derived from HIV-2 and 62 from SIV. Comparisons to known epitopes and between clades were made.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen HIV-1 infection
Species (MHC) human (A*0201, Cw*08)
References Shacklett *et al.* 2000
- HIV-1 specific, MHC class I-restricted CTL killing was detected in duodenal and rectal gut associated lymphoid tissue (GALT) sites from three infected individuals – the distribution of class I restricted CTL was different in the peripheral blood samples and GALT samples.

HXB2 Location Gag
Author Location Gag
Epitope
Epitope name Gag28-9
Immunogen HIV-1 infection

Species (MHC) human (A*2402)
Country Japan
Assay type Tetramer binding
Keywords supervised treatment interruptions (STI)
References Tanuma *et al.* 2008

- A longitudinal study of 3 immunodominant epitopes in early-ART patients given 5 STI series was undertaken to determine escape mechanisms during STI. Since all 12 patients' Nef138-10, RYPLTFGWCF, escaped to its Y2F variant RfPLTFG-WCF, it is suggested that mutations in the immunodominant CTL epitope may be one mechanism of escape, limiting immune control.
- Frequency of epitope Gag28-9 did not correlate with plasma viral load.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement
References Wu *et al.* 2005

- A flow cytometric assay for validation of HIV-1 gag- or pol-specific- CD8/HLA-A2 T-cells was shown to be sensitive and specific, being able to detect HIV-1 CTL at the single T-cell level. An inverse correlation between HIV plasma viremia and gag- and pol-specific-CD8/HLA-A2 T-cells was observed.

HXB2 Location Gag
Author Location Gag
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Keywords rate of progression
References Jin *et al.* 2002

- Patients with HLA-B*35 variants B*3502, B*3503, B*3504, and B*5301 tend to proceed to AIDS more quickly than those with B*3501.
- Of 32 patients with HLA-B*35 alleles CD8+ CTL responses were quantified using an intracellular cytokine staining assay – 75% had responses to Pol, 69% to Gag, 50% to Nef, and 41% to Env.
- The overall magnitude of CTL responses did not differ between those bearing B*3501 and the others. A higher percentage of Gag responses was observed in those that had lower RNA levels that carried B*3501, and there was a negative association with viral load and CTL activity. The data is consistent with higher levels of CTL responses contributing to protection in B*3501 individuals, but not in B*3502, B*3503, B*3504, and B*5301 individuals.

HXB2 Location Gag
Author Location Gag (54–52)
Epitope
Epitope name pSG9
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country Canada, South Africa
Assay type Other
Keywords escape, compensatory mutation
References Carlson *et al.* 2008

- A statistical model, the phylogenetic dependency network (PDN), was developed to differentiate the confounding effects of codon variation, linkage disequilibrium of HLA alleles and HIV phylogeny from HLA-associated evolution including HIV selection by HLA-pressure and codon evolution.
- This approach was applied to 2 cohorts of 1144 Gag sequences from HIV-infected individuals, generating associations between HIV codons themselves and codons with HLA alleles. Results generated predicted escapes that confirmed that escape kinetics and compensating mutations are consistent across clades. General patterns of covariation and CTL adaptation were determined. Some clade-based differences were identified.
- A putative epitope, pSG9, , shows escape that is correlated with escape at other epitopes, TW10, IW9 and QW9.

HXB2 Location Gag
Author Location
Epitope
Subtype A, B, C
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost, canarypox prime with gp160 boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* Gag, gp120, gp41, Nef, Pol
Species (MHC) human (B60)
Keywords subtype comparisons, vaccine-specific epitope characteristics
References Ferrari *et al.* 2001

- Different HIV strains were used for different regions: gp41 LAI, Gag LAI, gp120 MN, gp120 SF2
- HLA-B60 responses dominated the responses against an Gag vaccine in an individual (022G0Z) who was HLA A1, A11, B8, B60. The strongest response was against the MN peptide 107-136. Low level Gag responses were observed against B8 and A11 epitopes, no response was observed against A1 epitopes.
- Vaccinee 202T7 (HLA A2, B27, C25) made the strongest response to an epitope at positions 131-140 of Gag. The response was highly cross-reactive with D clade Gag expressed from vaccinia, less so with C, and only minimally cross-reactive with A and CRF01.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* p17/p24 Gag
Species (MHC) mouse (H-2^b, H-2^d, H-2^k)
References Iroegbu *et al.* 2000

- The p24 sequence is more conserved than is p17 within patient, and nonsynonymous substitutions are spread evenly throughout its coding regions, not concentrated in CTL epitopes.
- Minor changes in p24 did not alter the immunogenicity in H-2b,d, or k mice, while changes in p17 (92% similarity) did alter immunogenicity.

HXB2 Location Gag
Author Location Gag (SF2)
Epitope
Immunogen vaccine
Vector/Type: DNA, vaccinia *Strain:* B clade SF2 *HIV component:* Gag, Pol
Species (MHC) mouse (H-2^{bxd})
References Otten *et al.* 2000

- CB6F1 were primed with gag DNA by im injection and challenged with vaccinia expressing Gag/Pol (rVVgag-pol)
- Gag-specific CTL responses were detected by IFNgamma secretion in the spleen, independent of the route (intraperitoneal, intranasal or intrarectal) of rVV gag-pol challenge.
- The gag DNA vaccine induced CTL responses in 4/4 monkeys 2 weeks post immunization, but antibody responses were detected in only 1/4 monkeys after 3 immunizations.
- CTL cross-reactivity against Gag sequences 1-80, 254-323, and 421-496 was observed, suggesting multiple CTL epitope recognition.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Gag
Species (MHC) mouse (H-2^{d})
References Qiu *et al.* 2000

- Mice were injected with plasmid DNA at 0, 2 and 4 weeks and lymphocyte proliferation was measured after 6 weeks with recombinant p24 protein.
- Secreted HIV-1 Gag expression vectors generated a stronger response than standard Gag or cytoplasmic Gag expression vectors.
- IFN-gamma levels were increased compared to an undetectable IL-4 response.
- CTL levels were also increased in secreted Gag expression vaccination studies.

HXB2 Location Gag
Author Location Gag (SF2)
Epitope
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade SF2 *HIV component:* Gag, Protease
Species (MHC) macaque, mouse (H-2^{d})
References zur Megede *et al.* 2000

- Sequence-modified Rev-independent gag and gag-protease gene constructs lead to increased expression levels and elevated CTL and antibody immunogenicity in BALB/c and CB6F1 mice.
- A CTL response in mice could be detected after a single immunization with codon-optimized gag, using 2 ng of plasmid; wild type gag required 200 ng to detect a response.
- Recognition of 3 different Gag peptide pools was observed, indicating a polyclonal CTL response.
- Significant gag-specific CTL responses were detected in 4/4 rhesus monkeys, in contrast to 1/4 using wildtype gag.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen vaccine
Vector/Type: coxsackievirus *HIV component:* p24 Gag
Species (MHC) mouse (H-2^{d})
References Halim *et al.* 2000

- An avirulent recombinant coxsackievirus (CB4-P) construct was generated that can express p24 Gag sequences – CB4-P is attenuated even in immunodeficient mice and T help responses can be elicited from peptides embedded in a surface loop of the VP1 capsid.
- This paper describes the vaccine strategy and generation of constructs, and employs amino-terminal fusion of Gag sequences to the viral polyprotein with subsequent cleavage to elicit CTL responses via MHC class I presentation in BALB/c mice.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade HXB2, B clade NL43 *HIV component:* Gag, Pol
Species (MHC) mouse (H-2^{d})
References Huang *et al.* 2001

- Different HIV strains were used for different regions: gag HXB2, pol NL43
- Mice were immunized with four humanized DNA constructs: GagPol, that would form a pseudoparticle carrying Gag and Pol, Gag, Pol or a GagPol fusion construct.
- The GagPol pseudoparticle, Gag and GagPol fusion construct all elicited strong anti-Gag CTL, but only the GagPol fusion construct elicited strong anti-Pol CTL.

HXB2 Location Gag
Author Location Gag (HXB)
Epitope
Immunogen vaccine
Vector/Type: Listeria monocytogenes *Strain:* B clade HXB2 *HIV component:* Gag
Species (MHC) mouse (H-2^{b}, H-2^{d})
Keywords Th1
References Mata *et al.* 2001

- BALB/c and C57BL/6 mice were immunized with recombinant Listeria monocytogenes (Lm-Gag) expressing HIV-1 HXB2 Gag and mice were challenged with vaccinia expressing Gag.

CTL CD8+

- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phocytosis and lives in the cytoplasm – secreted L. monocytogenes antigens are processed and presented by both class I and class II pathways.
- CD4+ Th1 T-cells mediated the Gag specific immunological protection in mice immunized with Lm-Gag and challenged with vaccinia-Gag.
- Gag-specific CTL may enhance viral clearance via IFN-gamma secretion, but are not essential for immunity.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen vaccine
Vector/Type: Listeria monocytogenes *Strain:* B clade HXB2 *HIV component:* Gag
Species (MHC) mouse (H-2^b, H-2^d)
Keywords review, Th1
References Mata & Paterson 2000

- BALB/c and C57BL/6 mice were immunized with recombinant Listeria monocytogenes (Lm-Gag) expressing HIV-1 HXB2 Gag and mice were challenged with vaccinia expressing Gag.
- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted L. monocytogenes antigens are processed and presented by both class I and class II pathways.
- This article is a review of L. monocytogenes biology and its potential as a vaccine vector for HIV, comparing to other vector systems, and discussing CD4+ Th1 T-cells mediated Gag specific immunological protection in mice and the Gag CTL response.

HXB2 Location Gag
Author Location Gag (IIIB)
Epitope
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *HIV component:* Gag
Species (MHC) macaque
References Paliard *et al.* 2000

- CTLs primed by HIV-1 p55 gag virus-like particle (VLP) vaccination recognized epitopes in four different 20 amino acid peptides p17/4, p17/8, p24/13 and p14/9.
- Cytotoxic T cell response lasted greater than 8.5 months.

HXB2 Location Gag
Author Location Gag (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression, Th1
References Wasik *et al.* 2000

- HIV+ infants that progressed rapidly to AIDS had lower Th1 responses and decreased production of beta-chemokines and IL-2 relative to other HIV+ infants.
- HIV+ infants had no demonstrable CTL at birth, but Th1 responses accompanied by CTL responses developed in children with slowly progressive disease, and not in rapid progressors.
- CTLp frequencies were determined by limiting dilution using autologous B cells infected with vaccina/HIV constructs.

HXB2 Location Gag
Author Location Gag (LAI)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp41, Protease, V3
Species (MHC) human
References Salmon-Ceron *et al.* 1999

- The vaccine used was a rec canarypox with HIV-1 gp120 MN, tm/gag/protease LAI (vCP205), alone or with p24E-V3 MN synthetic peptide (CLTB-36))
- Twenty HIV negative subjects were vaccinated in phase I trial with combinations of vCP205 and CLTB-36.
- Immunization with vCP205 induced HIV-1-specific ABs to gp120, V3, and p24 antigens, and CTL immune responses against vCP205 were detected after the fourth immunization in 33% of the subjects against Env, Gag and Pol, but the CLTB-36 peptide did not produce AB or CTL immune responses against p24 or gp160.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *HIV component:* p17 Gag, p24 Gag
Species (MHC) human
References Klein *et al.* 1997

- Immunization of HIV+ people with an HIV-1 p17/p24 Ty virus-like particle (p24-VLP) resulted in a marginal, short-lived increased proliferative response to p24 and p17 and a transient elevation in viral load.
- Two of four subjects that received 500 or 1000 µg of p24-VLP had an increase in gag-specific CTL.

HXB2 Location Gag
Author Location p24 (SF2)
Epitope
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade SF2 *HIV component:* gp120, p24 Gag *Adjuvant:* MF59, PLG
Species (MHC) mouse, baboon
References O'Hagan *et al.* 2000

- PLG (Polylactide co-glycolide polymer) microparticles administered in MF59 emulsion induced gp120 Ab responses and CTL immune responses against p24 gag.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Lubaki *et al.* 1999

- Three strategies were used to analyze CTL activity: area under the net HIV-specific lysis curve (ACU), linear regression (LR) of net specific lysis, and the standard method, lytic units (LU20)
- A correlation between low HIV plasma viral load and increased levels of HIV-specific Gag and Nef CTL activity was observed using ACU and LR, but not LU20.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Kalams *et al.* 1999a

- The presence of HIV-1 p24-specific proliferative responses was positively correlated with Gag-specific memory CTL and negatively correlated with viral load in untreated subjects.
- Gag proliferative responses were the most readily detected – Gag CTL responses were the only responses with a significant correlation with Gag stimulated help, although there was a positive trend with Nef, Env and RT.

HXB2 Location Gag
Author Location p55 (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Greenough *et al.* 1999

- 7/128 HIV-1 infected hemophiliac were identified as long-term non-progressors (LTNPs) and were monitored for viral and host immune parameters over 15 years – LTNPs maintained a low viral load, high frequencies of CTL precursors directed against Gag antigen and low levels of HIV-specific effector CTL activity – effector cell activity suggests low level ongoing viral replication.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Trickett *et al.* 1998

- Twelve HIV-1 infected patients were re-infused with their own lymphocytes, cryopreserved from an earlier time point in the infection.
- Improvement in CD4+ and CD8+ T cells was seen in 7/12, and an increase in the CTL response to Gag was seen in one patient.

HXB2 Location Gag
Author Location Gag (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Betts *et al.* 1999

- This study demonstrated an inverse correlation between HIV Type I plasma viral load and CTL activity directed against HIV-1 Pol, and stronger combined effects of Pol- and Env-specific CTL, in long-term survivors (LTS) of HIV-1 infection.

HXB2 Location Gag
Author Location Gag (LAI)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Legrand *et al.* 1997

- Seventeen recently infected patients were tested for CTL response to HIV proteins Env, Gag, Pol, Rev, Nef, Vif and Tat.
- An early response (within a month following PI) was noted in 87% of the subjects to Gag, 75% to Env, and 50% to Nef.
- Early responses to Pol, Rev, Vif and Tat were rare.

HXB2 Location Gag
Author Location Gag (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Betts *et al.* 1997

- 6/8 individuals from Zambia infected with C clade virus had CTL that were able to make response to B clade HIV-1 IIIB vaccinia-expressed Gag, Pol and Env proteins.
- A vigorous cross-clade response was not limited to a particular protein, and the level of recognition of different proteins varied among the six patients.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References De Maria *et al.* 1997

- CD3+ cells that also carry a natural killer cell receptor (NKR+) can exhibit down regulation of T cell function.
- Anti-NKR IgM MAb masked this inhibitory function and increased HIV-1 specific CTL activity in phytohemagglutinin-activated PBMC cultured in the presence of IL-2 from 3/5 patients, and in one other case anti-NKR MAb brought HIV-1 specific CTL activity to detectable levels.

HXB2 Location Gag
Author Location Gag (LAI)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* Gag, gp120, gp41, Protease
Species (MHC) human
References Belshe *et al.* 1998

- The live canarypox vaccine ALVAC-HIV(vCP205) carrying MN gp120, LAI gp41, Gag and Protease, and boosted with SF-2 rpg120, was given to HIV-1 seronegative volunteers – HIV-specific Env or Gag CD8+ CTL were detected in 64% of the volunteers.

HXB2 Location Gag
Author Location Gag (LAI)

CTL CD8+

Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Buseyne *et al.* 1998a

- This study showed a correlation between strong CTL memory and breadth of response in 7-12 month old infants, and remaining AIDS-free for the first year of life, higher absolute CD4 and CD8 cells, and lower viral load.

HXB2 Location Gag
Author Location Gag (LAI)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Buseyne *et al.* 1998b

- In infants with positive CTL responses, most responses showed cross-clade reactivity with somewhat diminished recognition of epitopes from different subtypes.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen HIV-1 exposed seronegative
Species (MHC) human
References Goh *et al.* 1999

- 13/37 exposed uninfected individuals with repeated high-risk sexual exposure had HIV-1 specific CTL against Env, Gag, Pol, or a combination of proteins – CTL activity was correlated with a CCR5 wildtype genotype.
- In this group, the highest CTLp frequencies were directed at Gag, but the most common response was to Env and four individuals had responses to multiple HIV-1 proteins.

HXB2 Location Gag
Author Location Gag (LAI)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: canarypox *HIV component:* Gag, gp120, gp41, Nef, Protease, RT
Species (MHC) human
References Evans *et al.* 1999

- A Canarypox vaccine expressing gp120, gp41, Gag, Protease, Nef and Pol CTL epitopes gave rise to CTL that could be detected in 61% of the volunteers – responses to Gag, Env, Nef and Pol were detected 3-6 months after the last vaccination.

HXB2 Location Gag
Author Location p17
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing
References Kuiken *et al.* 1999

- A correlation between conserved regions of p17 or Nef and CTL epitope density was noted. The authors suggest that this may be due to a biological reason such as epitope processing, or may be an artifact of experimental strategy for epitope definition, such that conserved epitopes would tend to be identified because they are more likely to be cross-reactive with the test reagents.
- In contrast to p17 and Nef, p24 is a more conserved protein, and known epitopes are evenly distributed across p24.

HXB2 Location Gag
Author Location Gag (LAI)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost *Strain:* B clade LAI *HIV component:* Env, Gag
Species (MHC) macaque
Keywords Th1, Th2
References Kent *et al.* 1998

- Priming with an HIV-DNA vaccine and boosting with a vaccinia construct induced greater levels of HIV T cell immunity than either vaccine alone.
- The proliferative response to Env and Gag after the DNA vaccination had a mean SI of 1.5-4, but after boosting with rHIV-fowlpox virus, there was a 6-17 fold increase in the mean SI for HIV Gag and Env. The T help response happened despite a fall in antibody titers, suggesting that the Th response was primarily Th1, not Th2. The CTL response was also enhanced.

HXB2 Location Gag
Author Location Gag/Pol (LAI, MN)
Epitope
Immunogen vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Protease
Species (MHC) human
References Salmon-Ceron *et al.* 1999

- A live attenuated canarypox vector expressing MN gp120 and LAI gp41/gag/protease could induce CTL and a lymphoproliferative response in healthy, uninfected volunteers.

HXB2 Location Gag
Author Location Gag/Pol (MN)
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Env, Gag, Pol *Adjuvant:* CD80, CD86
Species (MHC) chimpanzee
References Kim *et al.* 1998

- The study explores the use of co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses.

HXB2 Location Gag
Author Location Gag (BRU)

Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Aladdin *et al.* 1999

- *In vitro* measurements of CTL-activity by Cr release assay in bulk culture showed no correlation between CTL-activity (gp120, Gag, Pol and Nef) and disease progression as measured by viral load, CD4 and time to death.

HXB2 Location Gag
Author Location p24 (C consensus)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons, immunodominance
References Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a HIV+ South African – this epitope did not fall within the five most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLK (p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen vaccine
Vector/Type: DNA *Strain:* ZF1 *HIV component:* complete genome
Species (MHC) macaque
References Akahata *et al.* 2000

- Rhesus macaques were vaccinated by i.m. injection with naked plasmid DNA carrying an HIV-1 complete genome vaccine, strain ZF1, with a mutated zinc finger in the nucleocapsid to prevent packaging.
- Env and Gag specific CTL but no antibody responses were induced in 2/4 vaccinated monkeys (MM145 and MM153)
- 2/4 monkeys (MM146 and MM143) produced antibodies against p24 and/or gp160, but no CTL response was detected.
- PBMC from all vaccinated monkeys produced IFN-gamma, in response to HIV-1 gp160, indicating a Th response – this response was 5 times higher in MM145, the animal with the strongest CTL response.
- 4 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM145 and MM153 (with a homologous Env) decreased to near or below the detection limit.
- 6-8 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM146 and MM143 decreased near or below the detection limit.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Salerno-Goncalves *et al.* 2000

- A general test of CD8 anti-viral activity was developed based on proviral load of coculture of autologous CD8+ cells with CD4+ cells after homogeneous superinfection with NSI virus.
- Significantly decreased the CD4+ T-cell proviral loads were found in 12 HIV+ slow progressors relative to 10 rapid progressors.
- Significant CD8+ mediated cytotoxicity directed against autologous cells infected with vaccinia carrying the HIV-1 gag gene was observed in slow progressors in contrast to rapid progressors, but no correlation was found between plasma viral load in 22/22 asymptomatic HIV infected individuals.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Young *et al.* 2001

- Addition of recombinant rec human IL12 (rhIL12) to cultures increased HIV-specific lysis of HIV-Gag, Pol and gp120 vaccinia expressed antigens (11/15 tested increased lysis by > 5%) if the culture was derived from HIV+ individuals who had CD4 cells/ul > 500.
- 2/10 individuals with <200 CD4 cells/ul, and 3/10 individuals with 200-500 CD4cells/ul, had an increase of >5% upon treatment of the culture with rhIL12, so a few individuals in late stage disease had CD8 cells that maintained responsiveness to rhIL12.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) mouse
References de Quiros *et al.* 2000

- CB-17 SCID-Hu mice engrafted with peripheral blood mononuclear cells of four long-term nonprogressors (viral load < 50 copies/ml) displayed resistance to challenge with HIV-1 SF162, mediated by CD8+ T-cells and associated with proliferation in response to p24 – these patients did not have a higher level of HIV-1 specific immunity *in vitro*, so the mechanism is unknown.

HXB2 Location Gag
Author Location Gag (subtype A, B, D)
Epitope
Subtype A, B, D
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Cao *et al.* 2000

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in HIV infected Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, RT or Nef from HIV-1 clades A, B, and D.
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References White *et al.* 2001

- HIV-specific CTL activity was detected in the female reproductive tract of only 1/3 HIV-infected women who underwent a hysterectomy, although CTL could be identified in the PBMC of all three women.

HXB2 Location Gag
Author Location Gag (HXB2)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Chun *et al.* 2001

- Suppression of viral replication in the resting CD4+ T-cell reservoir by autologous CD8+ T-cells via CD4+/CD8+ cell contacts was observed in long-term nonprogressors and patients undergoing antiretroviral treatment, but this activity appears to be independent of Gag-specific CTL activity.

HXB2 Location Gag
Author Location Gag (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Jin *et al.* 2000a

- The CTL precursor level (CTLp) was measured in long term non-progressors (LTNP) with low viral load using limiting dilution analysis and measuring CTL against Env Gag and Pol expressed in vaccinia in autologous targets.
- LTNPs have high memory CTL numbers and low viral load.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen HIV-1 exposed seronegative
Species (MHC) human
Keywords review, HIV exposed persistently seronegative (HEPS)
References Rowland-Jones *et al.* 2001

- This is a review that summarizes observations about HIV-specific CTL found in the HIV-1 exposed persistently seronegative (HEPS) population.
- The CTL responses assayed by ELISPOT and by CTL precursor frequencies by limiting dilution analysis indicate that CTL in HEPS individuals tend to be of a lower magnitude than in chronic HIV-1 infections – the responses in HEPS cases are below the level of detection by tetramer assays.
- CD8+ CTL responses tend to be detectable in HEPS subjects only if they are recently exposed, and the response diminishes if exposure is reduced – it is not clear if there is a stable memory population in HEPS cases.
- CD8+ CTL responses in the HEPS population are associated with HIV-1 specific CD4+ T cell responses, assayed by proliferation assays, IL-2 secretion, and ELISPOT, and the authors consider the possibility that HIV-1-specific T-help responses improve the "quality" of the CD8+ response in HEPS individuals relative to HIV-1 infected individuals, who tend to have a poor HIV-1-specific T-help response.
- HIV-1 specific CD8+ CTL responses in HIV-1 infected individuals show reduced levels of perforin, and the T cells may not mature properly, and although similar studies have not been conducted in HEPS individuals this is considered as a possible difference in the CTL immune response in HEPS and HIV-1 infected people.

HXB2 Location Gag
Author Location
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA *HIV component:* Env, Gag, Pol
Species (MHC) mouse
Keywords review, vaccine-specific epitope characteristics
References Nabel 2002

- Using DNA that had humanized codon usage, CTL responses to DNA vaccines containing either Gag, Pol, Gag-Pol fusion protein, or Gag-Pol pseudoparticles suggested that the greatest breadth and most potent response was to the Gag-Pol fusion protein. The Gag-Pol fusion lacks the Gag precursor protein required for viral assemble, so does not form releaseable particles; the author speculates that longer retention of the Gag-Pol protein with in the cell may enhance antigen presentation.

HXB2 Location Gag
Author Location
Epitope
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission
References De Maria *et al.* 1994; Kuhn *et al.* 2002

- 6/24 HIV uninfected infants (ages 15-50 months) born to HIV+ mothers had HIV-1 specific CTL responses to vaccinia-expressed Nef, Gag/Pol, Env.
- Reviewed in Kuhn *et al.* [2002].

HXB2 Location Gag
Author Location

CTL CD8+

Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission
References Aldhous *et al.* 1994; Kuhn *et al.* 2002

- Six of nine HIV vertically infected infants had HIV-1 specific CTL responses to vaccinia expressed Tat (4/6), Pol (6/6), Env (1/6), or Gag (1/6), but not all responses were detected at all time points.
- Two of eleven babies that were not infected though born to HIV+ mothers had detectable responses to Tat (1/2), Pol (2/2), Gag (1/2).
- Reviewed in Kuhn *et al.* [2002].

HXB2 Location Gag
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission, rate of progression
References Kuhn *et al.* 2002; Wasik *et al.* 1999

- In HIV-infected infants HIV-specific, CTL responses were not detectable in icord blood or in PBMC collected shortly after birth and were absent or remained very low in 3 infants with a rapidly progressive disease. For those who progressed more slowly, the HIV-specific CTL activity varied.
- The two infants with high levels of Env peptide-stimulated IL-2 responses had the highest CTLp frequencies.
- Stronger responses were detected after initiation of the antiretroviral therapy.
- Two babies that were not infected though born to HIV+ mothers had detectable though low HIV-specific CTLp responses to Env (1/2), Pol (2/2), Gag (1/2) cord blood and transiently in PBMC after birth.
- Reviewed in Kuhn *et al.* [2002].

HXB2 Location Gag
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission
References Kuhn *et al.* 2002; McFarland *et al.* 1994

- Only 9% of HIV+ infants had HIV-specific CTL against Env or Gag in unstimulated PBMC. After CD3 stimulation of PBMC, Gag and Env specific CTL were found in PBMC from 91% and 78% of HIV-infected children, respectively, with high precursor frequencies.
- Reviewed in Kuhn *et al.* [2002].

HXB2 Location Gag
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed. p17 is much more variable than p24.

HXB2 Location Gag
Author Location p24 (HXB)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, vaccine-specific epitope characteristics
References Lu *et al.* 2000a

- Bacillus anthrax lethal toxin (LFn)-HIV fusion proteins are candidate HIV vaccines that are safe in mice, and LFn-V3 region fusion proteins induce CD8 T cells in BALBc mice. LFn causes exogenous protein to be taken up and processed in a class I pathway. Expressed proteins from Gag p24 and Nef fragments cloned into the LFn expression plasmid stimulate gag-specific CD4 proliferation and CTL responses in HIV-infected donor PBMCs *in vitro*.

HXB2 Location Gag
Author Location (HXB2)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Edwards *et al.* 2002

- 96% (26/27) chronically infected HIV-1 infected patients elicited gamma-IFN CD8+ T-cell responses against Gag.
- Nef and/or Pol CTL responses were detected in 86% of the subjects.
- The magnitude and breadth of Gag and p24 T-cell responses correlated with absolute CD4 counts, and inversely correlated with viral load.
- Pol and Int CTL responses correlated positively with absolute CD4+ T-cell count.
- Nef and Env responses did not correlate with either CD4 counts or viral load.

HXB2 Location Gag
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, dendritic cells
References Larsson *et al.* 2002b

CTL CD8+

- Autologous mature dendritic cells with rec vaccinia expressing Gag, Pol, Nef and Env could amplify CD8+ T-cell Elispot responses 4-38 fold in five HIV+ patients on successful HAART treatment, relative to autologous monocytes. Some weak responses could only be detected using mature dendritic cells as APCs, and this approach could be useful for detection of low frequency memory cells.

HXB2 Location Gag
Author Location (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords immunotherapy
References Trickett *et al.* 2002

- Conditions were optimized for ex-vivo expansion of CD8+ and CD4+ T-cells with the goal of functional T-cell production for autologous immunotherapy. 10,000-fold expansions were obtained in 14 days with optimized concentrations of IL-2, anti-CD3 and anti-CD28 coated microspheres, and decreasing amounts of serum over the first 8 days.

HXB2 Location Gag
Author Location (IIIB)
Epitope
Subtype B
Immunogen HIV-1 and HCV co-infection
Species (MHC) human
Keywords rate of progression
References Lauer *et al.* 2002

- HIV-1 and HCV immune responses were studied in 22 individuals who were co-infected with HIV-1 and hepatitis C virus (HCV). IFNgamma production was measured in an Elispot assay of CD8+ T-cells using targets expressing either Gag, RT, Env and Nef in a vaccinia construct, or one of seven HCV proteins.
- All 22 patients targeted at least one protein. 20/22 patients recognized RT, 17/22 patients recognized Gag, 13/22 subjects recognized Env and 11/22 patients recognized Nef. Robust CTL activity was independent of disease progression or viral load.
- Despite high HCV viral loads, very few HCV CD8+ T-cell Elispot responses were detected. In a control HCV infected person who did not have HIV-1, strong anti-HCV responses were mounted.
- HIV-specific CD4 proliferative responses were detected in 9/17 coinfected patients, but no HCV responses were detected.

HXB2 Location Gag
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords responses in children
References Luzuriaga *et al.* 1995

- 2/3 infants infected in utero had detectable HIV-1 Gag and Env specific CTL responses, one by 4 months, one by 11 months of age. Levels of the responses varied at different time point. Pol responses were not detected.
- 2/4 infants infected intrapartum had detectable responses, one note until 11 months, one not until 42 months.
- HIV-specific CTL were not detected in ten HIV- infants that were born to HIV+ mothers.

HXB2 Location Gag
Author Location
Epitope
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN *HIV component:* Env, Gag
Species (MHC) human
References Gupta *et al.* 2002

- Different HIV strains were used for different regions: Gag, LAI; gp120, MN; and gp41, LAI
- A safety and immunogeniticity study of a vaccine dosing schedule was studied in a trial conducted in high and low risk study subjects. There was a 76% cumulative probability of detecting a Gag or Env CTL response by day 728.

HXB2 Location Gag
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, responses in children
References Scott *et al.* 2001

- CTL responses before and after initiation of ART were studied in 13 HIV-1 vertically infected infants <6 months of age, and 4 that were >6 months of age.
- Before ART 2/13 infants <6 months of age showed IFNgamma Elispot CD8+ T-cell responses, one to Nef and one to Env and Nef, and these responses became undetectable after successful therapy– 3 infants were coinfected with CMV and all 3 had CMV-specific CD8+ T-cell responses.
- One older infant, at 23 months, had CTL responses against all for proteins tested, Gag, Pol, Nef and Env, and had the lowest plasma viremia of the study group. 3/4 infants older than 6 months of age responded to either Nef or Pol.
- Administration of ART over 48 weeks broadened the HIV-1-specific CTL response in 2/4 of the older children that were incomplete responders.

HXB2 Location Gag
Author Location (IIIB, MN)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords dendritic cells
References Larsson *et al.* 2002a

- Dendritic cells acquire and present HIV-1 antigens derived from dead, apoptotic cells or from non-infectious, fusion-competent HIV-1 virions, and these DC cells could stimulate CD4+ and CD8+ T-cells resulting in IFNgamma production in an Elispot assay. Both HLA Class I and class II molecules were used for presentation. This may be an important aspect of the initial immune response to HIV-1 infection of CD4+ cells in the mucosal subepithelia.

HXB2 Location Gag
Author Location (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, supervised treatment interruptions (STI)
References Ortiz *et al.* 2001

- Immune responses in eight chronically HIV-1 infected patients undergoing HAART therapy structured treatment interruptions (STI) were studied. STI boosted HIV-1 specific CTL responses and elevated CTL responses were maintained up to 22 weeks after the last treatment interruption, but viral load rebound to pretreatment levels and CD4 T-cell count decline was observed. CD8 responses in PBMC were measured by cytokine flow cytometry with gp160, Gag p55, RT-Pol and Nef expressed in vaccinia.

HXB2 Location Gag
Author Location Gag
Epitope
Subtype AG, B
Immunogen
Species (MHC) human
References

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen
Species (MHC) human
References

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Assay type Intracellular cytokine staining
Keywords HAART, ART, computational epitope prediction, supervised treatment interruptions (STI)
References Amicosante *et al.* 2002

- A new assay was developed to detect CTL responses to HIV using 28 pooled 15-mer peptides from conserved regions in Gag that were selected to be rich in HLA class I motifs, carrying potential epitopes for more than 90% of HLA class I haplotypes, and to be conserved between subtypes. Some peptide variants were included, expanding the potential for cross-clade recognition. 12 Caucasians, even those on successful HAART, had detectable CTL responses using this assay, and as did five Africans. People with either B subtype or A-G recombinant infections all reacted.
- The Gag peptide ICS assay was more sensitive to picking up CTL reactivity than whole Gag in HAART treated people. Initiation of STI increased the number of IFN-gamma producing CD8+ T-cells detected using the peptide assay.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* Gag *Adjuvant:* block copolymer CRL8623
Species (MHC) macaque
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine-induced epitopes
References Caulfield *et al.* 2002

- Codon-optimized HIV Gag DNA vaccines were given i.m. with or without a nonionic block copolymer(CRL8623) as adjuvant. DNA-CRL8623 fourmulations induced 2-fold higher Elispot responses, shifting the response towards CD8+ T-cells.
- 23 monkeys recognized 25 different epitopes with an average of 2.7 epitopes per monkey, and a minimum of 1 and a maximum of 5 peptides per monkey.
- Responses were detected up to 18 months after vaccination.

HXB2 Location Gag
Author Location Gag
Epitope
Subtype multiple
Immunogen
Species (MHC) human
Assay type Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Currier *et al.* 2003

- CD8-cellular immune responses from 21 HIV-1 infected patients from Kenya infected with subtype A, C, D, and unique recombinants were studied for cross-recognition of Gag, Env, and Nef vaccinia-expressed proteins representing subtypes A-H, including CRF01.
- Both subtype-specific and cross-reactive CTL were observed, with a skewing of responses towards the infecting subtype in the nine subjects with full length sequence available. The magnitude of the responses to Gag were the highest, less to Nef, and still less to Env.
- For Gag, 8/21 subjects responded to at least 7/8 different subtype proteins, 7 had a mixed response, recognizing some subtypes but not others, and 6 responded to only one or none of the different subtype proteins. For Env, 4/19 subjects responded to at least 7/8 subtypes, 8 had a mixed response, and 7 responded to one or none. For Nef, 5/19 subjects responded to at least 7/8 subtypes, 8 had a mixed response, and 6 responded to one or none.

HXB2 Location Gag
Author Location Gag (SF2)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA, protein, virus-like particle (VLP), PLG microparticle *Strain:* B clade SF2 *HIV component:* Gag *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72), LTK63
Species (MHC) macaque
Assay type proliferation, Chromium-release assay
References Otten *et al.* 2003

CTL CD8+

- Immunization strategies for Gag (p55) in macaques were compared. GAG DNA prime with a boost of Gag adsorbed onto PLG (polyactide coglycolide) microparticles with LTK63 as adjuvant gave the strongest CD4+ T cell proliferative, CTL, and antibody responses, compared with Gag protein, or Gag virus-like particles (VLP). GAG DNA was best for inducing CTL responses, Gag-PLG for T-help and antibody; the prime-boost combination gave strong responses for all three.

HXB2 Location Gag
Author Location Gag
Epitope
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, acute/early infection, early-expressed proteins
References Masemola *et al.* 2004a

- Anti-HIV T-cell responses in subtype C HIV-1 infected individuals in the beginning of the infection target multiple protein regions, but the responses are dominated by Nef, making up almost one-third of the total responses; the second most targeted protein was p24. A correlation between Gag specific responses and plasma viral load was also found.
- Neither breadth nor magnitude of CD8+ T-cell responses were correlated with control of virus, however hierarchical preferential targeting of Gag was significantly associated with lower viral loads.

HXB2 Location Gag
Author Location Gag
Epitope
Subtype A
Immunogen vaccine
Vector/Type: DNA, modified vaccinia Ankara (MVA), polyepitope, DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17/p24 Gag
Species (MHC) human
Country United Kingdom
Assay type CD8 T-cell Elispot - IFNγ
Keywords epitope processing, vaccine-induced epitopes, vaccine antigen design
References Mwau *et al.* 2004

- Phase I clinical trial in healthy uninfected individuals was conducted evaluating the immunogenicities of candidate DNA- and MVA-vectored HIV vaccines. Both DNA and MVA vaccines alone and combined (DNA prime-MVA boost) were shown to be safe and induce HIV-specific responses in 78%, 88% and 89% of individuals, respectively. Responses in some individuals could be detected 1 year after vaccination.
- The vaccine in this case was a clade A p17/p24 antigen linked to a polyepitope string of A clade eptiopes. Reponses were tested with peptide pools, and multiple strong responses to the gag proteins and to the poylepitope region were observed. MVA alone did as well as a DNA prime, MVA boost in this study, although the study included small numbers.

HXB2 Location Gag
Author Location Gag
Epitope
Subtype B
Immunogen vaccine
Vector/Type: non-replicating adenovirus *Strain:* B clade *HIV component:* Gag
Species (MHC) mouse
Assay type Intracellular cytokine staining
Keywords Th1, Th2
References Pinto *et al.* 2003

- Heterologous prime boosts with replication-defective adenoviral vectors of different simian serotypes expressing the same transgene product of HIV-1 were shown to be highly efficient in increasing specific CD8+ T-cell responses.

HXB2 Location Gag
Author Location
Epitope
Subtype CRF02_AG
Immunogen vaccine
Vector/Type: virus-like particle (VLP), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* CRF02 IC0928 *HIV component:* Env, Gag, Pol
Species (MHC) macaque
Assay type T-cell Elispot, Intracellular cytokine staining
Keywords vaccine-specific epitope characteristics, vaccine antigen design
References Ellenberger *et al.* 2005

- Macaques were given a Gag-Pol-Env DNA prime followed by an MVA boost. Two DNA constructs were compared, one that resulted in mature VLPs with processed Gag (IC48) and one that had a point mutation in Gag that resulted in immature VLPs (IC1-90). IC48 DNA vaccinations, which produced mature VLPs, yielded 2-fold stronger T-cell responses with greater breadth. CD4 T-cells responded to 3-fold more peptide pools than did CD8.

HXB2 Location Gag
Author Location Gag
Epitope
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Ramduth *et al.* 2005

- The magnitude of HIV-specific CD8 responses in HIV-1 infected individuals from South Africa correlated with the CD4 responses. CD4 responses were much more narrowly focused, with Gag as dominant target, while CD8 responses were equally distributed among Gag, Pol and the regulatory and accessory proteins. An association between the preferential targeting of Gag by CD8 T-cells and viral control was found.

HXB2 Location Gag
Author Location Gag (Consensus B, DU422)
Epitope
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, subtype comparisons, variant cross-recognition or cross-neutralization
References Sabado *et al.* 2005

- CD8 T-cell responses were tested in HIV-1 clade B infected individuals using Gag peptides based on clade B consensus sequence and clade C primary isolate DU422. Peptides from both clades were shown to be of equal sensitivity, with equal numbers of discordantly detected responses. The majority of discordant detection was due to sequence differences between clades. Thus, clade B consensus peptides were not superior in detecting CD8 T-cell responses in clade B-infected individuals.

HXB2 Location Gag
Author Location Gag
Epitope
Subtype A, B, C, M
Immunogen HIV-1 infection
Species (MHC) human
Country United States, Zambia
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References Bansal *et al.* 2006

- This study compared T-cell reactivity to consensus A, B, C, M, ancestral B, M and HXB2 15-mer overlapping peptides in patients from US (subtype B) and Zambia (subtype C).
- Broad cross reactivity was demonstrated. Consensus M, B, ancestral B and HXB2 elicited similar levels of responses in US patients. Consensus C, M and ancestral M elicited similar levels of responses in Zambia patients.

HXB2 Location Gag
Author Location
Epitope
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost, DNA, Other *Strain:* Other *HIV component:* Env, Gag
Species (MHC) mouse
Assay type T-cell Elispot
Keywords vaccine-induced epitopes, vaccine antigen design
References Xu *et al.* 2006

- Sequential cross-clade vaccination strategy was tested in BALB/c and C57BL/6 mice. Vaccines used were C/B recombinant strain (CN54), B strain (RL42), A/E recombinant strain (AE2F).
- Sequential priming and boosting with heterologous HIV immunogens stimulated T cell immunity against conserved epitopes, while a single vaccine derived from one clade or the mixture of multiple vaccines from different clades raised T cells against less conservative or non-conservative epitopes.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type T-cell Elispot
References Wang *et al.* 2006b

- The association between T cell response and CD4+ T cell counts or CD4+ was investigated, using overlapping peptides corresponding to natural B clade and C consensus sequences.
- T cell responses and CD4+ count were correlated for Gag p24 and Gag p17 (B and C clades)and for Pol (C clade). CD4+ counts were higher in patients with Tat and /or Rev T cell response than in patients without Tat and Rev response.

HXB2 Location Gag
Author Location p17
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type T-cell Elispot
References Wang *et al.* 2006b

- The association between T cell response and CD4+ T cell counts or CD4+ was investigated, using overlapping peptides corresponding to natural B clade and C consensus sequences.
- T cell responses and CD4+ count were correlated for Gag p24 and Gag p17 (B and C clades)and for Pol (C clade). CD4+ counts were higher in patients with Tat and /or Rev T cell response than in patients without Tat and Rev response.

HXB2 Location Gag
Author Location Gag (HXB2)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Jiao *et al.* 2006

- CD8+ responses were compared in long-term nonprogressors, asymptomatic progressors and progressors. There were no significant differences among 3 cohorts. However, CD8 responses and CD4 counts in asymptomatic progressors, as well as CD4 responses and viral loads in progressors were inversely correlated. In addition, in 6 long-term nonprogressors, a quick loss of CD4 T-cells was associated with simultaneous vigorous CD8 responses.

HXB2 Location Gag
Author Location
Epitope
Immunogen vaccine

CTL CD8+

Vector/Type: adenovirus type 5 (Ad5) *HIV component:* Env, Gag *Adjuvant:* Cholera toxin (CT)
Species (MHC) macaque
Assay type proliferation, CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords vaccine antigen design
References Mercier *et al.* 2007

- 3 rhesus macaques were given oral immunizations with an enteric-coated mixture of adenoviral vectors expressing HIV-1 gag and a string of conserved env peptides representing broadly cross-reactive CD4+ and CD8+ epitopes. The macaques were boosted intranasally with a mixture of 6 HIV-1 envelope peptides plus cholera toxin adjuvant.
- The immunizations increased cellular immune responses, including antigen-specific IFNgamma-producing CD4+ and CD8+ effector memory T cells in the intestine. After only the oral immunization, there were no EliSpot responses to env peptides or to gag. After the intranasal boost, EliSpot responses against env peptides and against inactivated HIV were markedly increased, but gag responses were not.

HXB2 Location Gag
Author Location Gag (HXB2)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost *Strain:* B clade HXB2 *HIV component:* Gag
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords vaccine-induced epitopes, Th1
References Arruda *et al.* 2006

- p55 Gag cellular trafficking of two chimeras (DNA plasmid with either lysosomal-associated membrane protein LAMP/gag or human dendritic cell CD-LAMP/gag) was studied in mice. Both produces potent T and B cell immune responses, but DC-LAMP produces stronger Th1 response. The chimeras produces also significant responses to cryptic epitopes that were not recognized after immunization with native gag DNA.

HXB2 Location Gag
Author Location
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade
Species (MHC) macaque
Assay type Intracellular cytokine staining
Keywords subtype comparisons, vaccine antigen design
References Smith *et al.* 2005

- Macaques were immunized with a clade B HIV vaccine and tested for responses to pools of clade B and A/G Env and Gag peptides. While CD4 responses were more frequent than CD8 responses, higher cross-clade responses were found for CD8 responses. The authors suggest that the better cross-clade reactivity of the CD8 responses reflects the size difference between CD8 and CD4 epitopes; the smaller CD8 epitopes provide a smaller target for mutation.
- For both B and A/G Env and Gag peptides, 3/5 pools produced CD8+ T cells, suggesting the existence of 2 or 3 cross-reactive CD8 epitopes.

HXB2 Location Gag
Author Location Gag
Epitope
Subtype C
Immunogen vaccine
Vector/Type: DNA prime with virus-like particle (VLP) boost *Strain:* C clade Du422 *HIV component:* Gag
Species (MHC) human, baboon
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords vaccine-induced epitopes, vaccine antigen design
References Chege *et al.* 2008

- A DNA prime/VLP boost vaccine expressing southern African HIV-C was found to produce high magnitude CTL and multifunctional cytokine immune responses in Chacma baboons. A list of Gag peptides that elicited CTL responses is given (Table 1), including some previously known immunogenic peptides reported in HIV-C infected patients.

HXB2 Location Gag
Author Location
Epitope
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country Zambia
Keywords viral fitness and reversion, HLA associated polymorphism
References Goepfert *et al.* 2008

- A cohort of clade C-infected Zambian HIV-1 transmission pairs was studied. Accumulation in the donor of HLA-B restricted mutations in Gag, but not in Nef resulted in a reduced viral load in a recipient upon transmission.
- 20 mutations in Gag and 11 mutations in Nef, within or flanking CTL epitopes, were considered.

II-B-7 Gag/Pol CTL/CD8+ epitopes

HXB2 Location Gag/Pol
Author Location Gag/Pol (ARV-2 SF2)
Epitope
Immunogen vaccine

Vector/Type: fowlpoxvirus *Strain:* B clade ARV-2, B clade SF2 *HIV component:* Gag, Pol *Adjuvant:* IFNγ
Species (MHC) macaque
References Kent *et al.* 2000

- Vaccination with FPV Gag/Pol-IFN-gamma increased HIV-1 specific CTL and T cell proliferative responses to Gag/Pol antigens, respectively, in infected Macaca nemestrina.
- HIV-1 viral loads remained low and unchanged following vaccinations.

HXB2 Location Gag/Pol
Author Location RT
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Env, Gag, Pol, Vif *Adjuvant:* B7, IL-12
Species (MHC) mouse
References Kim *et al.* 1997d

- A Gag/Pol or Env DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules CD86, gave a dramatic increase in both the cytotoxic and proliferative responses in mice.
- When CD86 was present, CTL response could be detected even without *in vitro* stimulation.

HXB2 Location Gag/Pol
Author Location RT
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords TCR usage
References Gamberg *et al.* 1999

- 13/13 subjects with advanced HIV infections showed CD8 T cell proliferation and differentiation of CTL *in vitro*, and six individuals showed HIV-specific responses to Gag, Pol, Env or Nef antigens.
- Data suggests that the functional and genetic integrity of the CD8 T cell repertoire (TCR Vβ gene intrafamily genetic diversity) remains intact through advanced HIV infection, although HIV-specific CTL activity decreases.

HXB2 Location Gag/Pol
Author Location
Epitope
Immunogen vaccine
Vector/Type: adenovirus *HIV component:* Gag-Pol, Nef, Vpr
Species (MHC) mouse
References Muthumani *et al.* 2002

- Vpr can cause cells to go into G2 arrest, and it surpresses immune cell activation and inflammatory cytokine production, so co-immunization of BALB/c mice with recombinant adenovirus expressing Vpr and HIV-1 antigens Nef or Gag/Pol was tested to see if Vpr reduced the immune response to the other HIV antigens.
- Vpr compromised CD8+ T-cell lytic responses and T-helper proliferative responses in mice co-immunized with Vpr and Nef or Gag/Pol.
- In vitro, Vpr reduced T-cell cytokine production of IL-12 and TNFalpha, indicative of Vpr-mediated immune suppression.

II-B-8 Gag/Pol TF CTL/CD8+ epitopes

HXB2 Location Gag/Pol TF (6–24)
Author Location Protease
Epitope `LAFPQQGGEAREFPSEQTRAN`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- A sequence polymorphism at residue R in Protease reacting peptide LAFPQQGGEArEFPSEQTRAN was associated with host HLA-B*5301. No known HLA-B*53-restricted epitope was in this sequence.

HXB2 Location Gag/Pol TF (21–29)
Author Location Pol
Epitope `TRANSPTRR`
Epitope name TR9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- TR9, TRANSPTRR, is a novel HLA-B27-restricted epitope that elicits a CTL IFN-gamma response significantly lower than that of Los Alamos database peptides.

HXB2 Location Gag/Pol TF (24–31)
Author Location
Epitope `NSPTRREL`
Epitope name NL8
Immunogen
Species (MHC) human (Cw*0102)

CTL CD8+

Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a Cw*0102 epitope.

HXB2 Location Gag/Pol TF (24–31)
Author Location p6 (35–42 HXB2)
Epitope NSPTRREL
Epitope name NL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*0102)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- Position4 in the epitope had potentially experienced positive selection. NsptRREL and tSPTRREL escape variants were found.

HXB2 Location Gag/Pol TF (24–31)
Author Location Pol
Epitope NSPTRREL
Epitope name NL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*0102)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords binding affinity, escape, immune evasion, drug resistance
References Cao *et al.* 2008

- For the first time, viral immune evasion is reported via an insertion mutation, in an ART-naive patient. A 3 aa repeat, SPT inserted within p6<sup>Pol<sup> epitope NL8 is reported, changing it to NsptSPTRREL (NL11). This insertion is associated often with ART drug resistance to NRTI drugs. Thus immune pressure and drug resistance may cause HIV-1 to select the same variation.
- Insertion from NL8 to NL11 changes the minimum epitope to tSPTRREL. Another variant seen later was tSPTiREL.
- A concomitant insertion mutation APP, is seen in p6<sup>Gag<sup>, permitting viral budding.
- Epitope NSPTRREL escapes to NSPT(SPT)RREL in subject PIC1362. Addition of an N-terminal Alanine to NL8 (aNSPTRREL) does not affect in vitro MHC I binding. Deletion of the C-terminal L as in peptide aNSPTRRE (AE8), however, shows that Leu is necessary for MHC I binding.

HXB2 Location Gag/Pol TF (26–34)
Author Location Pol
Epitope PTRRELQVW
Epitope name PW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- PW9(Pol), PTRRELQVW, is a novel HLA-B57-restricted epitope that elicits a CTL IFN-gamma response in the same range as Los Alamos database peptides.

HXB2 Location Gag/Pol TF (44–52)
Author Location Pol (C-96BW15C05)
Epitope AGAERQGTL
Epitope name C
Subtype C
Immunogen vaccine
Vector/Type: DNA, alphavirus replicon *Strain:* C clade C-96BW04.09, C clade C-96BW15C05 *HIV component:* Gag, Gag-Pol, Pol
Species (MHC) mouse (H-2^d)
Assay type Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, vaccine antigen design
References Megede *et al.* 2006

- HIV clade C gag, pol and fusion gagpol vaccines were compared in mice. Breadth of T cell responses was improved in mice immunized with gagpol fusion genes, compared to single antigen constructs. 5 new murine CD8+ T cell epitopes were mapped.
- This is a novel epitope.

HXB2 Location Gag/Pol TF (54–6)
Author Location Pol
Epitope FSFPQITLW
Epitope name FW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- FW9, FSFPQITLW, is a novel HLA-B57-restricted epitope that elicits a CTL IFN-gamma response in the same range as Los Alamos database peptides.

II-B-9 Gag/Pol TF-Protease CTL/CD8+ epitopes

HXB2 Location Gag/Pol TF-Protease (54–6)
Author Location Pol
Epitope `FSFPQITLW`
Epitope name FW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- An escape mutation at position 2, fNfpqitlw, was found in the most polymorphic residue in the epitope. This is a novel partially mapped epitope.

II-B-10 Protease CTL/CD8+ epitopes

HXB2 Location Protease (2–19)
Author Location (C consensus)
Epitope `QITLWQRPLVSIKVGGQI`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location Protease (3–11)
Author Location RT (71–79 subtype A, B, D)
Epitope `ITLWQRPLV`
Subtype A, B, D
Immunogen
Species (MHC) human (A*6802)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*6802 epitope.

HXB2 Location Protease (3–11)
Author Location Pol
Epitope `ITLWQRPLV`
Subtype A, B, C, D
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human (A*6802)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location Protease (3–11)
Author Location Protease (71–79 LAI)
Epitope `ITLWQRPLV`
Subtype B
Immunogen
Species (MHC) human (A*6802, A*7401, A19)
Keywords subtype comparisons
References Dong 1998

- Predicted on binding motif, no truncations analyzed.
- Clade A/B/D consensus, S. Rowland-Jones, pers. comm.

CTL CD8+

HXB2 Location Protease (3–11)
Author Location RT (71–79 subtype A, B, D)
Epitope ITLWQRPLV
Subtype A, B, D
Immunogen
Species (MHC) human (A*7401)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*7401 epitope.

HXB2 Location Protease (3–11)
Author Location Pol (59–)
Epitope ITLWQRPLV
Epitope name Pol59
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* Protease *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) transgenic mouse (A2)
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was an intermediate A2 binder, and induced CTL and CD8+ T-cell IFN gamma responses in mice. Responses to the peptide were not detected in 17 HIV+ HLA-A2 subjects.

HXB2 Location Protease (3–11)
Author Location
Epitope ITLWQRPLV
Epitope name Pol 59
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Previously characterized HLA-A2 epitope, Pol 59 ITLWQRPLV, was present in 9 patients but none had a CTL immune response to it.

HXB2 Location Protease (3–11)
Author Location Pol (59–65)
Epitope ITLWQRPLV
Immunogen HIV-1 infection
Species (MHC) human (A28)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location Protease (3–11)
Author Location Pol (60–68)
Epitope ITLWQRPLV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A28)
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location Protease (3–11)
Author Location RT (71–79 LAI)
Epitope ITLWQRPLV
Epitope name P2
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A28 supertype)
Keywords HAART, ART, supertype
References Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNgamma production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

HXB2 Location Protease (3–11)
Author Location Protease
Epitope ITLWQRPLV
Epitope name IV9(Protease)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A68)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

CTL CD8+

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A68-restricted epitope ITLWQRPLV elicited an immune response in Chinese HIV-1 positive subjects as part of peptide SFSFPQITLWQRPLVTIK.

HXB2 Location Protease (3–11)
Author Location Pol
Epitope ITLWQRPLV
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A74)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ITLWQRPLV cross-reacts with clades A, B and D.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location Protease (4–14)
Author Location Pol (60–70 SF2)
Epitope TLWQRPLVTIR
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (A*3303)
Assay type Chromium-release assay
Keywords binding affinity, computational epitope prediction
References Hossain *et al.* 2003

- HLA-A*3303 is a common HLA allele in east and southeast Asia. Pol, Gag and Nef SF2 proteins were scanned for potential A*3303 epitopes. 99 potential epitopes were synthesized, and 52/99 bound to A*3303. Six of these served as peptide-targets for lysis by PBMC from infected individual, and clones derived from 4 of these 6 could lyse HIV-vaccinia infected target cells, indicating proper processing.
- This epitope is one of the 4 that are properly processed.

HXB2 Location Protease (7–15)
Author Location Protease
Epitope QRPLVTIKI
Epitope name QI9
Immunogen HIV-1 infection
Species (MHC) human (A*0101)
Donor MHC A*0101, A*0205, B*0702, B*0801, Cw*0701, Cw*0702
Country Australia
Assay type Intracellular cytokine staining
Keywords HAART, ART, immunotherapy, variant cross-recognition or cross-neutralization, optimal epitope
References Stratov *et al.* 2005

- CD8 T-cells targeting epitopes spanning drug resistance induced mutations were detected in 3/25 individuals harboring multidrug-resistant HIV-1. Novel CD8 T-cell responses were detected against epitopes with common protease inhibitor fitness mutations. T-cell immunity to drug-resistant variants was confirmed in SHIV-infected macaques, where CD8 and CD4 immune responses to RT and protease resistance mutations were elicited using peptide-based immunotherapy.
- QRPLVTIKI carries the the L10I protease inhibition mutation and was recognized in a multidrug resistant individual. Response against wild-type epitope qrpIvtiki was detected.
- The 3 people that responded to the drug resistant forms of the virus were among those that had the highest levels of CD4 and CD8 T-cell responses, indicating that they were among the most immunocompetent.

HXB2 Location Protease (7–16)
Author Location Protease (7–16 HXB2)
Epitope QRPLVTVKIG
Epitope name QG10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, HLA associated polymorphism, drug resistance
References Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. 10 new CTL epitopes were defined statistically and experimentally, and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01_AE, 1 CRF03_AB, 1 CRF15_01B and 2 subtype Ds.
- This newly defined epitope, QRPLVTVKIG, QG10, carried an HLA-B51-associated drug polymorphism at K14R, QRPLVTVrIG and another mutation at L10I, QRPiVTVKIG.

HXB2 Location Protease (11–20)
Author Location Pol (98–)
Epitope VTIKIGGQLK
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (A*0301)
Country Botswana, United States

Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008

- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location Protease (11–20)
Author Location Pol
Epitope VTIKIGGQLK
Epitope name Pol 98
Subtype M
Immunogen vaccine, in vitro stimulation or selection, computer prediction
Vector/Type: DNA, peptide *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, mouse, humanized mouse (A*1101)
Assay type Cytokine production, T-cell Elispot
Keywords subtype comparisons, computational epitope prediction, escape, TCR usage, variant cross-recognition or cross-neutralization
References McKinney *et al.* 2004

- This study examined variant recognition of epitopes presented by A*0201 and A*1101. Numerous amino acid substitutions can be introduced into epitopes without disrupting their recognition by CTLs, although epitopes with multiple substitutions were less recognized. An algorithm was constructed for prediction of epitopes capable of inducing responses to a great number of variant epitopes.
- A total of 30 variant forms of Pol 98 were identified. 50% of the variant epitopes were recognized by CTLs from mice immunized with the parental form.
- Pol 98 epitope was present in 71% of HIV sequences of many M group subtypes.

HXB2 Location Protease (11–20)
Author Location Pol
Epitope VTIKIGGQLK
Epitope name Pol98
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (A3)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- VTIKIGGQLK is a Pol epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location Protease (11–20)
Author Location Pol (91–100)
Epitope VTILIGGQLK
Immunogen HIV-1 infection
Species (MHC) human (A3 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801).

HXB2 Location Protease (11–20)
Author Location Pol
Epitope VTIKIGGQLK
Epitope name Pol98
Subtype B, C, D
Immunogen HIV-1 infection
Species (MHC) human, mouse (A3 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope VTIKIGGQLK of the HLA-A3 supertype bound most strongly to HLA-A*1101, and -A*6801 and also to -A*0301 but not to -A*3301 or -A*3101. It was conserved 63% in subtype B, 13% in C and 50% in subtype D. 4/23 HLA-A3 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Pol98.

HXB2 Location Protease (12–20)
Author Location Pol (92–100)
Epitope TIKIGGQLK
Immunogen HIV-1 infection
Species (MHC) human (A3 supertype)
Keywords supertype, rate of progression

References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801).

HXB2 Location Protease (23–32)
Author Location Pol
Epitope LLDTGADDTV
Epitope name L10V
Immunogen vaccine
Vector/Type: measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140ΔV3
Species (MHC) transgenic mouse (A*0201)
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells
References Lorin *et al.* 2005a

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

HXB2 Location Protease (23–33)
Author Location Protease (23–33 HXB2)
Epitope LLDTGADDTVL
Epitope name LL11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, HLA associated polymorphism, drug resistance
References Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. 10 new CTL epitopes were defined statistically and experimentally, and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01_AE, 1 CRF03_AB, 1 CRF15_01B and 2 subtype Ds.
- This newly defined epitope, LLDTGADDTVL, LL11, has a major mutation L33F, LLDTGADDTVf associated with HLA-A2.

HXB2 Location Protease (29–43)
Author Location
Epitope DDTVLEEMSLPGRWK
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost, polyepitope *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human
Donor MHC A*3001, A*3002; B*4201/02, B*4403/26/30
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location Protease (30–38)
Author Location Pol (subtype B)
Epitope DTVLEEMNL
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A*6802)
Keywords subtype comparisons
References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi—these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.

- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among B and D clade viruses.
- The Clade A version of the epitope: DTVLEDINL.
- This epitope was recognized by two different exposed and uninfected prostitutes.
- This epitope was identified by screening 49 HIV-1 peptides with the predicted A*6802 anchor residue motif x(VT)xxxxxx(VL)

HXB2 Location Protease (30–38)
Author Location Pol (subtype A)
Epitope DTVLEDINL
Subtype A
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A*6802)
References Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 IFNγ responses in the cervix—systemic CD8+ T cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T cell epitopes: DTVLEDINL (3 individuals), SLYNTVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

HXB2 Location Protease (30–38)
Author Location RT (85–93 subtype D)
Epitope DTVLEEWNL
Subtype D
Immunogen
Species (MHC) human (A*6802)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*6802 epitope.

HXB2 Location Protease (30–38)
Author Location Pol (subtype A)
Epitope DTVLEDINL
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (A*6802)
Keywords HIV exposed persistently seronegative (HEPS), escape
References Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- DTVLEDINL was recognized in 3 of the 6 women (ML857, ML1203, and ML1707), and the response was present in the last available sample prior to seroconversion, 3-7 months.
- In each of the three women, 20/20 sequences of the infecting strain had no substitutions in this epitope, all were DTVLEDINL, so there was no evidence for escape.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 3/22 HEPS sex worker controls, ML851, ML1432, and ML1601.

HXB2 Location Protease (30–38)
Author Location Pol (85–93)
Epitope DTVLEDINL
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A*6802)
Keywords HIV exposed persistently seronegative (HEPS), immunodominance
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-A*6802 women, 11/12 HEPS and 6/11 HIV-1 infected women recognized this epitope likelihood ratio 4.4, p value 0.08, and HEPS women tended to respond to DTVLEDINL, infected women tended to ETAYFILKL.
- The dominant response to this HLA allele was to this epitope in 10 of the 11/12 HEPS cases, but in only 4 of the 6/11 HIV-1 infected women.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.
- Four epitopes were considered to be "resistant epitopes", as they were preferentially reactive in HEPS women and so may confer resistance, and these were found in three different proteins: A2 ILK(D/E)PVHGV in RT, A*6802 DTVLEDINL in Protease, B14 DLN(M/T)LN(I/V)V in p24 and B18 FRDYVDRF(Y/F)K also in p24.
- Subject ML 857 shifted from a A*6802 DTVLEDINL and B35 (H/N)PDIVIYQY response prior to seroconversion to a B35 PPIPVGDIY and B35 VPLRPMTY response post-seroconversion, and the loss of the pre-seroconversion response was not due to sequence variation within these epitopes.
- Subject ML 1203 started with CTL responses to A*6802 DTVLEDINL and B7 FPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A*6802 ETAYFILKL which became dominant, B7 TPGPGV/IRYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV.
- Subject ML 1707 started with a CTL response to A*6802 DTVLEDINL prior to seroconversion, and switched to

A*6802 ETAYFILKL and A24 RDYVDRFFKTL post-seroconversion, and the loss of the pre-seroconversion response was not due to sequence variation within the epitope.
- Subject ML 1830 made no detectable response prior to seroconversion, but responded to A*6802 DTVLEDINL and A*6802 ETAYFILKL post-seroconversion.

HXB2 Location Protease (30–38)
Author Location Pol
Epitope DTVLEDINL
Immunogen HIV-1 infection
Species (MHC) human (A*6802)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2002

- Neisseria gonorrhea cervititis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
- Ghonorrhea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

HXB2 Location Protease (30–38)
Author Location Pol (87–95)
Epitope DTVLEEMNL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A28)
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location Protease (30–38)
Author Location (B consensus)
Epitope DTVLEEMNL
Epitope name DL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A68)
Donor MHC A31, A68, B07, B70, Cw1, Cw7
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location Protease (30–38)
Author Location
Epitope DTVLEEMNL
Immunogen HIV-1 infection
Species (MHC) human (A68)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope DTVLEEMNL elicited a magnitude of response of 565 SFC with a functional avidity of 0.5nM and binding affinity of >40,000nM.

HXB2 Location Protease (30–38)
Author Location Protease
Epitope DTVLEDMNL
Epitope name DL9(Protease)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope DTVLEDMNL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide as part of peptide GADDTVLEDMNLPGRWK. This epitope differs from the previously described HLA-A68-restricted epitope, DTVLEEWNL, at 2 residues, DTVLEdmNL.

CTL CD8+

HXB2 Location Protease (34–42)
Author Location Protease (34–42)
Epitope EEMNLPGRW
Epitope name EW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*44)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*44-associated substitutions within optimally defined epitope EEMNLPGRW are at positions E2 and N4, EeMnLPGRW.

HXB2 Location Protease (34–42)
Author Location Pol (2361–)
Epitope EEMNLPGRW
Immunogen HIV-1 infection
Species (MHC) human (B*4402)
Country Australia
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, HLA associated polymorphism
References Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore et al., Science 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- The fourth position of the epitope EEMnLPGRW has a mutational pattern that is correlated the host carrying HLA B*4402.

HXB2 Location Protease (34–42)
Author Location Pol (2355–)
Epitope EEMNLPGRW
Epitope name EW9
Immunogen HIV-1 infection
Species (MHC) human (B*4403)
Country Australia
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, HLA associated polymorphism
References Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore et al., Science 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- This HLA-B*4403 HIV mutation association was only picked up using statistics that incorporate the phylogeny. The second position, EeMNLPGRW, is the anchor residue association.

HXB2 Location Protease (34–42)
Author Location Protease
Epitope EEINLPGKW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4403)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- EEINLPGKW is a previously described HLA-B*4403-restricted epitope (part of Pol-Protease reacting peptides DTGADDTVLEeINLPGKWKPK and GADDTVLEEInLPGKWKPKMI) that contains a B*4403-associated sequence polymorphism at residues E and N (EeINLPGKW/EEInLPGKW).

HXB2 Location Protease (34–42)
Author Location Protease (34–42 HXB2)
Epitope EEMNLPGRW
Epitope name EW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B18, B40, B44)
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, variant cross-recognition or cross-neutralization, immune evasion, HLA associated polymorphism, drug resistance
References Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. 10 new CTL epitopes were defined statistically and experimentally, and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.

- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01_AE, 1 CRF03_AB, 1 CRF15_01B and 2 subtype Ds.
- This highly immunogenic index epitope, EEMNLPGRW, EW9, developed variants EEiNLPGRW, EW9 M/I, EEMdLPGRW, EW9 N/D, EdMNLPGRW, EW9 E/D, EdiNLPGRW, EW9 D/I, EEMNLPGkW, EW9 R/K, EEMNLsGRW, EW9 P/S. E35D and P39S mutants were located in the previously reported HLA-B44 restricted epitope EEMSLPGRW (EW9). The correlation between the minor drug mutation E35D and HLA-B44 was strong, while that of -B44 with P39S was weak. E35D mutations induced a strong decrease in CTL recognition, but few patient samples did mount specific responses against it giving a negative correlation between this mutation and HLA-B44. A novel association between the E35D mutant and HLA-B18 was also found.
- Cross-reactivity of CTL recognition of EW9 and variants occured for most patients. This showed that cells from several patients mount oligoclonal CTL responses, indicating immune system reactions to escape by recruitment of CTLs with new TCR specificities. On the other hand, most patients showed mutually exclusive recognition of variant epitopes containing either E35D or E35E; HLA-B44 subtypes and other factors tested could not explain this phenomenon.
- EW9 epitope and variant peptides include the S37N substitution when compared to HXB2 strain sequences.
- HLA-restrictions to this epitope were HLA-18, -40, -44.

HXB2 Location Protease (34–42)
Author Location Protease (34–42)
Epitope EEMNLPGRW
Immunogen
Species (MHC) human (B44)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Protease (34–42)
Author Location Protease
Epitope EEMNLPGRW
Epitope name EW9
Immunogen HIV-1 infection
Species (MHC) human (B44)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords epitope processing, supervised treatment interruptions (STI), immunodominance
References Rodriguez *et al.* 2004

- Protease and integrase are shown to be frequently targeted by CD8 T-cell responses (23% and 68% of 56 HIV+ patients, respectively). Responses tend to cluster in conserved regions of Int, although 1 high conserved region had no responses. CTL frequencies per unit protein length for Pro and Int were similar to other HIV non-structural proteins. Three novel HLA class I-restricted optimal epitopes were found and characterized with fine mapping.
- The epitope includes residue M36, which is a known accessory mutation site in individuals treated with PIs.

HXB2 Location Protease (34–42)
Author Location Protease (34–42)
Epitope EEINLPGKW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B44)
Assay type Other
Keywords HLA associated polymorphism
References Boutwell & Essex 2007

- Publicly available HIV-1 subtype C sequences from South Africa and Botswana were analyzed, and 94 HLA-associated amino acid polymorphisms were found. Many polymorphisms were associated with multiple HLA allele classes. 12% associations were negative: association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles accounted for 50% of associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes.
- EEINLPGKW was a previously defined B44 presented epitope that encompassed an associated polymorphism, EeINLPGKW,in the second position.

HXB2 Location Protease (34–42)
Author Location Protease
Epitope EDMNLPGRW
Epitope name EW9(Protease)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope EDMNLPGRW elicited an immune response in Chinese HIV-1 positive subjects as part of peptide GADDTVLEDMNLPGRWK. This epitope differs from the previously described HLA-B44-restricted epitope, EEMNLPGRW, at 1 residue, EdMNLPGRW.

CTL CD8+

- 1 of the 6 HLA-B44 carriers responded to EdMNLPGRW-containing peptide with average magnitude of CTL response of 300 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Protease (38–47)
Author Location Pol
Epitope LPGRWKPKMI
Epitope name Pol1134
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Novel Pol epitope LPGRWKPKMI elicits IFN-gamma ELISpot responses in 4/7 subjects; and bound HLA-B7 with low and high affinities in soluble and cell-based assays respectively.

HXB2 Location Protease (38–47)
Author Location Protease (38–47 HXB2)
Epitope LPGRWKPKMI
Epitope name LI10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw3)
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, HLA associated polymorphism, drug resistance
References Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. 10 new CTL epitopes were defined statistically and experimentally, and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01_AE, 1 CRF03_AB, 1 CRF15_01B and 2 subtype Ds.
- This newly defined HLA-Cw3-associated epitope LPGRWKPKMI, LI10, carries minor mutations at K43.

HXB2 Location Protease (42–50)
Author Location Protease (42–50 HXB2)
Epitope WKPKMIGGI
Epitope name WI9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw3)
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, drug resistance
References Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. 10 new CTL epitopes were defined statistically and experimentally, and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01_AE, 1 CRF03_AB, 1 CRF15_01B and 2 subtype Ds.
- This newly defined Cw3-associated epitope WKPKMIGGI, WI9, carries minor mutations at K43.
- HLA-restriction to this epitope was HLA-Cw3.

HXB2 Location Protease (45–53)
Author Location Protease (45–53 HXB2)
Epitope KMIGGIGGF
Epitope name KF9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62)
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, HLA associated polymorphism, drug resistance
References Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. 10 new CTL epitopes were defined statistically and experimentally, and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.

- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01_AE, 1 CRF03_AB, 1 CRF15_01B and 2 subtype Ds.
- This newly defined epitope, KMIGGIGGF, KF9, was the optimal HLA-B62 restricted epitope.

HXB2 Location Protease (45–54)
Author Location Protease (45–54)
Epitope KMIGGIGGFI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

HXB2 Location Protease (45–54)
Author Location Pol (45–54 IIIB)
Epitope KMIGGIGGFI
Epitope name pol45-54
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* Gag-Pol
Species (MHC) humanized mouse (A*0201)
Assay type Intracellular cytokine staining
Keywords epitope processing, vaccine-specific epitope characteristics, immunodominance, variant cross-recognition or cross-neutralization, vaccine antigen design
References Singh & Barry 2004

- When A*0201-C3H/J transgenic mice were immunized with plasmids encoding wild-type gag-pol, codon-optimized (CO) gag-pol, and an expression library vaccine expressing 16 fragments of gag-pol fused with ubiquitin for proteosome targeting (ELI), the ELI vaccine produced up to 10-fold higher CD8 T-cell responses than the other two vaccines. In contrast to the wt and CO vaccines, which tended to augment only immunodominant responses, boosting with the ELI vaccine resulted in many CD8 responses against variant epitopes from different HIV-1 clades, and against drug-resistant variants.
- The drug resistant variant of this epitope, kViVgiggfi, was tested. WT and CO vaccines produced low level CD8+ T-cell responses against the B clade form as well as against drug resistant variant, but the ELI vaccine produced much more intense responses against both the WT and the variant, including after boosting.

HXB2 Location Protease (45–54)
Author Location Pol (125–134)
Epitope KMIGGIGGFI
Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind three of the five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802).

HXB2 Location Protease (45–54)
Author Location Protease (45–54 HXB2)
Epitope KMIGGIGGFI
Epitope name KI10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2, B62)
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, HLA associated polymorphism, drug resistance
References Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. 10 new CTL epitopes were defined statistically and experimentally, and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.

CTL CD8+

- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01_AE, 1 CRF03_AB, 1 CRF15_01B and 2 subtype Ds.
- This previously known index epitope, KMIGGIGGFI, KI10, developed major mutations KiIGGIGGFI, KI10-I/L and variant KMIGGIGGFv, KI10-V. In most patients, CTL responses were generated against both index and variant epitopes, suggesting that different CTL clones within each patient show different recognition specificities. However, one patient was unable to recognize both M46I and I54V mutations, while others responded to mutants and not the index epitope. Other drug resistance-associated mutations for this epitope are I47A/V/L, G48V/M, I50L/V, F53L and I54A/L/M.
- HLA-restrictions to this epitope were HLA-A2, -B62. HLA-A2 showed greater correlations than HLA-B62 did for this epitope.

HXB2 Location Protease (55–63)
Author Location Protease (55–63 HXB2)
Epitope `KVRQYDQIL`
Epitope name KL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2, Cw6)
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, variant cross-recognition or cross-neutralization, immune evasion, HLA associated polymorphism, drug resistance
References Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. 10 new CTL epitopes were defined statistically and experimentally, and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01_AE, 1 CRF03_AB, 1 CRF15_01B and 2 subtype Ds.
- This newly defined epitope, KVRQYDQIL, KL9, carries a minor A2-associated minor mutation at I62V, KVRQYDQvL and an identical HLA-Cw6-associated drug polymorphism at the same position. HLA-restrictions to this epitope are HLA-A2 and -Cw6.

HXB2 Location Protease (56–66)
Author Location Protease (56–66 HXB2)
Epitope `VRQYDQIPIEI`
Epitope name VI11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B13)
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, HLA associated polymorphism, drug resistance
References Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. 10 new CTL epitopes were defined statistically and experimentally, and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01_AE, 1 CRF03_AB, 1 CRF15_01B and 2 subtype Ds.
- This newly defined HLA-B13-restricted epitope, VRQYDQIPIEI, VI11, carries drug-induced mutations I62V, VRQYDQvPIEI and E65D, VRQYDQIPIdI.
- VI11 epitope and variant peptides include the L63P substitution when compared to HXB2 strain sequences.

HXB2 Location Protease (57–66)
Author Location Pol (113–122)
Epitope `RQYDQILIEI`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*13)
Donor MHC A*0301, A*3001, B*1301, B*1402, Cw*0602, Cw*0802
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords epitope processing, immune evasion, viral fitness and reversion, HLA associated polymorphism
References Honeyborne *et al.* 2007

- To determine whether HLA-B*13-restricted CTL responses could partially explain low viremic loads in patients, a cohort of chronic C-clade infected subjects was studied. 6 novel B*13-restricted CTL epitopes were defined from both C- and B-clade viruses, 3 of which were within Gag. B*13-restricted CTL responses correlated with lower viremia, with most immunity targeted against Gag epitopes (p15, p17, p24). Gag epitope escape variants may exact a high viral fitness cost, mutations being seen within and around the optimal epitope.

HXB2 Location Protease (57–66)
Author Location Protease (57–66)
Epitope RQYDQILIEI
Epitope name RI10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*13)
Country Australia, Canada, Germany, United States
Keywords escape, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*13-associated substitutions within optimally defined epitope RQYDQILIEI are at positions L7 and E9, RQYDQIlIeI. RI10 was the 5th most rapidly escaping epitope.

HXB2 Location Protease (57–66)
Author Location
Epitope RQYDQILIEI
Epitope name RI10
Immunogen
Species (MHC) human (B13)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B13 epitope. Variant RQYDQIpIEI also noted.

HXB2 Location Protease (57–66)
Author Location Protease (57–66 HXB2)
Epitope RQYDQIPIEI
Epitope name RI10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B13)
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, HLA associated polymorphism, drug resistance
References Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. 10 new CTL epitopes were defined statistically and experimentally, and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
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- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01_AE, 1 CRF03_AB, 1 CRF15_01B and 2 subtype Ds.
- This newly defined B13-associated epitope, RQYDQIPIEI, RI10, carries drug-induced mutations at I62V, RQYDQvPIEI. RI10 does not have a published HLA-binding motif yet, but it overlaps with the Cw4-restricted epitope QYDQIPIEI, and shows similarity at the putative anchor binding positions of the B13-restricted Nef epitope, RQDILDLWI.

HXB2 Location Protease (57–66)
Author Location Protease
Epitope RQYDQIPIEI
Epitope name RI10(Protease)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope RQYDQIPIEI elicited an immune response in Chinese HIV-1 positive subjects as part of peptide KVRQYDQIPIEICGHKAI. This epitope differs from the previously described HLA-B13-restricted epitope sequence, RQYDQILIEI, at 1 residue, RQYDQIpIEI.
- 2 of the 29 HLA-B13 carriers responded to RQYDQIpIEI-containing peptide with average magnitude of CTL response of 160 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Protease (58–66)
Author Location Protease
Epitope QYDQIPIEI
Epitope name QI9
Immunogen HIV-1 infection
Species (MHC) human (Cw*0401)
Donor MHC A*0201, A*1101, B*1501, B*3501, Cw*0401, Cw*0701
Country Australia
Assay type Intracellular cytokine staining

CTL CD8+

Keywords HAART, ART, immunotherapy, variant cross-recognition or cross-neutralization, optimal epitope
References Stratov *et al.* 2005

- CD8 T-cells targeting epitopes spanning drug resistance induced mutations were detected in 3/25 individuals harboring multidrug-resistant HIV-1. Novel CD8 T-cell responses were detected against epitopes with common protease inhibitor fitness mutations. T-cell immunity to drug-resistant variants was confirmed in SHIV-infected macaques, where CD8 and CD4 immune responses to RT and protease resistance mutations were elicited using peptide-based immunotherapy.
- QYDQIPIEIW harbors the L63P protease inhibitor mutation, and this created an epitope. The wild-type epitope qydqiLiei was not recognized.
- The 3 people that responded to the drug resistant forms of the virus were among those that had the highest levels of CD4 and CD8 T-cell responses, indicating that they were among the most immunocompetent.

HXB2 Location Protease (62–70)
Author Location Protease (62–70 HXB2)
Epitope `ILIEICGHK`
Epitope name IK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords immune evasion, HLA associated polymorphism, drug resistance
References Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. 10 new CTL epitopes were defined statistically and experimentally, and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
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- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01_AE, 1 CRF03_AB, 1 CRF15_01B and 2 subtype Ds.
- This newly defined epitope, ILIEICGHK, IK9, has a variant K70R, ILIEICGHr, which strongly reduced recognition by CTL as it is a C-terminal anchor site. Also the minor mutation I64V, ILvEICGHK, is negatively associated with HLA-A3, indicating that it rarely occurs in A3-patients.

HXB2 Location Protease (64–73)
Author Location Protease (64–73 HXB2)
Epitope `IEICGHKAIG`
Epitope name IG10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B18, B40, B44)
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, variant cross-recognition or cross-neutralization, immune evasion, HLA associated polymorphism, drug resistance
References Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. 10 new CTL epitopes were defined statistically and experimentally, and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01_AE, 1 CRF03_AB, 1 CRF15_01B and 2 subtype Ds.
- This newly defined epitope, IEICGHKAIG, IG10, carries B44- and B18-associated minor mutations as A71V/T - IEICGHKvIG, IEICGHKtIG and a B18-associated polymorphism at K70 - IEICHHkAIG. IG10 was also recognized by B40-positive patients whose HLA belongs to the B44 supertype.
- HLA-restriction for this epitope was HLA-B18, -40, -44.

HXB2 Location Protease (68–76)
Author Location Protease (68–76)
Epitope `GKKAIGTVL`
Epitope name GL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*15)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.

- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*15-associated substitution within optimally defined epitope GKKAIGTVL is at position A4, GKKAIGTVL.

HXB2 Location Protease (68–76)
Author Location (C consensus)
Epitope GKKAIGTVL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- GKKAIGTVL is an optimal epitope.

HXB2 Location Protease (68–76)
Author Location
Epitope GKKAIGTVL
Epitope name GL9
Immunogen
Species (MHC) human (B*1503)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*1503 epitope.

HXB2 Location Protease (68–76)
Author Location Protease
Epitope GKKAIGTVL
Epitope name GL9(Protease)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- GHKAIGTVL elicited an immune response in Chinese HIV-1 positive subjects as peptide PIEICGHKAIGTVL. None of the 21 HLA-B15 carriers responded to peptide GHKAIGTVLVGPTPVNII. These peptide-contained epitopes differ from the previously described HLA-B15-restricted eptiope, GkKAIGTVL by 1 residue.

HXB2 Location Protease (69–83)
Author Location Protease (69–83)
Epitope HKAIGTVLVGPTPVN
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords TCR usage, characterizing CD8+ T cells
References Yang *et al.* 2005a

- CTL responses were evaluated in identical twins infected with HIV-1 from the same blood source. Targeting of the CTL was similar in the 2 patients, while their TCR profiles were highly dissimilar. It is suggested that CTL targeting is predominately genetically determined, while T-cell generation is a stochastic process; the responding CTLs differ at the TCR molecular level, leaving the viral escape and CTL efficacy unpredictable.
- HKAIGTVLVGPTPVN was the immunodominant epitope in each twin, but was recognized by T cells with distinctly different TCRs. The epitope was not defined within the epitope. The twins had very different patterns of HIV evolution in this region, with one carrying HKveGsVLiGPTPVN and the other HKAIGaVLiGPTPVN.

HXB2 Location Protease (69–83)
Author Location Protease (125–139)
Epitope HKAIGTVLVGPTPVN
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008

- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.
- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.
- CTL immune response to consensus sequence HKAIGTVLVGPTPVN was elicited in subject 00015. Consensus epitope of subject 00015 was qKAIGTVLVGPTPVN and of subject 00016 was qHKAIGTVLVGPTPVd.

HXB2 Location Protease (70–77)
Author Location
Epitope KAIGTVLV
Immunogen
Species (MHC) human (B57)
Keywords optimal epitope
References Llano *et al.* 2009

CTL CD8+

- C. Brander notes that this is an B57 epitope.

HXB2 Location Protease (70–77)
Author Location Protease
Epitope KAIGTVLV
Epitope name KV8
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B57, B58, B63)
Donor MHC A23, A30, B42, B57, Cw17
Assay type CD8 T-cell Elispot - IFNγ
Keywords cross-presentation by different HLA, optimal epitope
References Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- HLA-B63/57/58 epitope containing the B58 supertype binding motif. Significantly more often recognized by B63-positive subjects than by negative subjects. Optimal epitope was defined in a person who was B57+.

HXB2 Location Protease (75–84)
Author Location Protease (75–84 MN)
Epitope VLVGPTPVNI
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Keywords binding affinity
References Konya *et al.* 1997

- Peptide predicted to be reactive based on HLA-A*0201 binding motif.
- Peptide could stimulate CTL in PBMC from 5/6 seronegative donors.
- Peptide located in a highly conserved region of protease.
- Both 9-mer and 10-mer could stimulate CTL: VLVGPTPVNI and LVGPTPVNI.
- Binding affinity to A*0201 was measured, $C_{1/2\ max}\mu M = 6$ for 10-mer, 3 for 9-mer.
- MAL variant of Pr(75-84 MN), with substitutions V77, G78, and P79, gave reduced binding and CTL recognition.

HXB2 Location Protease (75–84)
Author Location Protease (175–184 MN)
Epitope VLVGPTPVNI
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* B clade MN *HIV component:* gp120, Protease, RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) humanized mouse (A*0201)
Assay type CD8 T-cell Elispot - IFNγ
Keywords epitope processing, vaccine-specific epitope characteristics, immunodominance, immunotherapy
References Isaguliants *et al.* 2004

- Immunization of HLA-A*0201-transgenic mice with synthetic genes encoding clusters of human A*0201 CTL epitopes located at the sites of drug resistance mutations, induced RT-specific cellular responses indicating the immunogenicity of these constructs. This vaccine strategy may be a first step towards a therapeutic vaccine against drug-resistant strains.
- This was one of five HLA-A*0201 epitopes from the RT or protease proteins that was included in the polyepitope vaccine. When the transgenic HLA A*0202 mice were vaccinated with the polyepitope construct or with a mixture of RT peptides, a sustained low level CD8+ T-cell gamma IFN response was observed, in contrast to when an intact RT gene was used for vaccination.

HXB2 Location Protease (75–84)
Author Location Pol (75–84 IIIB)
Epitope VLVGPTPVNI
Epitope name pol75-84
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* Gag-Pol
Species (MHC) humanized mouse (A*0201)
Assay type Intracellular cytokine staining
Keywords epitope processing, vaccine-specific epitope characteristics, immunodominance, variant cross-recognition or cross-neutralization, vaccine antigen design
References Singh & Barry 2004

- When A*0201-C3H/J transgenic mice were immunized with plasmids encoding wild-type gag-pol, codon-optimized (CO) gag-pol, and an expression library vaccine expressing 16 fragments of gag-pol fused with ubiquitin for proteosome targeting (ELI), the ELI vaccine produced up to 10-fold higher CD8 T-cell responses than the other two vaccines. In contrast to the wt and CO vaccines, which tended to augment only immunodominant responses, boosting with the ELI vaccine resulted in many CD8 responses against variant epitopes from different HIV-1 clades, and against drug-resistant variants.
- The drug resistant variant of this epitope,vlvgptpTnV, was tested. WT and CO vaccines produced low level CD8+ T-cell responses against the B clade form as well as against drug resistant variant, but the ELI vaccine produced much more intense responses against both the WT and the variant, including after boosting.

HXB2 Location Protease (75–84)
Author Location Protease (75–84)
Epitope VLVGPTPVNI
Immunogen vaccine
Vector/Type: peptide, Other *Strain:* multiple epitope immunogen *HIV component:* Protease *Adjuvant:* Incomplete Freund's Adjuvant (IFA), Other
Species (MHC) transgenic mouse (A*0201)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding

Keywords vaccine-specific epitope characteristics, drug resistance
References Boberg *et al.* 2006

- Binding of a protease epitope and its variants caused by drug-resistance mutations to HLA-A0201 and CTL responses in transgenic mice immunized with this epitope were analyzed. It was found that both the wild-type and resistance variants of the epitope bound well to HLA-A0201 and were strongly immunogenic in HLA-A0201 transgenic mice. Immunological cross-reactivity between different variants of the peptide was observed, suggesting that immunization with drug-resistance mutated epitopes could induce a broad immune response, which may cause a better outcome of antiretroviral therapy in HIV-1 infected individuals.
- An interesting epitope from the HIV-1 protease (PR) protein was found VLVGPTPVNI, and mutant variants - VLVGPTPaNI, VLVGPTPfNI, VLVGPTPVNv, VLVGPTPfNv. The epitope, VLVGPTPVNI, and its drug-induced mutant version VLVGPTPfNv, were studied and were able to elicit responses both by peptide constructs and multi-CTL epitope constructs.

HXB2 Location Protease (76–84)
Author Location Protease (76–84)
Epitope `LVGPTPVNI`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

HXB2 Location Protease (76–84)
Author Location Pol (163–)
Epitope `LVGPTPVNI`
Epitope name Pol-163
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords binding affinity, subtype comparisons, supertype, computational epitope prediction
References Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- LVGPTPVNI binds to 4/5 HLA-A2 supertype alleles: A*0201, A*0202, A*0206 (highest affinity) and A*6802, but not A*0203.
- 1/22 individuals with chronic HIV-1 infection recognized this epitope by ELISPOT.
- 0/12 acutely infected individuals recognized this epitope.

HXB2 Location Protease (76–84)
Author Location Protease (76–84)
Epitope `LVGPTPVNI`
Epitope name LI9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a A*0201 epitope.

HXB2 Location Protease (76–84)
Author Location Protease (76–84)
Epitope `LVGPTPVNI`
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope LVGPTPVNI was predicted to be restricted by HLA A*0201, A*0202, A*0205,A*0209, B*1501 and B*1516.

HXB2 Location Protease (76–84)
Author Location Protease
Epitope `LVGPTPANI`

CTL CD8+

Immunogen HIV-1 infection
Species (MHC) human, macaque (A*0205)
Donor MHC A*0101, A*0205, B*0702, B*0801, Cw*0701, Cw*0702
Country Australia
Assay type Intracellular cytokine staining
Keywords HAART, ART, immunotherapy, variant cross-recognition or cross-neutralization
References Stratov *et al.* 2005

- CD8 T-cells targeting epitopes spanning drug resistance induced mutations were detected in 3/25 individuals harboring multidrug-resistant HIV-1. Novel CD8 T-cell responses were detected against epitopes with common protease inhibitor fitness mutations. T-cell immunity to drug-resistant variants was confirmed in SHIV-infected macaques, where CD8 and CD4 immune responses to RT and protease resistance mutations were elicited using peptide-based immunotherapy.
- A response against the peptide harboring the protease drug resistance mutation V82A, LVGPTPANI, was detected in one individual, but the wildtype epitope was not recognized, lvgptpVni. This epitope response was not fine-mapped, and is based on analogy to a previously described A2 epitope.
- Other drug resistant variants were not recognized: V82T and I84V.
- The 3 people that responded to the drug resistant forms of the virus were among those that had the highest levels of CD4 and CD8 T-cell responses, indicating that they were among the most immunocompetent.

HXB2 Location Protease (76–84)
Author Location
Epitope `LVGPTPVNI`
Immunogen HIV-1 infection
Species (MHC) human (A02)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope LVGPTPVNI elicited a magnitude of response of 480 SFC with a functional avidity of 0.005nM and binding affinity of 10.1nM.

HXB2 Location Protease (76–84)
Author Location Protease (76–84 HXB2)
Epitope `LVGPTPVNI`
Epitope name PR82V
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type Intracellular cytokine staining, Chromium-release assay
Keywords HAART, ART, escape
References Karlsson *et al.* 2003

- This epitope contains two positions that are commonly associated with protease inhibitor escape, lvgptpAni (V82A) and lvgptpvnV (I84V). 29 HIV-1 infected patients (15 were HLA-A2+) with a history of protease inhibitor failure were screened for mutations within the protease gene and CD8+ T cells recognition of the wt and V82A variant peptides. CTL pressure alone, despite high functional avidity, did not drive the V82A substitution. Suprisingly V82A was found more frequently among HLA-A2- individuals (10/14) than HLA-A2+ (7/15), despite the mutation conferring not only drug resistance but CTL escape.
- 8/15 HLA-A2+ patients carried had a Val at position 82; 7/8 of these recognized the WT peptide, but only 3/8 could also recognize V82A.
- 7/15 had the V82A substitution; 2/7 recognized the wt and the V82A mutation, 1/7 recognized only the peptide with the V82A substitution.

HXB2 Location Protease (76–84)
Author Location Protease (76–84)
Epitope `LVGPTPVNI`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Canada
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords HAART, ART, escape, immunotherapy, variant cross-recognition or cross-neutralization
References Mason *et al.* 2004

- Accumulation of specific antiretroviral drug-resistance mutations in Pol gene was shown to sustain and even enhance the antigenicity and immunogenicity of HIV-1 CTL epitopes in this region. Several different patterns of cross-reactivity and selective recognition of wild-type and variant epitopes were found.
- LVGPTPVNv variant is detected due to appearence of I84V resistance mutation. Three patients receiving PIs had viral sequences obtained, and two had the I84V mutation. EliSpot reactivity to this epitope in either form was evident in these patients, showing drug resistnace can persist coincident with an active CTL response.

HXB2 Location Protease (76–84)
Author Location Protease (76–84)
Epitope `LVGPTPVNI`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords acute/early infection, optimal epitope
References Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized during chronic infection.

HXB2 Location Protease (76–84)
Author Location Protease (76–84)
Epitope LVGPTPVNI
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Canada
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords variant cross-recognition or cross-neutralization, characterizing CD8+ T cells, mimics
References Mason *et al.* 2005

- CTL responses against the human IP-30 signal peptide sequence LLDVPTAAV were shown to be elicited by stimulation of PBMCs from HIV-1 infected individuals with HIV protease peptide 76-84, LVGPTPVNI. In vitro stimulation with HIV PR 76-84 or the IP-30 signal peptide was shown to activate a comparable population of cross-reactive effector cells. None of the peptides activated CTL in non-HIV-infected individuals. IP-30 signal peptide was shown to have lower avidity T-cell interactions than the HIV peptide.
- As a control, responses to A2-restricted HIV epitopes ALVEICTEM, EELRQHLLRW, and LSPRTLNAW were shown not to give IP-30 responses.

HXB2 Location Protease (76–84)
Author Location Protease
Epitope LVGPTPVNI
Epitope name A2-LI9(Pro)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Protease (76–84)
Author Location Pol (156–164)
Epitope LVGPTPVNI
Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind three of the five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802).

HXB2 Location Protease (76–84)
Author Location Protease
Epitope LVGPTPVNI
Epitope name LI9(Proteasee)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A2-restricted epitope LVGPTPVNI elicited an immune response in Chinese HIV-1 positive subjects as part of peptides GHKAIGTVLVGPTPVNII and LVGPTPVNIIGRNLLTQL.
- 8 of the 55 HLA-A2 carriers responded to LVGPTPVNI-containing peptide with average magnitude of CTL response of 213 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Protease (76–85)
Author Location (C consensus)
Epitope LVGPTPVNII
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0205)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

CTL CD8+

- LVGPTPVNII is an optimal epitope.

HXB2 Location Protease (77–85)
Author Location Protease (C-96BW15C05)
Epitope `IGPTPVNII`
Epitope name D
Subtype C
Immunogen vaccine
Vector/Type: DNA, alphavirus replicon *Strain:* C clade C-96BW04.09, C clade C-96BW15C05 *HIV component:* Gag, Gag-Pol, Pol
Species (MHC) mouse (H-2^d)
Assay type Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, vaccine antigen design
References Megede *et al.* 2006

- HIV clade C gag, pol and fusion gagpol vaccines were compared in mice. Breadth of T cell responses was improved in mice immunized with gagpol fusion genes, compared to single antigen constructs. 5 new murine CD8+ T cell epitopes were mapped.
- This is a novel epitope.

HXB2 Location Protease (77–85)
Author Location Pol
Epitope `VGPTPVNII`
Epitope name V
Subtype B
Immunogen vaccine
Vector/Type: DNA with CMV promotor, modified vaccinia Ankara (MVA), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade, B clade, C clade Du422, Other *HIV component:* Gag, Nef, RT
Species (MHC) mouse (H-2D^d)
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords subtype comparisons, vaccine-induced epitopes, variant cross-recognition or cross-neutralization, antagonism
References Larke *et al.* 2007

- Cross-clade vaccine recognition was studied using either single-, multi or several anatomically separated single-clade vaccines. Limited cross-clade response was seen with single-clade administrations. Multi-clade vaccines gave immune interference (antagonism and original antigenic sin), reducing CTL response. Simultaneously administered but anatomically separated vaccines from clades A, B, C decreased antagonism and increased immune responses.
- Clade-B vaccination induced recognition of index epitope VGPTPVNII and variant VGPTPiNII.

HXB2 Location Protease (79–89)
Author Location Protease
Epitope `PTPVNIIGRNL`
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B63)
Assay type CD8 T-cell Elispot - IFNγ
Keywords cross-presentation by different HLA, optimal epitope
References Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- Putative HLA-B63/57/58 epitope containing the B58 supertype binding motif. Significantly more often recognized by B63-positive subjects than by negative subjects, trend towards being more often recognized in those with B57/B58.

HXB2 Location Protease (80–89)
Author Location Pol
Epitope `TPVNIIGRNL`
Epitope name Pol1151
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Epitope TPVNIIGRNL elicits IFN-gamma ELISpot responses in 3/7 subjects; and bound HLA-B7 with low and high affinities in soluble and cell-based assays respectively. Previously published HLA restrictions of this epitope include B63, B57, B58 (LANL database).

HXB2 Location Protease (80–90)
Author Location (C consensus)
Epitope `TPVNIIGRNML`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- TPVNIIGRNML is an optimal epitope.

HXB2 Location Protease (80–90)
Author Location Protease (80–90)
Epitope `TPVNIIGRNML`

Epitope name TL11
Immunogen peptide-HLA interaction
Species (MHC) human (B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords optimal epitope
References Honeyborne *et al.* 2006

- Novel epitopes are defined for four HLA-alleles common in South African Zulu/Xhosa populations: B*3910, B*4201, B*8101 and Cw*1801, by motif inference. HLA-A*2902 was found to overlap those of A1 and A24 supertypes.
- TPVNIIGRNML (TL11) was the optimal epitope for HLA-B*8101 with variants TPVNIIGRNM, PVNIIGRNML, TPVNIIGRNMLt, pTPVNIIGRNML having been tested.

HXB2 Location Protease (80–90)
Author Location
Epitope `TPVNIIGRNML`
Epitope name TL11
Immunogen
Species (MHC) human (B81)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B81 epitope.

HXB2 Location Protease (80–90)
Author Location Protease (80–90)
Epitope `TPVNIIGRNML`
Epitope name TL11
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Other
Keywords supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism
References Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alelles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Statistically significant associations between numbers of HLA-8101 expressing subjects and epitope TPVNIIGRNML were found.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope TL11 restriction.

HXB2 Location Protease (85–99)
Author Location Protease (141–155)
Epitope `IGRNLLTQIGCTLNF`
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008

- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.
- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.
- CTL immune response to consensus sequence IGRNLLTQIGCTLNF was elicited in subject 00016. Consensus epitope of subjects was the same as Clade B consensus.

HXB2 Location Protease (91–99)
Author Location Pol (2529–)
Epitope `TQIGCTLNF`
Epitope name B*1501 TF9
Subtype B, C, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (B*1501)
Country Australia
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, HLA associated polymorphism
References Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore et al., Science 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- The mutational pattern in the third position in this epitope TQiGCTLNF, is correlated with the host carrying HLA B*1501.
- This epitope was experimentally tested using Interferon-g Elispot and functional avidity studies. For one of six patients tested, the form TQ(L)GCTLNF showed decreased functional avidity relative to TQiGCTLNF. In all other patients, the form TQ(L)GCTLNF had greater functional avidity than the form TQiGCTLNF.

HXB2 Location Protease (91–99)

CTL CD8+

Author Location Protease
Epitope TQIGCTLNF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, rate of progression, immunodominance
References Frahm *et al.* 2006

- CTL responses restricted by HLA-B*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects inspite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominanat CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.
- TQIGCTLNF of clade B is a potential HLA-B*1503-restricted epitope, with epitope TQlGCTLNF found in clade C.

HXB2 Location Protease (91–99)
Author Location Protease (91–99 HXB2)
Epitope TQICGTLNF
Epitope name TF9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62, Cw3)
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, HLA associated polymorphism, drug resistance
References Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. 10 new CTL epitopes were defined statistically and experimentally, and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01_AE, 1 CRF03_AB, 1 CRF15_01B and 2 subtype Ds.
- This newly defined epitope, TQICGTLNF, TF9, carries minor HLA-B62 and -Cw3-associated mutations at I93L, viz. TQlCGTLNF.

II-B-11 Protease-RT CTL/CD8+ epitopes

HXB2 Location Protease-RT (95–5)
Author Location Gag (175–184)
Epitope CTLNFPISPI
Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- The epitope starts in Protease and ends in RT.
- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind all five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802)

HXB2 Location Protease-RT (96–5)
Author Location Pol (176–184)
Epitope TLNFPISPI
Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind three of the five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802).

HXB2 Location Protease-RT (96–5)
Author Location Pol (152–160)
Epitope TLNFPISPI
Immunogen HIV-1 infection
Species (MHC) human
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope TLNFPISPI was predicted to be restricted by HLA A*0201 and A*0207.

HXB2 Location Protease-RT (99–8)
Author Location Pol (155–163)
Epitope FPISPIETV
Epitope name FP9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5401)
Country Japan
Assay type Intracellular cytokine staining, Chromium-release assay
Keywords optimal epitope
References Kitano *et al.* 2008

- Asian-expressed HLA-B*5401-restricted epitopes were identified using overlapping-peptide methods and characterized. 5 epitopes from Pol and Nef induced CTL responses that killed target cells in more than 25% of B*5401-carrying tested patients.
- 7 peptides from Pol and Nef are listed in Fig. 2 as candidates for B*5401 restriction. No Gag-specific epitopes were identified in this study from the patient whose lymphocytes were screened.
- FPISPIETV was defined as an optimal epitope for HLA-B*5401 restriction, using truncated peptides.

HXB2 Location Protease-RT (99–9)
Author Location Pol (155–164)
Epitope FPISPIETVP
Epitope name FP10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5401)
Donor MHC A*0206, B*4801, B*5401
Country Japan
Assay type Intracellular cytokine staining, Chromium-release assay
Keywords optimal epitope
References Kitano *et al.* 2008

- Asian-expressed HLA-B*5401-restricted epitopes were identified using overlapping-peptide methods and characterized. 5 epitopes from Pol and Nef induced CTL responses that killed target cells in more than 25% of B*5401-carrying tested patients.
- 7 peptides from Pol and Nef are listed in Fig. 2 as candidates for B*5401 restriction. No Gag-specific epitopes were identified in this study from the patient whose lymphocytes were screened.
- FPISPIETVP was defined as an HLA-B*5401 restricted optimal epitope, using truncated peptides.

II-B-12 RT CTL/CD8+ epitopes

HXB2 Location RT (1–16)
Author Location (C consensus)
Epitope PISPIETVPVKLKPGM
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*3910)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location RT (3–12)
Author Location RT (3–12)
Epitope SPIETVPVKL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

HXB2 Location RT (3–12)
Author Location RT (LAI)
Epitope SPIETVPVKL
Subtype B
Immunogen HIV-1 infection

CTL CD8+

Species (MHC) human (A2, B61)
References van der Burg *et al.* 1997
- Recognized by CTL from a long-term survivor, EILKEPVGHGV was also recognized.
- Highly conserved across clades.

HXB2 Location RT (3–12)
Author Location (C consensus)
Epitope SPIETVPVKL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the P2 residue of SPIETVPVKL are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location RT (3–12)
Author Location Pol
Epitope SPIETVPVKL
Epitope name SL10
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, HLA associated polymorphism
References Frater *et al.* 2007
- To study whether CTL responses restricted by "good" HLA I molecules exert stronger immune selection than other HLA I molecules, 54 and 70 optimal epitopes within HIV-1 Gag, Pol and Nef genes for Caucasian and African cohorts were tested in patients over a mean of 14 months. "Good", advantageous HLA allele-restricted epitopes were much more polymorphic than epitopes restricted by other, non-advantageous HLA in patients, suggesting that benefits associated with HLA Class I alleles of elite controllers of disease progression are epitope-specific. Such "driver" epitopes with high polymorphism had high frequency of immune response, allowing them to be ranked for recognition and polymorphism.
- Patients with higher proportions of mutated epitopes also had lower plasma viral loads, and mean epitope variability correlated negatively with relative hazard of disease progression.
- Variants SsIETVPVKL and SPIkTVPVKL at positions 2 and 4 were the predominant polymorphisms found.

HXB2 Location RT (3–12)
Author Location RT
Epitope SPIETVPVKL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008
- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- SPIETVPVKL is a previously described HLA-B*8101-restricted epitope (part of Pol(RT) reacting peptides LGCTLNFPISpIETVPVKLP and CTLNFPISPIeTVPVKLKPGM) that contain a B*8101-associated reversion at residues P and E (SpIETVPVKL/SPIeTVPVKL).

HXB2 Location RT (3–12)
Author Location Pol
Epitope SPIETVPVKL
Immunogen
Species (MHC) human (B7)
References De Groot *et al.* 2001
- The program Epimatrix was used in conjunction with the program Conservatrix to identify conservered regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFNγ production in an ELISPOT assay.
- SPIETVPVKL was newly identified as HLA-B7 epitope in this study, it had been previously shown to be presented by HLA-A2 and B61.

HXB2 Location RT (3–12)
Author Location Pol
Epitope SPIETVPVKL
Epitope name 1307
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A2, B61, B7, B8)
Donor MHC A03, A24, B07, B38, Cw07, Cw12/13; A29, A30, B08, B44, Cw07, Cw16
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References De Groot *et al.* 2003
- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for SPIETVPVKL: 12%. Promiscuous epitope binding to A02, B07, B08 and B61.

HXB2 Location RT (3–12)

Author Location RT (3–12)
Epitope SPIETVPVKL
Epitope name SL10
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Other
Keywords supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism
References Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alelles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Statistically significant associations between numbers of HLA-8101 expressing subjects and epitope SPIETVPVKL were found.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope SL10 restriction.

HXB2 Location RT (5–12)
Author Location RT (5–12)
Epitope IETVPVKL
Epitope name IL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*40)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLAs-B*40-associated substitutions within optimally defined epitope IETVPVKL are at positions E2 and K7, IeTVPVkL.

HXB2 Location RT (5–12)
Author Location RT (5–12)
Epitope IETVPVKL
Immunogen HIV-1 infection
Species (MHC) human (B*4001)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location RT (5–12)
Author Location Pol (160–167)
Epitope IETVPVKL
Epitope name IL8
Immunogen HIV-1 infection
Species (MHC) human (B*4001)
Donor MHC A*0201, A*2402, B*4001, B*5001, Cw03, Cw04
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords immunodominance, escape, variant cross-recognition or cross-neutralization
References Draenert *et al.* 2006

- HIV-specific cellular and humoral immune responses were examined in monozygotic male twins infected simultaneously with the same virus. 15 of 17 targeted epitopes were identical in the twins, including two immunodominant responses. 3 of 4 declining responses in the twins showed mutations at the same residue. Evolving antibody responses cross-neutralized the other twin's virus. The results were compared with a third brother, infected by the twins' virus 13 months after their seroconversion. The data show similarity in disease course in persons of identical genetic background infected with the same strain of HIV-1.
- This epitope, IETVPVKL (IL8), restricted by HLA-B*4001, had variants IdTVPVKL and IETVPVrL arise.

HXB2 Location RT (5–12)
Author Location Pol
Epitope IETVPVKL
Epitope name IL-8
Immunogen HIV-1 infection
Species (MHC) human (B40)
Keywords escape, TCR usage, immune evasion
References Yu *et al.* 2007b

- The dependence of TCR clonotype recruitment on genetic background was determined by studying monozygotic twins infected with the same HIV-1 strain. After an early, initial correlation in the magnitude, specificity and immunodominance of CTL response [Draenert et al. J. Exp. Med. 203:529-539(2006)], subsequent disease was mixed with respect to CTL epitopes' mutational escape. TCR alpha and beta chain repertoires were analyzed and it was found that their clonotypes in HIV-specific CTLs were broadly heterogeneous for both concordant and discordant epitope sequence evolution between the twins. Therefore initial TCR recruitment appears to be an entirely random process independent of genetic background of the infected individual.
- This epitope, IL8, showed discordant epitope evolution between the twins, and both alpha and beta TCR chains recruited were entirely different between them.

HXB2 Location RT (5–12)
Author Location RT
Epitope IETVPVKL
Epitope name IL8(RT)
Subtype B

CTL CD8+

Immunogen HIV-1 infection
Species (MHC) human (B40)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B40-restricted epitope IETVPVKL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide PISPIETVPVKLKPGM.
- 5 of the 20 HLA-B40 carriers responded to a IETVPVKL-containing peptide with average magnitude of CTL response of 664 SFC/million PBMC.

HXB2 Location RT (5–29)
Author Location RT (160–184 HXB2)
Epitope `IETVPVKLKPGMDGPKVKQWPLTEE`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Walker *et al.* 1989

- One of five epitopes defined for RT-specific CTL clones in this study.

HXB2 Location RT (14–23)
Author Location Pol
Epitope `PGMDGPKVKQ`
Epitope name 1276
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A68, B42, B45, Cw16, Cw17
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for PGMDGPKVKQ:52% Promiscuous epitope binding to A11 or A68, previously published B8.

HXB2 Location RT (15–32)
Author Location (C consensus)
Epitope `GMDGPKVKQWPLTEEKIK`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4202)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location RT (18–26)
Author Location RT (185–193 LAI)
Epitope `GPKVKQWPL`
Subtype B
Immunogen
Species (MHC) human (B*0801)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*0801 epitope.

HXB2 Location RT (18–26)
Author Location RT (18–26)
Epitope `GPKVKQWPL`
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope GPKVKQWPL was predicted to be restricted by HLA B*0702, B*0801, B*3501, B8.

HXB2 Location RT (18–26)
Author Location p24
Epitope `GPKVKQWPL`
Epitope name GL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay

Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- 261 days after first testing, epitope GPKVKQWPL showed no variation in a treated patient. Previously published HLA-restriction for GL9 is HLA-B7.

HXB2 Location RT (18–26)
Author Location RT (18–26)
Epitope GPKVKQWPL
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Meier *et al.* 1995; Menendez-Arias *et al.* 1998

- HIV proteins with mutations in this epitope allowed transactive inhibition of specific CTL-mediated lysis.
- Article reviewed in Menendez-Arias *et al.* [1998], with a discussion of antagonism.

HXB2 Location RT (18–26)
Author Location RT (173–181)
Epitope GPKVKQWPL
Immunogen
Species (MHC) human (B8)
References Goulder *et al.* 1997g; Menendez-Arias *et al.* 1998

- Included in a study of the B8 binding motif.
- Article reviewed in Menendez-Arias *et al.* [1998], with a discussion of antagonism.

HXB2 Location RT (18–26)
Author Location RT (185–193 LAI)
Epitope GPKVKQWPL
Subtype B
Immunogen
Species (MHC) human (B8)
References Sutton *et al.* 1993

- Predicted epitope based on B8-binding motifs, from larger peptide IETVPVKLKPGMDGPKVKQWPLTEE.

HXB2 Location RT (18–26)
Author Location RT (185–193 LAI)
Epitope GPKVKQWPL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Klenerman *et al.* 1995; Menendez-Arias *et al.* 1998

- Naturally occurring antagonist GPRVKQWPL found in viral PBMC DNA and RNA.
- Article reviewed in Menendez-Arias *et al.* [1998] with a discussion of antagonism.

HXB2 Location RT (18–26)
Author Location RT (18–26)
Epitope GPKVKQWPL
Immunogen in vitro stimulation or selection
Species (MHC) human (B8)
Keywords dendritic cells
References Zarling *et al.* 1999

- This study compares the ability of macrophages and dendritic cells to stimulate primary responses in CD8+ lymphocytes isolated from HLA-appropriate HIV-uninfected donors using peptide-pulsed APC – the dendritic cells performed better as APC for the stimulation of primary responses.
- Strong CTL responses were elicited by the epitopes DRFYKTLRA and GEIYKRWII when presented by either immature or mature dendritic cells – macrophages were not able to prime a CTL response against DRFYKTLRA.
- A weak response to KLTPLCVSL was stimulated using macrophages as the APC.
- No detectable response was observed for the following previously-defined HIV epitopes: KIRLRPGGK, ILKEPVHGV, IRLRPGGK, GPKVKQWPL.

HXB2 Location RT (18–26)
Author Location RT (185–193)
Epitope GPKVKQWPL
Epitope name GPK
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART, supervised treatment interruptions (STI), immunodominance, escape, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- Two of the 7/8 study subjects that were HLA B8+ recognized this epitope.
- Patient SC2 (HLA A1, B7/8, Cw0701/0702, DR4/53, DQ7) had CTL responsiveness against epitopes FLKEKGGL, GPKVKQWPL, and GEIYKRWII peptides – FLKEKGGL tetramer staining steadily declined and at day 1340 the FLKEKGGL stained cells were no longer detected and the escape mutant FLKENGGI was found in 8/10 clones.
- Patient SC11(HLA A1, B8, Cw0201, DR3/11, DR52, DQ2/7) started therapy early, remained on therapy for 40 days, then reinitiated HAART at day 640 had a CTL response to FLKEKGGL, GPKVKQWPL, and GEIYKRWII throughout and received a benefit from the early limited course therapy.

HXB2 Location RT (18–26)
Author Location Pol
Epitope GPKVKQWPL
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART

CTL CD8+

References Seth *et al.* 2001
- CTL responses were studied by tetramer staining in 41 patients with combination therapy – activated CD8+ T-cells decline as the viral load drops in response to therapy, but the overall level of antigen-specific cells capable of differentiating into effectors stays constant and new epitopes may be recognized.

HXB2 Location RT (18–26)
Author Location RT (185–193 SF2)
Epitope GPKVKQWPL
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b
- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with preseroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B8+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 0/3 group 2, and 2/2 group 3.

HXB2 Location RT (18–26)
Author Location Pol (171–180)
Epitope GPKVKQWPL
Subtype A, B, C, D
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B8)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a
- GPKVKQWPL is cross-reactive for clades A, B, C, and D.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location RT (18–26)
Author Location RT (18–26)
Epitope GPKVKQWPL
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Day *et al.* 2001
- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual.

HXB2 Location RT (18–26)
Author Location RT
Epitope GPKVKQWPL
Epitope name GPK
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART, supervised treatment interruptions (STI)
References Oxenius *et al.* 2002b
- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFNgamma Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

HXB2 Location RT (18–26)
Author Location Pol (171–180)
Epitope GPKVKQWPL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords Th1, characterizing CD8+ T cells
References Kleen *et al.* 2004
- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- One of the patients responded to this peptide with GzB producing cells, while two different patients responded with IFN-gamma producing cells.

HXB2 Location RT (18–26)
Author Location (B consensus)
Epitope GPKVKQWPL
Epitope name GL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A25, A32, B08, B14, Cw7, Cw8
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c
- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location RT (18–26)

Author Location Pol (173–181)
Epitope GPKVKQWPL
Epitope name GL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A*01, A*11, B*08, B*15, Cw*04, Cw*07
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords escape, variant cross-recognition or cross-neutralization, optimal epitope
References Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- The GL9 variant GPrVKQWPL was essentially the only form of the epitope detected over a 5-year period in this person. Elispot reactions were roughly equivalent between the autologous form and the B clade consensus form, GPKVKQWPL. A single variant was observed in 1/8 clones at the 5-year time point, GPrVKQgPL.

HXB2 Location RT (18–26)
Author Location RT
Epitope GPKVKQWPL
Epitope name B8-GL9(RT)
Immunogen HIV-1 infection
Species (MHC) human (B8)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (18–26)
Author Location
Epitope GPKVKQWPL
Immunogen
Species (MHC) (B8)
Keywords review, immunodominance, escape, vaccine antigen design
References Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection.

HXB2 Location RT (18–27)
Author Location Pol
Epitope GPKVKQWPLT
Immunogen
Species (MHC) human (B7, B8)
References De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conservered regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFNγ production in an ELISPOT assay.
- GPKVKQWPLT was confirmed as a previously identified HLA-B8 epitope, and newly identified as an HLA-B7 epitope in this study.

HXB2 Location RT (18–27)
Author Location Pol
Epitope GPKVKQWPLT
Epitope name 1293
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (B7, B8)
Donor MHC A03, A24, B07, B38, Cw07, Cw12/13; A29, A30, B08, B44, Cw07, Cw16
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for GPKVKQWPLT: 27% Promiscuous epitope binding to B07 and B08.

HXB2 Location RT (33–41)
Author Location RT (33–41)
Epitope ALVEICTEM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Donor MHC A*01, B*08
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion

CTL CD8+

References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- In one patient, initially the consensus sequence ALVEICTEM was not found. Instead the 35I variant ALiEICTEM was seen, followed by the emergence of the 35M variant, ALmEICTEM, and finally, emergence of the consensus B sequence, ALvEICTEM. Strongest immune responses were detected to the 35M variant and weaker responses to the 35I variant, while negligible responses were seen to the consensus, ALVEICTEM. This is an example of CTL-responses against variant epitopes causing virus evolution to the consensus B sequence. Other variants that emerged were ALtEICTEM, ALiEICTEt, ALiEICTdM, ALmkICTEM and ALmEICaEM.
- Responses to epitope ALVEICTEM were seen in early chronic infection. This was one of the epitopes targeted by broad HLA-A2-restricted CTL responses.

HXB2 Location RT (33–41)
Author Location RT (33–41 LAI)
Epitope ALVEICTEM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*0201 epitope.

HXB2 Location RT (33–41)
Author Location RT (33–41 LAI)
Epitope ALVEICTEL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords binding affinity, computational epitope prediction
References Samri *et al.* 2000

- This epitope contains the mutation M41L, a mutation induced by nucleosidee reverse transcriptase inhibitors.
- Patient 201#5, (A*0201), was found by ELISPOT to recognize the mutated peptide after zidovudine treatment, but not the wild-type peptide – the mutation M41L gave an increased A2 binding score (`http://bimas.dcrt.nih.gov/molbio/hla_bind`) compared to the wildtype RT sequence.
- Three additional A*0201 individuals and one B27 individual did not respond to this epitope before or after treatment.
- M41L occurred at anchor positions p2 and p9 in several computer predicted RT epitopes (33-41, 32-41, and 40-49) (http//bimas.dcrt.nih.gov/molbio/hla_bind), and increased the predicted binding affinity for 6 HLA molecules (B2705, B5102, C3, A0201, B2705 and B3901)

HXB2 Location RT (33–41)
Author Location RT (33–41 MN)
Epitope ALVEICTEM
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* B clade MN *HIV component:* gp120, Protease, RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) humanized mouse (A*0201)
Assay type CD8 T-cell Elispot - IFNγ
Keywords epitope processing, vaccine-specific epitope characteristics, immunodominance, immunotherapy
References Isaguliants *et al.* 2004

- Immunization of HLA-A*0201-transgenic mice with synthetic genes encoding clusters of human A*0201 CTL epitopes located at the sites of drug resistance mutations, induced RT-specific cellular responses indicating the immunogenicity of these constructs. This vaccine strategy may be a first step towards a therapeutic vaccine against drug-resistant strains.
- This was one of five HLA-A*0201 epitopes from the RT or protease proteins that was included in the polyepitope vaccine. When the transgenic HLA A*0202 mice were vaccinated with the polyepitope construct or with a mixture of RT peptides, a sustained low level CD8+ T-cell gamma IFN response was observed, in contrast to when an intact RT gene was used for vaccination.

HXB2 Location RT (33–41)
Author Location Pol (132–140 IIIB)
Epitope ALVEICTEM
Epitope name pol132-140
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* Gag-Pol
Species (MHC) humanized mouse (A*0201)
Assay type Intracellular cytokine staining
Keywords subtype comparisons, vaccine-specific epitope characteristics, immunodominance, variant cross-recognition or cross-neutralization, vaccine antigen design
References Singh & Barry 2004

- When A*0201-C3H/J transgenic mice were immunized with plasmids encoding wild-type gag-pol, codon-optimized (CO) gag-pol, and an expression library vaccine expressing 16 fragments of gag-pol fused with ubiquitin for proteosome targeting (ELI), the ELI vaccine produced up to 10-fold higher CD8 T-cell responses than the other two vaccines. In contrast to the wt and CO vaccines, which tended to augment only immunodominant responses, boosting with the ELI vaccine resulted in many CD8 responses against variant epitopes from different HIV-1 clades, and against drug-resistant variants.

- Different variants of this epitope from different clades were tested. WT and CO vaccines produced low level CD8+ T-cell responses against the B clade form as well as against variants from other clades, but the ELI vaccine produced much more intense responses against the B clade and all variants tested, including after boosting. The variants were: clade A, alTDictem; clade C, atTAicEem; and clade D, alIeicSem.

HXB2 Location RT (33–41)
Author Location Pol
Epitope `ALVEICTEM`
Epitope name A9M
Immunogen vaccine
Vector/Type: measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140ΔV3
Species (MHC) transgenic mouse (A*0201)
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells
References Lorin *et al.* 2005a

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

HXB2 Location RT (33–41)
Author Location RT (33–41)
Epitope `ALVEICTEM`
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Haas *et al.* 1998

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules.

HXB2 Location RT (33–41)
Author Location RT (33–41)
Epitope `ALVEICTEM`
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- SLYNTVATL was the dominant A2 epitope recognized in patients with chronic infection, except for Subject 11841 who recognized 5/8 epitopes and who had a dominant A-2 response to ALVEICTEM.

HXB2 Location RT (33–41)
Author Location RT (33–41)
Epitope `ALVEICTEM`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords acute/early infection, optimal epitope
References Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized in chronic infection, and even then was recognized infrequently.

HXB2 Location RT (33–41)
Author Location RT (33–41)
Epitope `ALVEICTEM`
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Canada
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords mimics
References Mason *et al.* 2005

- CTL responses against the human IP-30 signal peptide sequence LLDVPTAAV were shown to be elicited by stimulation of PBMCs from HIV-1 infected individuals with HIV protease peptide 76-84, LVGPTPVNI. In vitro stimulation with HIV PR 76-84 or the IP-30 signal peptide was shown to activate a comparable population of cross-reactive effector cells. None of the peptides activated CTL in non-HIV-infected individuals. IP-30 signal peptide was shown to have lower avidity T-cell interactions than the HIV peptide.
- As a control, responses to A2-restricted HIV epitopes ALVEICTEM, EELRQHLLRW, and LSPRTLNAW were shown not to give IP-30 responses.

HXB2 Location RT (33–41)
Author Location RT
Epitope `ALVEICTEM`
Epitope name A2-AM9(RT)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

CTL CD8+

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (33–41)
Author Location Pol
Epitope ALVEICTEM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A1, A19, B*3501, B44, Cw16, Cw7; A*0201, A19, B14, B44, Cw16, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
References Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-A2 restricted epitope, ALVEICTEM was mutated to ALiEICTEM in the daughter D2 isolate.

HXB2 Location RT (33–41)
Author Location RT
Epitope ALVEICTEM
Epitope name AM9(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide sequence contains the exact sequence of a previously described HLA-A2 optimal epitope, ALVEICTEM, none of the 55 HLA-A2 carriers responded to it (author communication and Fig.1).

HXB2 Location RT (33–41)
Author Location RT (33–41)
Epitope ALVEICTEM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2, A3)
Country Canada
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords HAART, ART, immunotherapy, variant cross-recognition or cross-neutralization
References Mason *et al.* 2004

- Accumulation of specific antiretroviral drug-resistance mutations in Pol gene was shown to sustain and even enhance the antigenicity and immunogenicity of HIV-1 CTL epitopes in this region. Several different patterns of cross-reactivity and selective recognition of wild-type and variant epitopes were found.
- ALVEICTEl variant is detected due to appearence of M41L resistance mutation. The M41L variant peptide was almost always preferentially recognized by CTLs from patients undergoing antiretroviral therapy.

HXB2 Location RT (33–43)
Author Location RT (33–43)
Epitope ALVEICTEMEK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
References Haas *et al.* 1998

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules.
- C. Brander notes that this is an A*0301 epitope in the 1999 database, G. Haas, pers. comm.

HXB2 Location RT (33–43)
Author Location RT (33–43)
Epitope ALVEICTEMEK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*0301 epitope.

HXB2 Location RT (33–43)
Author Location RT (33–43)
Epitope ALVEICTEMEK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant.

HXB2 Location RT (33–43)
Author Location RT Pol (188–198)
Epitope ALVICTEMEK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong T-helper cell responses. Only patients starting with moderately high viral load (VL) were able to reduce the VL set point. HIV-1 specific CD8+ T-cell responses were shown to increase significantely until the end of the follow up.
- Less than 2 of 14 patients recognized this epitope.

HXB2 Location RT (33–43)
Author Location RT
Epitope ALVEICTEMEK
Epitope name A3-AK11(RT)
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (33–43)
Author Location RT
Epitope ALVEICTEMEK
Epitope name AK11(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A3-restricted epitope ALVEICTEMEK elicited no immune response in Chinese HIV-1 positive subjects as part of peptide EEKIKALVEICTEMEK.
- Although the tested peptide sequence contains the exact sequence of a previously described HLA-A3 optimal epitope, ALVEICTEMEK, none of the 3 HLA-A3 carriers responded to it (author communication and Fig.1).

HXB2 Location RT (38–52)
Author Location RT (203–209)
Epitope CTEMEKEGKISKIGP
Immunogen vaccine
Vector/Type: Salmonella *HIV component:* RT
Species (MHC) mouse (H-2^d)
References Burnett *et al.* 2000

- A live attenuated bacterial vaccine, Salmonella SL3261-pHART, with an inserted HIV epitope in the Lpp-OmpA-HIV fusion protein, induced a specific CTL response in BALB/c mice (<15% lysis assayed by Cr-release of target cells)

HXB2 Location RT (38–52)
Author Location RT (205–219 BRU)
Epitope CTEMEKEGKISKIGP
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU *HIV component:* RT
Species (MHC) mouse (H-2^k)
Keywords review
References De Groot *et al.* 1991; Menendez-Arias *et al.* 1998

- Murine and human helper and CTL epitope.

CTL CD8+

- Epitope noted in a review by Menendez-Arias *et al.* [1998] to be located in the "fingers" domain of RT and is a helper and CTL epitope.

HXB2 Location RT (38–52)
Author Location RT (205–219)
Epitope CTEMEKEGKISKIGP
Immunogen HIV-1 infection
Species (MHC) human
Keywords review
References Hosmalin *et al.* 1990; Menendez-Arias *et al.* 1998

- Murine and human helper and CTL epitope.
- Epitope noted in a review by Menendez-Arias *et al.* [1998] to be located in the "fingers" domain of RT and is a helper and CTL epitope.

HXB2 Location RT (39–47)
Author Location RT
Epitope TEMEKEGKI
Immunogen
Species (MHC) mouse (H-2K^{k})
References Leggatt *et al.* 1998

- Epitope variants were examined for CTL response in concert with H-2K^{k} MHC class I binding – all of the following combinations were observed: (i) two single mutations which did not alone abrogated CTL activity did abrogate activity when combined, (ii) loss of recognition of a single substitution could be restored by an additional substitution, and (iii) sometimes there was recognition of two single substitutions as well as the combination of those substitutions.
- 2E and 9I are anchor residues for H-2K^{k}—if you have M in the third position, it enhances H-2K^{k} binding 10-fold, but polymorphism at this site is important for the overall conformation of the peptide and can influence T cell recognition.

HXB2 Location RT (39–47)
Author Location RT (206–214)
Epitope TEMEAEGKI
Immunogen in vitro stimulation or selection
Species (MHC) mouse
Keywords TCR usage
References Leggatt *et al.* 1997

- Ala-substituted nonamer-peptide used to test a non-radioactive assay for murine CTL recognition of peptide-MHC class I complexes.
- The new assay is CTL adherence assay (CAA), and is based on the discovery that CTL develop adhesive properties upon TCR triggering.
- Substitutions in TEMEAEGKI that reduce cytolytic activity were correctly detected by CAA.

HXB2 Location RT (42–50)
Author Location RT (42–50 LAI)
Epitope EKEGKISKI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*5101 epitope.

HXB2 Location RT (42–50)
Author Location RT (42–50 HXB2)
Epitope EKEGKISKI
Epitope name EI9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.

HXB2 Location RT (42–50)
Author Location RT (42–50)
Epitope EKEGKISKI
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope EKEGKISKI was predicted to be restricted by HLA B*2701, B*3801, B*3901, B*3909, B*4402, B*5101, B8.

HXB2 Location RT (42–50)
Author Location RT (42–50 LAI)
Epitope EKEGKISKI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
References Haas *et al.* 1998

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules.

HXB2 Location RT (42–50)
Author Location RT (42–50)
Epitope EKEGKISKI
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these eptiopes, but this increased over time.

HXB2 Location RT (42–50)
Author Location
Epitope EKEGKISKI
Immunogen HIV-1 infection
Species (MHC) human (B51)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope EKEGKISKI elicited a magnitude of response of 270 SFC with a functional avidity of 0.1nM and binding affinity of 14059nM.

HXB2 Location RT (42–50)
Author Location RT
Epitope EKEGKISKI
Epitope name EI9(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide sequence contains the exact sequence of a previously described HLA-B51 optimal epitope, EKEGKISKI, none of the 15 HLA-B51 carriers responded to it (author communication and Fig.1).

HXB2 Location RT (55–72)
Author Location (C consensus)
Epitope PYNTPVFAIKKKDSTKWR
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*6801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location RT (57–65)
Author Location RT (57–65)
Epitope NTPVFAIKK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.

CTL CD8+

- A more detailed evaluation of HIV-naiive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A0201) HLA-restriction. Thus, CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope NTPVFAIKK was predicted to be restricted by HLA A*0301, A*6601, C*0102.

HXB2 Location RT (57–65)
Author Location RT
Epitope NTPVFAIKK
Immunogen HIV-1 infection, vaccine
Species (MHC) human (A*6801, A3 supertype)
Country Australia
Assay type Intracellular cytokine staining
Keywords HAART, ART, immunotherapy, variant cross-recognition or cross-neutralization, optimal epitope
References Stratov *et al.* 2005

- CD8 T-cells targeting epitopes spanning drug resistance induced mutations were detected in 3/25 individuals harboring multidrug-resistant HIV-1. Novel CD8 T-cell responses were detected against epitopes with common protease inhibitor fitness mutations. T-cell immunity to drug-resistant variants was confirmed in SHIV-infected macaques, where CD8 and CD4 immune responses to RT and protease resistance mutations were elicited using peptide-based immunotherapy.
- The immune response to this peptide was cross-reactive for both the wild type and RT drug resistance mutation K65R, and NTPVFAIKK and ntpvfaikR stimulated CD8 T-cell responses with equal efficiency. The C-terminal R or K is required for a full response; NTPVFAIK stimulated a much weaker response.
- The 3 people that responded to the drug resistant forms of the virus were among those that had the highest levels of CD4 and CD8 T-cell responses, indicating that they were among the most immunocompetent.

HXB2 Location RT (57–65)
Author Location Pol (236–244)
Epitope NTPVFAIKK
Immunogen HIV-1 infection
Species (MHC) human (A3 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801).

HXB2 Location RT (57–66)
Author Location Pol
Epitope NTPVFAIKKK
Epitope name 1274
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) chimpanzee, goat, baboon (A11, A68, B8)
Donor MHC A01, A68, B15, B40, Cw03; A25, A68, B18, B27
Country United States
Assay type T-cell Elispot
Keywords binding affinity, supertype, computational epitope prediction, immunodominance, cross-presentation by different HLA
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for NTPVFAIKKK:53%. Epitope binds to A11 and A68 supertype, and is immunodominant.

HXB2 Location RT (57–66)
Author Location Pol (209–221)
Epitope NTPVFAIKKK
Subtype B
Immunogen HIV-1 infection, peptide-HLA interaction
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance
References Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, NTPVFAIKKK, is similar to human protein HERV, sequence SPwNTPVFvIKKK.

HXB2 Location RT (73–82)
Author Location RT (73–82)
Epitope KLVDFRELNK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)

Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location RT (73–82)
Author Location RT (73–82 LAI)
Epitope KLVDFRELNK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Samri *et al.* 2000

- This epitope contains the mutation L74V, a frequent mutation induced by nucleoside reverse transcriptase inhibitors.
- The wild-type, but not the mutated peptide, was recognized before and after zidovudine treatment in A3-restricted patients 252#0 and 252#4.
- Mutation L74V affects the p2 anchor position in RT epitopes and was predicted to reduce binding to A3 (http://bimas.dcrt.nih.gov/molbio/hla_bind)

HXB2 Location RT (73–82)
Author Location RT (228–237)
Epitope KLVDFRELNK
Epitope name A3-KK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 3/7 individuals began to have detectable responses to this epitope after STI.

HXB2 Location RT (73–82)
Author Location RT (73–82)
Epitope KLVDFRELNK
Epitope name A3-KK10 Pol
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), escape, early treatment, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response, but in this case the epitope did not vary.

HXB2 Location RT (73–82)
Author Location Pol
Epitope KLVDFRELNK
Epitope name 1340
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, A23, B49, B57; A02, A03, B08, B51, Cw01, Cw07; A03, A11, B05, B14, Cw08
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for KLVDFRELNK: 36%.

HXB2 Location RT (73–82)
Author Location (B consensus)
Epitope KLVDFRELNK
Epitope name KK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, B07, Cw7
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location RT (73–82)
Author Location RT
Epitope KLVDFRELNK
Epitope name A3-KK10(RT)
Immunogen HIV-1 infection

Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (73–82)
Author Location RT
Epitope `KLVDFRELNK`
Epitope name KK10(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide sequence contains the exact sequence of a previously described HLA-A3 optimal epitope, KLVDFRELNK, none of the 3 HLA-A3 carriers responded to it (author communication and Fig.1).

HXB2 Location RT (87–104)
Author Location (C consensus)
Epitope `FWEVQLGIPHPAGLKKKK`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*6801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location RT (93–101)
Author Location (LAI)
Epitope `GIPHPAGLK`
Subtype B
Immunogen
Species (MHC) human (A*0301)
Keywords optimal epitope
References Altfeld 2000; Llano *et al.* 2009

HXB2 Location RT (93–101)
Author Location RT (248–257)
Epitope `GIPHPAGLK`
Epitope name A3-GK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 1/7 individuals began to have detectable responses to this epitope after STI.

HXB2 Location RT (93–101)
Author Location RT (93–101)
Epitope `GIPHPAGLK`
Epitope name A3-GK9 Pol
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), escape, early treatment, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response, but in this case the epitope did not vary.

HXB2 Location RT (93–101)
Author Location Pol
Epitope `GIPHPAGLK`
Epitope name 1337
Subtype multiple
Immunogen HIV-1 infection

Species (MHC) human (A3)
Donor MHC A03, A23, B49, B57
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for GIPHPAGLK: 20%.

HXB2 Location RT (93–101)
Author Location (B consensus)
Epitope GIPHPAGLK
Epitope name GK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, B07, Cw7
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location RT (93–101)
Author Location RT
Epitope GIPHPAGLK
Epitope name A3-GK9(RT)
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (93–101)
Author Location RT
Epitope GIPHPAGLK
Epitope name GK9(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide sequence contains the exact sequence of a previously described HLA-A3 optimal epitope, GIPHPAGLK, none of the 3 HLA-A3 carriers responded to it (author communication and Fig.1).

HXB2 Location RT (93–102)
Author Location Pol (240–249 93TH253 subtype CRF01)
Epitope GIPHPAGLKK
Epitope name P248-257
Subtype CRF01_AE
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A11)
Keywords HIV exposed persistently seronegative (HEPS)
References Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was weakly reactive in the HEPS study subject 265 who was HLA A2/A11 and after a second stimulation *in vitro* gave a strong response in HEPS study subject 128 who was HLA A11/A33.

HXB2 Location RT (93–102)
Author Location Pol (240–249 93TH253 subtype CRF01)
Epitope GIPHPAGLKK
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A11)

Keywords subtype comparisons
References Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This is one of the new A11 epitopes identified through the streamlined EpiMatrix method, and 2/8 tested FSWs recognized it.
- This epitope was highly conserved in other subtypes, and exact matches were common.

HXB2 Location RT (94–102)
Author Location Pol
Epitope IPHPAGLKK
Epitope name Pol1167
Subtype C
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Epitope IPHPAGLKK elicits IFN-gamma ELISpot responses in 1/7 subjects; and bound HLA-B7 with low and high affinities in soluble and cell-based assays respectively. Previously published HLA restriction of this epitope includes A11 (LANL database).

HXB2 Location RT (98–113)
Author Location RT (252–266)
Epitope AGLKKKKSVTVLDVGD
Immunogen HIV-1 infection
Species (MHC) human (Cw4)
References Bernard *et al.* 1998

- This study focuses on six rare long-term survivor HIV-infected people who were infected for many years without exhibiting immune dysregulation – such immunologically normal HIV-infected (INHI) cases occur at a frequency between 0.1 and 1% in the infected population.
- No direct CTL were found in any of the six INHIs, but above background CTLp activity was founded in 3/6 INHIs.

HXB2 Location RT (98–113)
Author Location Pol (254–264 BH10, LAI)
Epitope AGLKKKKSVTVLDVGD
Immunogen HIV-1 infection
Species (MHC) human
References Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is GLKKKKSVTVL) has similarity with the CD166 antigen (activated leukocyte-cell adhesion molecule), fragment GLKKRESLTLI.

HXB2 Location RT (102–118)
Author Location (C consensus)
Epitope KKKSVTVLDVGDAYFSV
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0401)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location RT (103–117)
Author Location RT (257–251)
Epitope KKSVTVLDVGDAYFS
Immunogen HIV-1 infection
Species (MHC) human (Cw4)
References Bernard *et al.* 1998

- This study focuses on six rare long-term survivor HIV-infected people who were infected for many years without exhibiting immune.
- No direct CTL were found in any of the six INHIs, but above background CTLp activity was founded in 3/6 INHIs.

HXB2 Location RT (107–115)
Author Location RT (262–270 IIIB)
Epitope TVLDVGDAY
Immunogen
Species (MHC) human (B*3501)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*3501 epitope.

HXB2 Location RT (107–115)
Author Location Pol (262–270)
Epitope TVLDVGDAY
Epitope name TY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Donor MHC A*0201, A*0301, B*3501, B*51, Cw*04, Cw*06
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords escape, acute/early infection
References Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- The response to this epitope was not evident until month 20, and increased over time.

HXB2 Location RT (107–115)
Author Location RT (107–115)
Epitope TVLDVGDAY
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope TVLDVGDAY was predicted to be restricted by HLA B0702, B3501, B5102, B5103, B5301, B5401 and B5502 as well. B*1501, B*3501, B*5701, C*0304.

HXB2 Location RT (107–115)
Author Location RT (262–270 IIIB)
Epitope TVLDVGDAY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords review, responses in children, mother-to-infant transmission
References Menendez-Arias *et al.* 1998; Wilson *et al.* 1996

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.
- TVLDMGDAC is a naturally occurring variant that is less reactive.
- Menendez-Arias *et al.* [1998], in a review, notes that this epitope includes a catalytic residue (Asp-110) in the active site of RT.

HXB2 Location RT (107–115)
Author Location Pol (262–270 IIIB)
Epitope TVLDVGDAY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords responses in children, mother-to-infant transmission, escape
References Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- An additional variant that gave a positive CTL response: TVLDMGDAC.

HXB2 Location RT (107–115)
Author Location Pol (262–270)
Epitope TVLDVGDAY
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location RT (107–115)
Author Location RT (262–270 SF2)
Epitope TVLDVGDAY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 1/2 group 1, 0/2 group 2, and 0/1 group 3.

HXB2 Location RT (107–115)
Author Location
Epitope TVLDVGDAY
Epitope name Pol-TY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B35, 8/21 (38%) recognized this epitope.

HXB2 Location RT (107–115)
Author Location Pol

CTL CD8+

Epitope TVLDVGDAY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC A11, A3, B35, B51
Keywords mother-to-infant transmission
References Sabbaj *et al.* 2002

- IFNgamma T-cell responses in breast milk of 5 HIV-1 infected women from the US and 6 from Zambia were tested with using Elispot. 11/11 women responded to Gag, 8/11 responded to Pol, 7/11 women to Nef, and 2/5 women to Env peptide pools. These responses were shown to be primarily due to CD8+ T-cells in one woman, and another woman had cytolytic responses measured by Cr-release.
- T-cells in breast milk from a volunteer who was HLA A3, A11, B35, B51 induced IFNgamma after stimulation with either of two overlapping peptides that carry known B35 epitope TVLDVGDAY.
- The frequencies of responses in the two compartments differed, and 2/4 women that responded to epitopes in Nef 101-205 and Pol 601-710 showed responses in breast milk but no detectable responses in peripheral blood cells.

HXB2 Location RT (107–115)
Author Location RT (107–115)
Epitope TVLDVGDAY
Subtype AG
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country Canada
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords HAART, ART, immunotherapy, variant cross-recognition or cross-neutralization
References Mason *et al.* 2004

- Accumulation of specific antiretroviral drug-resistance mutations in Pol gene was shown to sustain and even enhance the antigenicity and immunogenicity of HIV-1 CTL epitopes in this region. Several different patterns of cross-reactivity and selective recognition of wild-type and variant epitopes were found.
- TiLDVGDAY, TVLDVGDAf and TiLDVGDAf variants are detected due to appearence of V108I and Y115F resistance mutations. Complete cross-reactivity of wild-type and variant peptides was observed.

HXB2 Location RT (107–115)
Author Location RT Pol (262–270)
Epitope TVLDVGDIY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 5/9 patients recognized this epitope.

HXB2 Location RT (107–115)
Author Location RT
Epitope TVLDVGDAY
Epitope name B35-TY9(RT)
Immunogen HIV-1 infection
Species (MHC) human (B35)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (107–115)
Author Location RT
Epitope TVLDVGDAY
Epitope name TY9(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B35-restricted epitope TVLDVGDAY elicited an immune response in Chinese HIV-1 positive subjects as part of peptide KKKSVTVLDVGDAYFSV.
- 5 of the 12 HLA-B35 carriers responded to a TVLDVGDAY-containing peptide with average magnitude of CTL response of 604 SFC/million PBMC.

HXB2 Location RT (108–118)
Author Location RT (108–118)
Epitope VLDVGDAYFSV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

HXB2 Location RT (108–118)
Author Location RT (108–118)
Epitope VLDVGDAYFSV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, VLDVGDAYFSV, was detected within overlapping peptide KKKSVTVLDVGDAYFSV.

HXB2 Location RT (108–118)
Author Location RT (267–277)
Epitope VLDVGDAYFSV
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
References van der Burg *et al.* 1996

- High dissociation rate, but immunogenic in primary CTL induction after repeated stimulations with peptide.
- CTL generated by *in vitro* stimulation of PBMC derived from uninfected individual.

HXB2 Location RT (108–118)
Author Location Pol
Epitope VLDVGDAYFSV
Epitope name V11V
Immunogen vaccine
Vector/Type: measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140ΔV3
Species (MHC) transgenic mouse (A*0201)
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells
References Lorin *et al.* 2005a

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

HXB2 Location RT (108–118)
Author Location RT (267–277)
Epitope VLDVGDAYFSV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords dendritic cells
References Kundu *et al.* 1998b

- Allogeneic dendritic cells (DCs) were obtained from HLA-identical siblings, pulsed with rgp160 MN or A2-restricted HIV-1 epitope peptides, and infused monthly into six HIV-infected patients.
- 1/6 showed increased env-specific CTL and increased lymphoproliferative responses, 2/6 showed increase only in proliferative responses, and 3/6 showed no change – pulsed DCs were well tolerated.
- VLDVGDAYFSV is a conserved HLA-A2 epitope included in this study – 4/6 patients had this sequence as their HIV direct sequence, but only one of these had a detectable CTL response – the other two had the sequences EEDVGDAYFSV and ELDVGDAYFSV and no detectable CTL response.

HXB2 Location RT (108–118)
Author Location RT (267–277)
Epitope VLDVGDAYFSV
Immunogen in vitro stimulation or selection
Species (MHC) human (A2)
References van der Burg *et al.* 1995

- Binds HLA-A*0201 – CTL generated by *in vitro* stimulation of PBMC from an HIV negative donor.
- VLDVGDAYFSV is in a functional domain.

HXB2 Location RT (108–118)
Author Location RT Pol (263–273)
Epitope VLDVGDAYFSV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 19 patients recognized this epitope.

HXB2 Location RT (108–118)
Author Location Pol (263–273)
Epitope VLDVGDAYFSV
Immunogen HIV-1 infection
Species (MHC) human (A*0201, A2)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location RT (108–122)
Author Location RT (257–251)
Epitope VLDVGDAYFSVPLDE
Immunogen HIV-1 infection
Species (MHC) human (Cw4)
References Bernard *et al.* 1998

- This study focuses on six rare long-term survivor HIV-infected people who were infected for many years without exhibiting immune dysregulation – such immunologically normal HIV-infected (INHI) cases occur at a frequency between 0.1 and 1% in the infected population.
- No direct CTL were found in any of the six INHIs, but above background CTLp activity was founded in 3/6 INHIs.

HXB2 Location RT (113–120)
Author Location Pol (268–275 SF2)
Epitope DAYFSVPL
Immunogen HIV-1 infection
Species (MHC) human (A24, B*5101)
Keywords subtype comparisons, rate of progression
References Tomiyama *et al.* 1999

- HLA-B27, -B51, and -B57 are associated with slow progression to AIDS, while HLA -B35, -B8, -B24 are associated with a rapid progression to AIDS (Nat. Med. 2:405, 1996;Lancet 22:1187, 1986;Hum Immunol 22:73, 1988;Hum Immunol 44:156, 1995)
- 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%
- Of the 172 HIV-1 peptides with HLA-B*5101 anchor residues, 33 bound to HLA-B*5101, seven of these peptides were reactive with CTL from 3 B*5101 positive individuals, and six were properly processed.
- Four of the six epitopes were highly conserved among B subtype sequences, DAYFSVPL is conserved.

HXB2 Location RT (113–120)
Author Location RT (113–120)
Epitope DAYFSVPL
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these eptiopes, but this increased over time.

HXB2 Location RT (116–124)
Author Location (C consensus)
Epitope FSVPLDEDF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the E7 residue of FSVPLDEDF are associated with the presence of the HLA presenting molecule in the host.
- FSVPLDEDF not optimized.

HXB2 Location RT (116–124)
Author Location (C consensus)
Epitope FSVPLDEDF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5702)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope

References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- FSVPLDEDF is an optimal epitope.

HXB2 Location RT (116–124)
Author Location (C consensus)
Epitope `FSVPLDEDF`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5703)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- FSVPLDEDF is an optimal epitope.

HXB2 Location RT (116–135)
Author Location Pol (271–290)
Epitope `FSVPLDEDFRKYTAFTIPSI`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location RT (117–126)
Author Location Pol (264–273 93TH253 subtype CRF01)
Epitope `SVPLDESFRK`
Epitope name P272-281
Subtype CRF01_AE
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A11)
Keywords HIV exposed persistently seronegative (HEPS)
References Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope after a second stimulation *in vitro* gave a strong response in HEPS study subject 128 who was HLA A11/A33.

HXB2 Location RT (117–126)
Author Location Pol (264–273 93TH253 subtype CRF01)
Epitope `SVPLDESFRK`
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords subtype comparisons
References Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This is one of the new A11 epitopes identified through the streamlined EpiMatrix method, and 3/8 tested FSWs recognized it.
- This epitope was only conserved in CRF01, and subtype A and B, and exact matches were uncommon.

HXB2 Location RT (118–127)
Author Location (C consensus)
Epitope `VPLDEDFRKY`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location RT (118–127)
Author Location RT (118–127)
Epitope `VPLDEDFRKY`
Epitope name VY10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

CTL CD8+

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLAs-B*35-associated substitution within optimally defined epitope VPLDEDFRKY is at position D6, VPLDEdFRKY.

HXB2 Location RT (118–127)
Author Location RT (273–282 SF2)
Epitope VPLDKDFRKY
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Keywords review
References Menendez-Arias *et al.* 1998; Tomiyama *et al.* 1997

- A CTL clone responsive to this epitope was obtained.
- 4/7 B35-positive individuals had a CTL response to this epitope.
- A K to E substitution at position 5 abrogates specific lysis, and reduces binding to B*3501.
- Menendez-Arias *et al.* [1998], in a review, notes that a Glu to Lys (E to K) change abrogates CTL activity, but that both VPLDEDFRKY and VPLDKDFRKY can serve as HLA-B35 epitopes, so the change must alter T cell receptor binding – residues in this epitope may be important for polymerase activity.

HXB2 Location RT (118–127)
Author Location RT (273–282 IIIB)
Epitope VPLDEDFRKY
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*3501 epitope.

HXB2 Location RT (118–127)
Author Location Pol (273–282)
Epitope VPLDKDFRKY
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
References Tomiyama *et al.* 2000a

- CD8+ T-cells that bound one of six HIV-specific B*3501-epitope tetramers did not express CD28 or CD45A.
- A significant increase in CD28-CD45RA- cells and a decrease of CD28+CD45RA+ cells was observed in chronically HIV-1-infected individuals relative to healthy individuals.
- CD28-CD45RA- cells are likely to be effector cells and have high levels of perforin in their cytoplasm.
- The mean percentage of total CD28- CD8+ cells in chronically infected HIV-1-infected patients was 76.6% in comparison to HIV-1-uninfected individuals (40.6%)

HXB2 Location RT (118–127)
Author Location (SF2)
Epitope VPLDEDFRKY
Epitope name HIV-B3501-SF2-4
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
References Tomiyama *et al.* 2000b

- B*3501 VPLDEDFRKY tetramer binding did not inhibit CTL activity of a clone that react with both HLA-B*3501 than HLA-B*5101 presentation of the epitope IPLTEEAEL.

HXB2 Location RT (118–127)
Author Location RT (118–127)
Epitope VPLDEDFRKY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Donor MHC A*2301, B*1503, B*3501, Cw2, Cw7
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

HXB2 Location RT (118–127)
Author Location Pol (273–282)
Epitope VPLDEDFRKY
Epitope name VY10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Donor MHC A*0201, A*0301, B*3501, B*51, Cw*04, Cw*06
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords escape, acute/early infection
References Bansal *et al.* 2005

CTL CD8+

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- The response to this epitope was not detected until month 25, and increased over time.

HXB2 Location RT (118–127)
Author Location Pol (273–282)
Epitope VPLDKDFRKY
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Country Japan
Assay type Cytokine production, Tetramer binding, CTL suppression of replication, Other, HLA binding
Keywords class I down-regulation by Nef
References Ueno *et al.* 2008

- The balance between Nef selective pressures to modulate HLA I or its escape mutations reducing Nef HLA I down-regulating activity is studied.
- Nef mutations had the effect of increasing cytolytic activity of CTL clones with other specificities like CTLs specific for Pol-VPLDKDFRKY.

HXB2 Location RT (118–127)
Author Location RT
Epitope VPLDEGFRKY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- VPLDEGFRKY is a previously described HLA-B*3501-restricted epitope (part of Pol(RT) reacting peptide GDAYFSVPLDeGFRKYTAFTI) that contains a B*35(01)-associated sequence polymorphism at residue E (VPLDeGFRKY).

HXB2 Location RT (118–127)
Author Location RT (273–282 IIIB)
Epitope VPLDEDFRKY
Immunogen HIV-1 infection
Species (MHC) human (B*3501, B35)
References Shiga *et al.* 1996

- Binds HLA-B*3501.

HXB2 Location RT (118–127)
Author Location (SF2)
Epitope VPLDKDFRKY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords binding affinity, rate of progression, escape
References Kawana *et al.* 1999

- HLA B35 is associated with rapid disease progression.
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals.
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals – only one of these reduced the binding of the peptide to B35 and was shown to be an escape mutation.
- —–E—- was found in 8/10 of the B35+ individuals, and three of the B35- individuals – the D –> E substituted peptide had similar binding affinity to B35 and was equally susceptible to a CTL clone.

HXB2 Location RT (118–127)
Author Location RT (273–282 IIIB)
Epitope VPLDEDFRKY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords subtype comparisons
References Sipsas *et al.* 1997

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by three lab workers accidentally infected with HIV-1 IIIB.
- VPLDKDFRKY, a variant found in HIV MN, was not recognized.
- VPHDEDFRKY, a variant found in HIV YU2, was not recognized.
- This epitope was type-specific and conserved in only one other B subtype sequence.

HXB2 Location RT (118–127)
Author Location RT (273–282 SF2)
Epitope VPLDEDFRKY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 1/2 group 1, 0/2 group 2, and 1/1 group 3.

HXB2 Location RT (118–127)

CTL CD8+

Author Location
Epitope VPLDEDFRKY
Epitope name Pol-VY10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B35, 5/21 (24%) recognized this epitope.

HXB2 Location RT (118–127)
Author Location RT Pol (273–282)
Epitope VPLDEDFRKY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 5/9 patients recognized this epitope.

HXB2 Location RT (118–127)
Author Location RT
Epitope VPLDEDFRKY
Epitope name B35-VY10(RT)
Immunogen HIV-1 infection
Species (MHC) human (B35)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (118–127)
Author Location RT
Epitope VPLDKDFRKY
Epitope name VY10(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope VPLDKDFRKY elicited an immune response in Chinese HIV-1 positive subjects as part of peptide SVPLDKDFRKYTAFTI. This epitope differs from the previously described HLA-B35-restricted epitope, VPLDEDFRKY, at 1 residue, VPLDkDFRKY.
- 2 of the 12 HLA-B35 carriers responded to VPLDkDFRKY-containing peptide with average magnitude of CTL response of 210 SFC/million PBMC (author communication and Fig.1).

HXB2 Location RT (118–127)
Author Location RT
Epitope VPLDEDFRKY
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
References Garrison *et al.* 2007

- The study examined the influence of HIV-1 infection on human endogenous retroviruses (HERVs) activity and explored T cells cross-reactivity in regions of HIV-1/HERV similarity.
- T cell responses to HERV peptides were identified in HIV-1 positive individuals. There was an inverse correlation between anti-HERV T cell responses and HIV-1 viral load.
- HIV-1 VPLDEDFRKY was used in qualitative compaarison of HERV-specific CD8+ T cells with those specific for other viruses. To minimize cross-reactivity, the HERV peptide used was IPVHKAHKKQ which has only 2 amino acids in common with VPLDEDFRKY.

HXB2 Location RT (126–135)
Author Location RT (293–302 HXB)
Epitope KYTAFTIPSI
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HAART, ART
References Shankar *et al.* 1998

- A novel CTL clone was defined with a panel of recombinant vaccinia-RT-infected B-LCL target cells using PBMCs donated by a patient who was HIV-seropositive for 6 years and had not received any antiretroviral therapy.

- There is evidence that some CTL epitopes are poorly presented on the surface of infected cells, but this RT epitope was recognized as effectively on HIV-infected cells as on peptide-pulsed targets.

HXB2 Location RT (127–135)
Author Location (C consensus)
Epitope YTAFTIPSI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0205)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- YTAFTIPSI is an optimal epitope.

HXB2 Location RT (127–135)
Author Location Pol
Epitope YTAFTIPSV
Epitope name YV-9
Immunogen HIV-1 infection
Species (MHC) human (A02)
Keywords escape, TCR usage, immune evasion
References Yu *et al.* 2007b

- The dependence of TCR clonotype recruitment on genetic background was determined by studying monozygotic twins infected with the same HIV-1 strain. After an early, initial correlation in the magnitude, specificity and immunodominance of CTL response [Draenert et al. J. Exp. Med. 203:529-539(2006)], subsequent disease was mixed with respect to CTL epitopes' mutational escape. TCR alpha and beta chain repertoires were analyzed and it was found that their clonotypes in HIV-specific CTLs were broadly heterogeneous for both concordant and discordant epitope sequence evolution between the twins. Therefore initial TCR recruitment appears to be an entirely random process independent of genetic background of the infected individual.
- This epitope, YV9, showed discordant epitope evolution between the twins, and both alpha and beta TCR chains recruited were entirely different between them.

HXB2 Location RT (127–135)
Author Location Pol (316–)
Epitope YTAFTIPSI
Epitope name Pol-316
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords binding affinity, subtype comparisons, supertype, computational epitope prediction
References Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- 2/22 individuals with chronic HIV-1 infection recognized this epitope in ELISPOT.
- 0/12 acutely infected individuals recognized this epitope.
- YTAFTIPSI binds to five HLA-A2 supertype alleles: A*0201, A*0202,A*0203, A*0206 and A*6802 (highest affinity)

HXB2 Location RT (127–135)
Author Location RT (127–135)
Epitope YTAFTIPSV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location RT (127–135)
Author Location RT (127–135)
Epitope YTAFTIPSI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords acute/early infection, optimal epitope
References Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized during chronic infection.

HXB2 Location RT (127–135)
Author Location RT
Epitope YTAFTIPSI
Epitope name A2-YI9(RT)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.

- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (127–135)
Author Location RT
Epitope YTAFTIPSI
Epitope name A2-YI9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, A68, B14, B44, Cw5, Cw8
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape, acute/early infection, antibody generation, co-receptor, immune evasion
References Streeck *et al.* 2007b

- A subject with acute and rapid disease progression to AIDS showed no neutralizing antibody activity and rapid decline in HIV-specific CTL response by 6 months post-infection. Virus from this rapid progressor was resistant to neutralization by plasma from a long-term progressor. Viral epitopes did not vary much. This suggests viral immune evasion in the absence of viral sequence variation.
- This epitope, YTAFTIPSI, elicited the dominant CTL response, detectable until 4 months post-infection. YI9 and its flanking sequences FRKYTAFTIPSINNE did not show any escape mutations.

HXB2 Location RT (127–135)
Author Location Pol (282–290)
Epitope YTAFTIPSV
Epitope name YV9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A*0201, A*2402, B*4001, B*5001, Cw03, Cw04
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords immunodominance, escape, variant cross-recognition or cross-neutralization
References Draenert *et al.* 2006

- HIV-specific cellular and humoral immune responses were examined in monozygotic male twins infected simultaneously with the same virus. 15 of 17 targeted epitopes were identical in the twins, including two immunodominant responses. 3 of 4 declining responses in the twins showed mutations at the same residue. Evolving antibody responses cross-neutralized the other twin's virus. The results were compared with a third brother, infected by the twins' virus 13 months after their seroconversion. The data show similarity in disease course in persons of identical genetic background infected with the same strain of HIV-1.
- This epitope, YTAFTIPSV (YV9) was restricted by HLA-A02. A variant that arose was YTAFTIPSi.

HXB2 Location RT (127–135)
Author Location RT
Epitope YTAFTIPSI
Epitope name YI9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- One patient with epitope YTAFTIPSI maintained a mono- and dual-functional response profile.
- 141 days after first testing, epitope YTAFTIPSI showed no variation in a treated patient and after 182 days it varied to YTAFTIPSa/YTAFTIPSt/YTAFTIPSv in an untreated patient. Previously published HLA-restriction for YI9 is HLA-A2.

HXB2 Location RT (127–135)
Author Location RT
Epitope YTAFTIPSI
Epitope name YI9(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A2-restricted epitope YTAFTIPSI elicited an immune response in Chinese HIV-1 positive subjects as part of peptide DFRKYTAFTIPSINNETPGI.
- 4 of the 55 HLA-A2 carriers responded to YTAFTIPSI-containing peptide with average magnitude of CTL response of 140 SFC/million PBMC.

HXB2 Location RT (127–135)
Author Location Pol (306–314)
Epitope YTAFTIPSI

Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind all five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802)

HXB2 Location RT (128–135)
Author Location Pol (283–290)
Epitope `TAFTIPSI`
Epitope name TI8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Donor MHC A*0201, A*0301, B*3501, B*51, Cw*04, Cw*06
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords escape, acute/early infection, characterizing CD8+ T cells
References Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- The response to this epitope was weak and sporadic.

HXB2 Location RT (128–135)
Author Location
Epitope `TAFTIPSI`
Epitope name Pol-TI8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0217, B*5101)
Donor MHC 01RCH46: A*0201, A*0217, B*0801, B*4002, Cw*0303, Cw*0701
Keywords HAART, ART
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Patient 01RCH46 was Hispanic, on HAART, and had a viral load of 21000 and CD4 count of 623 – she also recognized GELDRWEKI, p17(11-19), HLA B*4002, and KETINEEAA p24(70-78), HLA B*4002.
- Among HIV+ individuals who carried HLA A*02, 7/36 (19%) recognized this epitope, two of which also carried B*5101 which can also restrict this epitope.

HXB2 Location RT (128–135)
Author Location Pol
Epitope `TAFTIPSI`
Epitope name TI8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*51)
Country Switzerland
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, HLA associated polymorphism
References Frater *et al.* 2007

- To study whether CTL responses restricted by "good" HLA I molecules exert stronger immune selection than other HLA I molecules, 54 and 70 optimal epitopes within HIV-1 Gag, Pol and Nef genes for Caucasian and African cohorts were tested in patients over a mean of 14 months. "Good", advantageous HLA allele-restricted epitopes were much more polymorphic than epitopes restricted by other, non-advantageous HLA in patients, suggesting that benefits associated with HLA Class I alleles of elite controllers of disease progression are epitope-specific. Such "driver" epitopes with high polymorphism had high frequency of immune response, allowing them to be ranked for recognition and polymorphism.
- Patients with higher proportions of mutated epitopes also had lower plasma viral loads, and mean epitope variability correlated negatively with relative hazard of disease progression.
- TAFTIPSI escapes very soon after seroconversion to the variant TAFTIPSt with change at its carboxyl terminus, position 8, which has been identified by phylogenetic analysis to be under strong positive selection pressure. It was present in 7/8 of HLA-matched patients and 21/57 of HLA-unmatched patients.

HXB2 Location RT (128–135)
Author Location RT (128–135)
Epitope `TAFTIPSI`
Epitope name TI8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*51)
Country Australia, Canada, Germany, United States
Keywords escape, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag

B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLAs-B*51-associated substitution within optimally defined epitope TAFTIPSI is at position I8, TAFTIPSi. TI8 was the 9th most rapidly escaping epitope after which immune response to it declined.

HXB2 Location RT (128–135)
Author Location RT (295–302 IIIB)
Epitope TAFTIPSI
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Keywords optimal epitope
References Llano *et al.* 2009
- C. Brander notes this is a B*5101 epitope.

HXB2 Location RT (128–135)
Author Location Pol (283–290 SF2)
Epitope TAFTIPSI
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Keywords subtype comparisons, rate of progression
References Tomiyama *et al.* 1999
- HLA-B27, -B51, and -B57 are associated with slow progression to AIDS, while HLA-B35, -B8, -B24 are associated with a rapid progression to AIDS (Nat. Med. 2:405, 1996;Lancet 22:1187, 1986;Hum Immunol 22:73, 1988;Hum Immunol 44:156, 1995)
- 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%
- Of the 172 HIV-1 peptides with HLA-B*5101 anchor residues, 33 bound to HLA-B*5101, seven of these peptides were reactive with CTL from 3 B*5101 positive individuals, and six were properly processed.
- Four of the six epitopes were highly conserved among B subtype sequences, but TAFTIPSI is somewhat variable.

HXB2 Location RT (128–135)
Author Location RT (295–302)
Epitope TAFTIPSI
Epitope name P5
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Keywords HAART, ART, escape
References Samri *et al.* 2000
- The epitope TAFTIPSI was recognized by patient 246#1 in a study of the effects of therapy escape mutations on CTL recognition.

HXB2 Location RT (128–135)
Author Location RT (128–135 IIIB)
Epitope TAFTIPSI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Keywords epitope processing, escape
References Moore *et al.* 2002b
- HIV polymorphisms in the RT protein were examined relation to HLA alleles found in a population of 473 participants in the Western Australian HIV Cohort Study. 64 significant associations between polymorphisms at particular positions and HLA alleles were detected, for HLA-B7, -B12, -B35 and -B15. Fifteen of these were in positions with known epitopes, 4 in anchor residues, 11 in other positions. Six additional polymorphic sites associated with particular HLA molecules flanked known epitopes and may relate to processing.
- TAFTIPSI was one of two epitopes characterized in detail. C-terminal I135x substitutions were associated with people who carried HLA-B5 – 39/40 (98%) of HLA-B*5101 individuals had substitutions in this position, while only 127/431 (29%) who did not have HLA-B*5101 did. The predominant substitution was kytaftipsT, and this mutation is predicted to abrogate binding to HLA-B*5101.

HXB2 Location RT (128–135)
Author Location RT (128–135 HXB2)
Epitope TAFTIPSI
Epitope name TI8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b
- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- Last position (8) of the epitope had potentially experienced positive selection. TAFTIPSt, TAFTIPSr and TAFTIPSv escape variants were found.

HXB2 Location RT (128–135)
Author Location Pol (283–288 NL-432)
Epitope TAFTIPSI
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Assay type Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay, CTL suppression of replication
Keywords binding affinity, class I down-regulation by Nef, rate of progression
References Tomiyama *et al.* 2005
- HLA-B*5101 associated with slow progression to the disease state was studied as related to Nef-mediated HLA class I downregulation. It was shown that different CTLs have different ranges of ability to kill HIV-1 infected CD4+ T cells and suppress HIV-1 replication. This was found to be a function

CTL CD8+

of the specific HIV-1 epitope presented by the corresponding HLA allele to the CTL.
- Certain epitope recognising CTL clones or lines were therefore, capable of killing HIV-1 infected cells even in the presence of Nef-mediated MHC 1 downregulation, while other CTL clones recognising different epitopes were not so capable.
- There was no significant difference in cytokine production or cytokine producing cells between CTLs that were capable of killing CD4+ T-cells infected with HIV-1 and those CTLs that could not kill such HIV-1 infected cells.
- On the basis of studies involving binding abilities and cytolytic activities for four different epitopes that correlate with HLA-B*5101-restricted CTLs, it is suggested that the ability of CTLs to kill infected CD4+ T cells is due to the number of epitopes presented by the HLA on the surface of the CD4+ T cells rather than the ability of TCR to recognise the epitope.

HXB2 Location RT (128–135)
Author Location RT (295–302 IIIB)
Epitope TAFTIPSI
Immunogen HIV-1 infection
Species (MHC) human (B51)
Keywords review
References Menendez-Arias *et al.* 1998; Sipsas *et al.* 1997

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB.
- TAFTIPST, a variant found in HIV-1 CAM1, was also recognized but 100-fold more peptide was needed.
- TAFTIPSV, a variant found in HIV-1 VE1RT, was also recognized, but 10-fold more peptide was needed.
- TVFTIPSI, a variant found in HIV-1 MANC, was also recognized.
- Menendez-Arias *et al.* [1998], in a review, notes that this epitope includes a region near the active site of RT – the substitution of the position two conservative change from A to V decreases CTL recognition.

HXB2 Location RT (128–135)
Author Location RT (295–302)
Epitope TAFTIPSI
Immunogen HIV-1 infection
Species (MHC) human (B51)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- Three of the four individuals that responded to SLYNTVATL recognized additional HIV epitopes, and all three were also HLA B51 and recognized this epitope as well as other epitopes.

HXB2 Location RT (128–135)
Author Location RT (295–302)
Epitope TAFTIPSI
Epitope name TAF
Immunogen HIV-1 infection
Species (MHC) human (B51)
Keywords HAART, ART, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- None of the 8 study subjects recognized this epitope but none were HLA B51+

HXB2 Location RT (128–135)
Author Location RT (295–302 LAI)
Epitope TAFTIPSI
Epitope name P5
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
Keywords HAART, ART
References Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNgamma production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

HXB2 Location RT (128–135)
Author Location Pol
Epitope TAFTIPSI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A11, A3, B35, B51
Keywords mother-to-infant transmission
References Sabbaj *et al.* 2002

- IFNgamma T-cell responses in breast milk of 5 HIV-1 infected women from the US and 6 from Zambia were tested with using Elispot. 11/11 women responded to Gag, 8/11 responded to Pol, 7/11 women to Nef, and 2/5 women to Env peptide pools. These responses were shown to be primarily due to CD8+ T-cells in one woman, and another woman had cytolytic responses measured by Cr-release.
- T-cells in breast milk from a volunteer who was HLA A3, A11, B35, B51 induced IFNgamma after stimulation with either of two overlapping peptides that carry known B51 epitope TAFTIPSI.

CTL CD8+

- The frequencies of responses in the two compartments differed, and 2/4 women that responded to epitopes in Nef 101-205 and Pol 601-710 showed responses in breast milk but no detectable responses in peripheral blood cells.

HXB2 Location RT (128–135)
Author Location RT (128–135)
Epitope TAFTIPSI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A*0201, A11, B51, B61, Cw*14, Cw2
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

HXB2 Location RT (128–135)
Author Location RT (128–135)
Epitope TAFTIPSI
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 5 epitopes from this individual that varied over time where the internal mutations became fixed; a dramatic decrease in CTL activity against the wild type epitope was observed as the mutation arose. The taftipsT variant residue found at 47 months postseroconversion.

HXB2 Location RT (128–135)
Author Location Pol
Epitope TAFTIPSI
Epitope name TI8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 8, taftipsT, was found in the most polymorphic residue in the epitope. This was shared between clades B and C.

HXB2 Location RT (128–135)
Author Location Pol (295–302)
Epitope TAFTIPSI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A2, A31, B51, B58w4
Country United States
Assay type Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, escape, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells
References Casazza *et al.* 2005

- Evidence of continued viral evolution during HAART therapy despite low viral load was found in 1/5 patients studied. This epitope provided the best evidence for apparent immune escape during HAART.
- Prior to the initiation of therapy, taftipsT variant was found in 24/24 clones. At week 14 of therapy, this variant was completely replaced with taftipsI. By week 19, a complete replacement occurred again, this time to taftipsM. The change at nucleotide level suggests a stepwise progression from ACA to ATA to ATG.
- The taftipsT and taftipsM variants had lower avidity than the taftipsI variant, but this wasn't evident at saturating conditions; only careful titrations revealed the difference. HLA-B51 stabilization studies revealed the increased stabilization with the taftipsI form. Also, CD3 down-regulation was larger in response to taftipsI.
- The viral shift to the taftipsM variant during HAART was predicted to have minimal or undetectable effect on drug sensitivity.

HXB2 Location RT (128–135)
Author Location RT
Epitope TAFTIPSI
Epitope name B51-TI8(RT)
Immunogen HIV-1 infection

Species (MHC) human (B51)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (128–135)
Author Location
Epitope TAFTIPSI
Immunogen HIV-1 infection
Species (MHC) human (B51)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B51), 2 additional HLAs (B35, B40) were statistically predicted to be associated with this epitope.

HXB2 Location RT (128–135)
Author Location RT
Epitope TAFTIPSI
Epitope name TI8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- Epitope TAFTIPSI varied to TAFTIPSa, TAFTIPSt and TAFTIPSv in an untreated patient. Previously published HLA-restriction for TI8 is HLA-B51.

HXB2 Location RT (128–135)
Author Location
Epitope TAFTIPSI
Epitope name TI8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
Country United States
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Chromium-release assay
Keywords TCR usage, characterizing CD8+ T cells
References Alter *et al.* 2008

- By studying HIV-1 dysregulation of CTLs at different infection stages induced by inhibitory KIRs (Killer Immunoglobulin-like receptors), it was determined that KIR surface expression on memory T cells correlates with HIV replication. It results in reduced activation, proliferation, cytokine secretion, and killing following TCR stimulation. Since non-TCR-dependent CTL stimulation was unaffected, TCR-mediated stimulation appears to be defective. KIR induced suppression of CTL function was found to be KIR-ligand-independent.
- TI8-specific, HLA-B51-restricted CTL were used for an HIV inhibition assay.

HXB2 Location RT (128–135)
Author Location RT
Epitope TAFTIPSI
Epitope name TI8(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B51-restricted epitope TAFTIPSI elicited an immune response in Chinese HIV-1 positive subjects as part of peptide DRFKYTAFTIPSINNETPGI.
- 3 of the 15 HLA-B51 carriers responded to TAFTIPSI-containing peptide with average magnitude of CTL response of 173 SFC/million PBMC.

HXB2 Location RT (128–135)
Author Location RT Pol (128–135)
Epitope TAFTIPSI
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A3, A32, B15, B51
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, YFPDWQDYT, was found to be 0.002/day (optimistic escape rate = 0.012), with SE of 0.001.
- In the subject studied, the monotonic outgrowth of a I290T mutation in Pol was observed over a period of 817 days.

HXB2 Location RT (128–135)
Author Location RT
Epitope TAFTIPSI
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Garrison *et al.* 2007

- The study examined the influence of HIV-1 infection on human endogenous retroviruses (HERVs) activity and explored T cells cross-reactivity in regions of HIV-1/HERV similarity.
- T cell responses to HERV peptides were identified in HIV-1 positive individuals. There was an inverse correlation between anti-HERV T cell responses and HIV-1 viral load.
- HIV-1 epitope TAFTIPSI has a corresponding HERV peptide FAFTIPAI. These 2 peptides were used in measuring IFN-γ ELISPOT responses in HIV-1-positive and -negative individuals.

HXB2 Location RT (130–144)
Author Location RT (130–144)
Epitope FTIPSINNETPGIRY
Immunogen HIV-1 infection
Species (MHC) human (A25)
Assay type Chromium-release assay
Keywords assay standardization/improvement
References Lubong *et al.* 2004

- Using IL7 or IL15 in culturing of HIV-1-specific CTL clones was inferior to using IL-2 alone; the addition of these cytokines to IL-2 did not show any advantage. Neither proliferation, survival, nor lytic capacity of HIV-1-specific CTLs was significantly enhanced by addition of IL7 or IL15.

HXB2 Location RT (132–141)
Author Location Pol
Epitope IPSTNNETPG
Epitope name Pol1165
Subtype A1
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Novel Pol epitope IPSTNNETPG elicits IFN-gamma ELISpot responses in 1/7 subjects; and bound HLA-B7 with high affinity in cell-based assays.

HXB2 Location RT (136–144)
Author Location RT (136–144 HXB2)
Epitope NNETPGVRY
Epitope name NY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1801)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- NNETPGiRY, NsETPGVRY, NNEiPGVRY, NNEiPGiRY, NNgTPGVRY and NNEvPGiRY escape variants were found.

HXB2 Location RT (136–144)
Author Location RT
Epitope NNETPGIRY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ

Keywords HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- NNETPGIRY is a previously described HLA-B*1801-restricted epitope (part of Pol(RT) reacting peptide TAFTIPSINNeTPGIRYQYNV) that contains a B*1801-associated sequence polymorphism at residue E (NNeTPGIRY).

HXB2 Location RT (137–146)
Author Location (C consensus)
Epitope `NETPGIRYQY`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*18)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the E2 residue of NETPGIRYQY are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location RT (137–146)
Author Location RT (137–146)
Epitope `NETPGIRYQY`
Epitope name NY10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*18)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLAs-B*15-associated substitutions within optimally defined epitope NETPGIRYQY are at positions 2E and 6I, NeTPGiRYQY.

HXB2 Location RT (137–146)
Author Location
Epitope `NETPGIRYQY`
Epitope name NY10
Immunogen
Species (MHC) human (B18)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B18 epitope.

HXB2 Location RT (139–148)
Author Location Pol
Epitope `TPGIRYQYNV`
Epitope name Pol1157
Subtype C
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Novel Pol epitope TPGIRYQYNV elicits IFN-gamma ELISpot responses in 1/7 subjects; and bound HLA-B7 with low and high affinities in soluble and cell-based assays respectively.

HXB2 Location RT (142–149)
Author Location (C consensus)
Epitope `IRYQYNVL`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1401)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- IRYQYNVL is an optimal epitope.

HXB2 Location RT (142–149)
Author Location
Epitope `IRYQYNVL`
Epitope name IL9
Immunogen
Species (MHC) human (B*1401)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*1401 epitope.

HXB2 Location RT (149–158)
Author Location Pol (303–312)
Epitope `LPQGWKGSPA`

Epitope name LA10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5401)
Country Japan
Assay type Intracellular cytokine staining, Chromium-release assay
Keywords optimal epitope
References Kitano *et al.* 2008

- Asian-expressed HLA-B*5401-restricted epitopes were identified using overlapping-peptide methods and characterized. 5 epitopes from Pol and Nef induced CTL responses that killed target cells in more than 25% of B*5401-carrying tested patients.
- 7 peptides from Pol and Nef are listed in Fig. 2 as candidates for B*5401 restriction. No Gag-specific epitopes were identified in this study from the patient whose lymphocytes were screened.
- LPQGWKGSPA was defined as an optimal epitope for HLA-B*5401 restriction, using truncated peptides.

HXB2 Location RT (149–159)
Author Location (C consensus)
Epitope `LPQGWKGSPAI`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*3910)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- LPQGWKGSPAI is an optimal epitope.

HXB2 Location RT (151–159)
Author Location Pol (306–314 SF2)
Epitope `QGWKGSPAI`
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Keywords subtype comparisons, rate of progression
References Tomiyama *et al.* 1999

- HLA-B27, -B51, and -B57 are associated with slow progression to AIDS.
- 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%
- Of the 172 HIV-1 peptides with HLA-B*5101 anchor residues, 33 bound to HLA-B*5101, seven of these peptides were reactive with CTL from 3 B*5101 positive individuals, and six were properly processed.
- Four of the six epitopes were highly conserved among B subtype sequences, QGWKGSPAI is conserved.

HXB2 Location RT (151–168)
Author Location RT (151–168 HXB2)
Epitope `QGWKGSPAIFQSSMTKIL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 19% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location RT (153–165)
Author Location RT (308–320)
Epitope `WKGSPAIFQSSMT`
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords responses in children, mother-to-infant transmission
References Brander & Walker 1995

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.

HXB2 Location RT (153–165)
Author Location Pol (308–320)
Epitope `WKGSPAIFQSSMT`
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location RT (153–167)
Author Location RT (SF2)
Epitope `WKGSPAIFQSSMTKI`
Immunogen HIV-1 infection
Species (MHC) human
References Altfeld *et al.* 2001a

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- RT peptides SQIYPGIKVRQLCKL and WKGSPAIFQSSMTKI were recognized.

HXB2 Location RT (156–164)
Author Location RT (156–164)
Epitope `SPAIFQSSM`
Epitope name SM9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0702)
Country United Kingdom
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords epitope processing, computational epitope prediction, escape
References Zimbwa *et al.* 2007

- E169D is a processing mutation for HLA-B*0702 restricted SPAIFQSSM (SM9) as well as an epitope variation for HLA-A*0301 restricted MTKILEPFR (MR9).
- CTL recognition of SM9 was detected 5 days post-infection with wild type (169E) HIV-1, but not with mutant 169D virus.
- Mutation 169D is five residues downstream of SM9. In vitro proteasome processing assays showed that the 27-mer synthetic peptide QGWKGSPAIFQSSMTKILEPFRKQNPD released intermediate peptide QGWKGSPAIFQSSM within 6 h. Mutant peptide QGWKGSPAIFQSSMTKILdPFRKQNPD did not release this SM9-appropriate intermediate.

HXB2 Location RT (156–164)
Author Location RT (156–164)
Epitope `SPAIFQSSM`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*07)
Assay type Other
Keywords HLA associated polymorphism
References Boutwell & Essex 2007

- Publicly available HIV-1 subtype C sequences from South Africa and Botswana were analyzed, and 94 HLA-associated amino acid polymorphisms were found. Many polymorphisms were associated with multiple HLA allele classes. 12% associations were negative: association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles accounted for 50% of associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes.
- SPAIFQSSM was a previously defined B*07 presented epitope that encompassed a B*0702-associated polymorphism, SPAIFQsSM,in the seventh position.

HXB2 Location RT (156–164)
Author Location RT (156–164)
Epitope `SPAIFQSSM`
Epitope name SM9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*07)
Country Australia, Canada, Germany, United States
Keywords escape, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLAs-B*07-associated substitution within optimally defined epitope SPAIFQSSM is at position S7, SPAIFQsSM. SM9 recognition frequency is ∼20% and escape occurs at >3 months post-infection.

HXB2 Location RT (156–164)
Author Location RT
Epitope `SPAIFQSSM`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- SPAIFQSSM is a previously described HLA-B*0702-restricted epitope (part of Pol(RT) reacting peptide GWKGSPAIFQsSMTKILEPFR) that contains a B*0702-associated sequence polymorphism at residue S (SPAIFQsSM).

HXB2 Location RT (156–164)
Author Location RT (311–319 SF2)
Epitope `SPAIFQSSM`
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Keywords review
References Menendez-Arias *et al.* 1998; Tomiyama *et al.* 1997

- A CTL clone responsive to this epitope was obtained.
- Only 1/7 B35-positive individuals had a CTL response to this epitope.
- Menendez-Arias *et al.* [1998], in a review, notes that this epitope is near the active site of RT.

HXB2 Location RT (156–164)
Author Location (C consensus)
Epitope `SPAIFQSSM`

Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4202)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- SPAIFQSSM is an optimal epitope.

HXB2 Location RT (156–164)
Author Location (C consensus)
Epitope `SPAIFQSSM`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0702, B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords cross-presentation by different HLA, characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location RT (156–164)
Author Location RT (311–319 SF2)
Epitope `SPAIFQSSM`
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords review
References Menendez-Arias *et al.* 1998; Shiga *et al.* 1996

- Binds HLA-B*3501.
- Menendez-Arias *et al.* [1998], in a review, notes that this epitope includes catalytic residues in the active site of RT.

HXB2 Location RT (156–164)
Author Location Pol (311–319)
Epitope `SPAIFQSSM`
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location RT (156–164)
Author Location RT Pol (311–319)
Epitope `SPAIFQSSM`
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 5/9 patients recognized this epitope.

HXB2 Location RT (156–164)
Author Location Pol (156–164 HXB2)
Epitope `SPAIFQSSM`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords rate of progression, immunodominance
References Hay *et al.* 1999

- CTL response to IPRRIRQGL was the immunodominant response in a rapid progressor – there was a subdominant response to SPAIFQSSM in Pol, and interestingly, no response to commonly immunodominant HLA A*0201 epitope SLYNTVATL, although this individual was HLA A*0201.
- The individual showed a strong initial CTL response at the time of the initial drop in viremia, but it was quickly lost, although memory cells persisted.
- Despite the initial narrow response to two epitopes, no other CTL responses developed.
- No HIV-specific lymphoproliferative responses were detected in this patient, and neutralizing antibody response was weak.
- Variants of this epitopes were observed *in vivo* (spaifqCsm, spSifqssm), but the binding motifs for B7 were preserved (P2, and C-term aromatic or hydrophobic)

HXB2 Location RT (156–164)
Author Location Pol
Epitope `SPAIFQSSM`
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords rate of progression, acute/early infection
References Islam *et al.* 2001

- Subject 053i was followed longitudinally from acute infection through death, and had rapid progression to AIDS.
- This individual had a dominant response to IPRRIRQGL with strong *in vivo* activated responses and *in vitro* stimulated memory responses and a subdominant response to SPAIFQSSM – during the course of disease progression (4 Years), the functional CTL responses were lost and no sequence variation occurred with in both epitopes, but CTL clones specific for IPRRIRQGL persisted throughout.

HXB2 Location RT (156–164)
Author Location RT (323–331 SF2)
Epitope SPAIFQSSM
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 0/4 group 1, 0/3 group 2, and 1/1 group 3.

HXB2 Location RT (156–164)
Author Location RT (156–164)
Epitope SPAIFQSSM
Epitope name B7-SM9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 1/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 3/4 individuals had detectable responses to this epitope after STI.

HXB2 Location RT (156–164)
Author Location RT (156–164)
Epitope SPAIFQSSM
Epitope name B7-SM9 Pol
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), escape, early treatment, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response; this epitope did not vary.

HXB2 Location RT (156–164)
Author Location
Epitope SPAIFQSSM
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, epitope processing
References Draenert *et al.* 2004a

- 96% of optimally defined epitopes have one of only nine amino acids serving as the C-terminal anchor position. Seven amino acids are never found in this position and four are only present in 4% of cases. CD8 T-cell response to an epitope is shown to be best detected when the epitope is situated at the C-terminal end of a longer peptide, and authors suggest that Elispot reagents would be better designed if peptides ended on known C-terminal anchors.
- SPAIFQSSM is suggested to be the optimal epitope instead of SPAIFQSSMT.

HXB2 Location RT (156–164)
Author Location (B consensus)
Epitope SPAIFQSSM
Epitope name SM9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A03, B07, Cw7
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location RT (156–164)
Author Location Pol
Epitope SPAIFQSSM
Epitope name SM9
Subtype B
Immunogen HIV-1 infection

Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 7, spaifqCsm, was found in the most polymorphic residue in the epitope. This was shared between clades B and C.

HXB2 Location RT (156–164)
Author Location Pol (312–320)
Epitope SPAIFQSSM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location RT (156–164)
Author Location
Epitope SPAIFQSSM
Epitope name SM9
Immunogen
Species (MHC) human (B7)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B07 epitope.

HXB2 Location RT (156–164)
Author Location RT
Epitope SPAIFQSSM
Epitope name B7-SM9(RT)
Immunogen HIV-1 infection
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (156–164)
Author Location RT (156–164)
Epitope SPAIFQSSM
Epitope name SM9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Other
Keywords supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism
References Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alelles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope restriction
- Statistically significant associations between numbers of HLA-0702 and -B8101 expressing subjects and epitope SPAIFQSSM were found.
- Only B*0702 was found to be associated with polymorphism in SM9.

HXB2 Location RT (156–164)
Author Location Pol
Epitope SPAIFQSSM
Subtype B, C, D, A1, AE
Immunogen HIV-1 infection
Species (MHC) human
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.

- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- Broadly immunogenic epitope SPAIFQSSM, had subtype variants that were recognized by less than half its patient responders. This epitope is predicted to be restricted by HLA supertype B7.

HXB2 Location RT (156–164)
Author Location RT
Epitope `SPAIFQSSM`
Epitope name SM9(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords non-susceptible form
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- The tested peptide sequence, QGWKGSPAIFQCSMTKIL, contains a variant, SPAIFQcSM, that differs by 1 substitution from the previously described HLA-B7 epitope SPAIFQSSM. None of the 16 HLA-B7 carriers responded to a variant SPAIFQcSM.

HXB2 Location RT (156–165)
Author Location RT (311–319 LAI)
Epitope `SPAIFQSSMT`
Epitope name P4
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords HAART, ART, escape
References Samri *et al.* 2000

- This epitope contains the mutation P157S which can be induced by nucleosidee reverse transcriptase inhibitors.
- It was recognized by patient 252#0 in a study of the effects of therapy escape mutations on CTL recognition.

HXB2 Location RT (156–165)
Author Location RT (311–319 SF2)
Epitope `SPAIFQSSMT`
Immunogen
Species (MHC) human (B7)
Keywords review
References Brander & Walker 1997; Menendez-Arias *et al.* 1998

- Pers. comm. from C. Hey and D. Ruhl to C. Brander and B. Walker.
- Menendez-Arias *et al.* [1998], in a review, notes that this epitope includes catalytic residues in the active site of RT.

HXB2 Location RT (156–165)
Author Location RT (311–319 SF2)
Epitope `SPAIFQSSMT`
Epitope name P4
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords HAART, ART
References Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNgamma production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

HXB2 Location RT (156–165)
Author Location Pol
Epitope `SPAIFQSSMT`
Immunogen
Species (MHC) human (B7)
References De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conservered regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFNγ production in an ELISPOT assay.
- SPAIFQSSMT was confirmed as a previously identified HLA-B7 epitope in this study.

HXB2 Location RT (156–165)
Author Location RT (IIIB)
Epitope `SPAIFQSSMT`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords epitope processing, escape
References Moore *et al.* 2002b

- HIV polymorphisms in the RT protein were examined relation to HLA alleles found in a population of 473 participants in the Western Australian HIV Cohort Study. 64 significant associations between polymorphisms at particular positions and HLA alleles were detected, for HLA-B7, -B12, -B35 and -B15. Fifteen of these were in positions with known epitopes, 4 in anchor residues, 11 in other positions. Six additional polymorphic sites associated with particular HLA molecules flanked known epitopes and may relate to processing.
- HLA-B7+ individuals with a S162x (18/33) substitution had higher viral loads than those that did not, suggesting escape was associated with diminished immune control of viremia.

HXB2 Location RT (156–165)
Author Location Pol
Epitope SPAIFQSSMT
Epitope name 1306
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A03, A24, B07, B38, Cw07, Cw12/13
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for SPAIFQSSMT: 13%

HXB2 Location RT (156–165)
Author Location RT Pol (311–319)
Epitope SPAIFQSSMT
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 5/7 patients recognized this epitope.

HXB2 Location RT (158–166)
Author Location RT (158–166)
Epitope AIFQSSMTK
Epitope name AK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*03, A*11)
Country Australia, Canada, Germany, United States
Keywords escape, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLAs-A*03 and A*11-associated substitution within optimally defined epitope AIFQSSMTK is at position K9, AIFQSSMTk. AK9 has a low recognition frequency and very low number of escapes.

HXB2 Location RT (158–166)
Author Location RT (325–333)
Epitope AIFQSSMTK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords responses in children, mother-to-infant transmission
References Brander & Walker 1995

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.

HXB2 Location RT (158–166)
Author Location RT (325–333 LAI)
Epitope AIFQSSMTK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*0301 epitope.

HXB2 Location RT (158–166)
Author Location
Epitope AIFQSSMTK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords acute/early infection
References Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B2705; and A*0201, A*0301, B2705, B39.

- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK.
- The subject with A*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705.
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

HXB2 Location RT (158–166)
Author Location RT (325–333)
Epitope AIFQSSMTK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the A2+ individuals was HLA A3 and reacted with this epitope as well as two other A3.1 epitopes.

HXB2 Location RT (158–166)
Author Location RT
Epitope AIFQSSMTK
Immunogen
Species (MHC) human (A*0301)
References Zimbwa *et al.* 2007

- E169D is a processing mutation for HLA-B*0702 restricted SPAIFQSSM (SM9) as well as an epitope variation for HLA-A*0301 restricted MTKILEPFR (MR9).
- Mutation 169D lies outside AIFQSSMTK. In vitro proteasome processing assays showed that both wild type or variant 27-mer synthetic peptide QGWKGSPAIFQSSMTK-ILE(d)PFRKQNPD released appropriate AIFQSSMTK-intermediate peptides within 6 h.

HXB2 Location RT (158–166)
Author Location Pol (347–)
Epitope AIFQSSMTK
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (A*0301)
Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008

- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location RT (158–166)
Author Location Pol
Epitope AIFQSSMTK
Subtype A, B, C, D
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human, macaque (A*0301, A11, A33)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location RT (158–166)
Author Location RT (325–333 LAI)
Epitope AIFQSSMTK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*1101 epitope.

HXB2 Location RT (158–166)
Author Location Pol (313–321)
Epitope AIFQSSMTK
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Keywords subtype comparisons

CTL CD8+

References Fukada *et al.* 2002

- Counterparts for eight known clade B HLA A*1101 epitopes were generated for clade E (CRF01). Three epitopes, identical among clade A-E, were cross-reactive and recognized by clade E infected individuals. The clade E and B analogs to three more HLA A*1101 epitopes was recognized in a clade specific manner. Two other HLA A*1101 clade B defined epitopes were found not to have stimulated a response in clade E infected individuals.
- AIFQSSMTK is commonly found in viruses representing subtypes A-E. It was strongly recognized by CTL from 2/5 B clade infected Japanese subjects, and 5/6 E clade infected Thai subjects.

HXB2 Location RT (158–166)
Author Location RT (313–321)
Epitope AIFQSSMTK
Subtype B, CRF01_AE
Immunogen
Species (MHC) human (A*1101)
Country Thailand
Keywords HIV exposed persistently seronegative (HEPS), structure
References Li & Bouvier 2004

- HLA-A*1101 has been associated with resistance to acquisition of HIV-1 infection in female sex-workers in Thailand. Its crystal structure has been determined in association with two immunodominant A*1101 HIV-1 CTL epitopes. Its anchor residues are confirmed as P2(Ile/Val) and C-term (Lys). The backbone conformation of the peptides is defined as two bulges separated by a secondary anchor residue (P6 Ser or Met) that may offer various advantages in the selection and presentation of CTL epitopes by HLA-A*1101.

HXB2 Location RT (158–166)
Author Location RT (325–333)
Epitope AIFQSSMTK
Immunogen HIV-1 infection
Species (MHC) human (A*0301, A*1101, A*6801, A3)
References Menendez-Arias *et al.* 1998; Threlkeld *et al.* 1997

- Study of the fine specificity of an A3-like super-type epitope (the A3 super-type includes A*0301, A*1101, A*3101, A*3301, and A*6801)
- A3 super-type is characterized by a hydrophobic or hydroxyl containing anchor residue at position 2, and a positive charge in the C-term position.
- While most lines were specific, promiscuous cloned CTL lines were also derived from HIV+ donors that could recognize epitope presented by either A3 or A11 or A*6801.
- Alanine substitutions throughout the epitope and natural variants indicate that the same amino acid positions are critical for presentation by either MHC molecule, A3 or A11.
- AIFQSSMTK is presented by three members of the A3 superfamily: A*0301, A*1101, and A*6801, and the naturally occurring variants A1S and K9R are recognized with similar efficiency to wild type epitope – AIFQRSMTR can also bind to two additional members of the A3 superfamily, A*3101 and A*3301.

HXB2 Location RT (158–166)
Author Location RT (158–166)
Epitope AIFQSSMTK
Epitope name AK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*6801)
Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-A*6801-restricted autologous epitope AIFQSSMTK was able to elicit CTL response only by the last time point. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location RT (158–166)
Author Location RT
Epitope AIFQSSMTK
Immunogen HIV-1 infection
Species (MHC) human (A11)
References Wagner *et al.* 1998a

- CTL specific for HIV epitopes were used to show that the mediators of both the cytolytic (granzyme A was used as the marker) and non-cytolytic (HIV-1 inhibitory chemokines MIP-1 α and RANTES were used as markers) anti-viral responses are localized within the CTL's cytotoxic granules.

HXB2 Location RT (158–166)
Author Location RT (325–333 LAI)
Epitope AIFQSSMTK
Subtype B
Immunogen peptide-HLA interaction
Species (MHC) human (A11)
References Menendez-Arias *et al.* 1998; Zhang *et al.* 1993

- Exploration of A11 binding motif, based on Nixon *et al.* 1991.

HXB2 Location RT (158–166)
Author Location RT (325–333 LAI)
Epitope AIFQSSMTK
Subtype B
Immunogen HIV-1 infection

Species (MHC) human (A11)
Keywords review
References McMichael & Walker 1994

- Review of HIV CTL epitopes.

HXB2 Location RT (158–166)
Author Location Pol (305–313 93TH253 subtype CRF01)
Epitope AIFQSSMTK
Epitope name P313-321
Subtype CRF01_AE
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A11)
Keywords HIV exposed persistently seronegative (HEPS)
References Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was weakly reactive in the HEPS study subject 128 who was HLA A11/A33.
- This epitope was strongly reactive in HIV+ study subjects 053 and 184 who carried HLA-A11.

HXB2 Location RT (158–166)
Author Location Pol (305–313 93TH253 subtype CRF01)
Epitope AIFQSSMTK
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords subtype comparisons
References Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This epitope was predicted by the EpiMatrix method to be likely to bind to A11, and it served as an epitope in the FSWs, it was one of the six A11 epitopes that had been previously defined.
- 6/8 tested FSWs recognized this epitope.
- An HLA-A11 tetramer was made for this epitope, which was recognized by two subjects – and both subjects had expanded tetramer staining T-cell populations after *in vitro* stimulation.
- This epitope was highly conserved in other subtypes, and exact matches were common.

HXB2 Location RT (158–166)
Author Location RT (158–166 IIIB)
Epitope AIFQSSMTK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords epitope processing, escape
References Moore *et al.* 2002b

- HIV polymorphisms in the RT protein were examined relation to HLA alleles found in a population of 473 participants in the Western Australian HIV Cohort Study. 64 significant associations between polymorphisms at particular positions and HLA alleles were detected, for HLA-B7, -B12, -B35 and -B15. Fifteen of these were in positions with known epitopes, 4 in anchor residues, 11 in other positions. Six additional polymorphic sites associated with particular HLA molecules flanked known epitopes and may relate to processing.
- HLA-A11+ individuals with a K166x (4/19) substitution had higher viral loads than those that did not, suggesting escape was associated with diminished immune control of viremia.

HXB2 Location RT (158–166)
Author Location Pol
Epitope SIFQSSMTK
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A2, B60, B8, Bw6
Keywords HAART, ART
References Appay *et al.* 2002

- Four HIV patients with prolonged clinically successful antiviral therapy but with ongoing evidence of replication and Nef mRNA transcription, showed specific T-cell responses by Elispot and Tetramer staining, maintained for 2-4 years after initiation of HAART.
- Nef epitope recognition was detected in all 4 subjects, gp120, Pol and Gag-specific in 1 or 2 subjects.
- The HIV-specific CD8+ T-cells had an intermediate maturation phenotype characterized by low levels of perforin and high levels of CD27 expression.

HXB2 Location RT (158–166)
Author Location Pol (314–322)
Epitope AIFQSSMTK
Epitope name AK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords optimal epitope
References Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For one of the escape variants, a novel CD8 T-cell response equal in magnitude to the wild type, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wild type.
- This epitope did not vary.

HXB2 Location RT (158–166)
Author Location Pol (314–322)

CTL CD8+

Epitope AIFQSSMTK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location RT (158–166)
Author Location Pol (313–321)
Epitope AIFQSSMTK
Epitope name AK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A*01, A*11, B*08, B*15, Cw*04, Cw*07
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords escape, optimal epitope
References Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- The AK9 variant AIFQSSMTr was essentially the only form of the epitope detected over a 5-year period in this person. Elispot reactions indicated the T-cell clones only recognized the autologous form, not the B clade consensus, AIFQSSMTK. Two rare variants were observed at the 5-year time point, tIFQSSMTr and AIFQSSMar.

HXB2 Location RT (158–166)
Author Location RT
Epitope AIFQSSMTK
Epitope name A11-AK9 (RT)
Immunogen HIV-1 infection
Species (MHC) human (A11)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (158–166)
Author Location Pol (325–333)
Epitope AIFQSSMTK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301, A11, A33)
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords Th1, characterizing CD8+ T cells
References Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- One of the patients responded to this peptide with GzB producing cells, while none of the patients responded with IFN-gamma producing cells.

HXB2 Location RT (158–166)
Author Location RT (B consensus)
Epitope AIFQSSMTK
Epitope name ATK9
Immunogen HIV-1 infection
Species (MHC) human (A11, A3)
Donor MHC A02, A11, B18, B44, Cw12, Cw5; A03, B14, B60, Cw3, Cw7; A01, A03, B08, B14, Cw7, Cw8
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, cross-presentation by different HLA, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 3/9 individuals recognized this epitope, two presented by HLA-A3, one presented by HLA-A11.

HXB2 Location RT (158–166)
Author Location RT (325–333 IIIB)
Epitope AIFQSSMTK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords responses in children, mother-to-infant transmission
References Wilson *et al.* 1996

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.
- AIFQSSMTR and AILQSSMTK, naturally occurring variants, were found in infant, and are recognized.
- TISQSSMTK, a naturally occurring variant, was found in infant and is not recognized.

HXB2 Location RT (158–166)
Author Location RT (325–333 LAI)
Epitope AIFQSSMTK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords subtype comparisons
References Cao *et al.* 1997a

- The consensus peptide of B and D clade viruses is AIFQSSMTK.
- The consensus peptide of a subset of As is AIFQASMTK and it is less able to stimulate the CTL clone.
- The consensus peptide of a subset of As is SIFQSSMTK and is as reactive as the originally defined epitope.

HXB2 Location RT (158–166)
Author Location Pol (325–333 IIIB)
Epitope AIFQSSMTK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords responses in children, mother-to-infant transmission, escape
References Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- One variant found in an infant gave a positive CTL response: AIFQSSMTR.
- AIFLSSMTK and TISQSSMTK were escape mutants.

HXB2 Location RT (158–166)
Author Location RT (325–333 SF2)
Epitope AIFQSSMTK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A3+ individuals that had a CTL response to this epitope broken down by group: 0/7 group 1, 0/4 group 2, and 1/2 group 3.

HXB2 Location RT (158–166)
Author Location RT (158–166)
Epitope AIFQSSMTK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant.
- In two of the subjects, AIFQSSMTK was the dominant epitope.

HXB2 Location RT (158–166)
Author Location RT Pol (313–321)
Epitope AIFQSSMTK
Epitope name A3-ATK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 3/7 individuals began to have detectable responses to this epitope after STI.

CTL CD8+

HXB2 Location RT (158–166)
Author Location RT (158–166)
Epitope AIFQSSMTK
Epitope name A3-AK9 Pol
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), escape, early treatment, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The second infecting strain had the variant aifqssmIk. The CTL response to the second variant was zero or low at all timepoints. The CTL response to the first variant was also low, and declined over time.

HXB2 Location RT (158–166)
Author Location RT (158–166)
Epitope AIFQSSMTK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these eptiopes, but this increased over time.

HXB2 Location RT (158–166)
Author Location RT Pol (313–333)
Epitope AIFQSSMTK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 5/14 patients recognized this epitope.

HXB2 Location RT (158–166)
Author Location Pol
Epitope AIFQSSMTK
Epitope name AK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 9, aifqssmtI, was found not to correspond to the most polymorphic residues in the epitope.

HXB2 Location RT (158–166)
Author Location RT
Epitope AIFQSSMTK
Epitope name A3-ATK9(RT)
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (158–166)
Author Location Pol
Epitope AIFQSSMTK
Epitope name Pol347

Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (A3)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- AIFQSSMTK is a Pol epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location RT (158–166)
Author Location RT (325–333 LAI)
Epitope AIFQSSMTK
Epitope name P3
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3 supertype)
Keywords HAART, ART, supertype
References Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNgamma production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

HXB2 Location RT (158–166)
Author Location Pol (337–345)
Epitope AIFQSSMTK
Immunogen HIV-1 infection
Species (MHC) human (A3 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801).

HXB2 Location RT (158–166)
Author Location Pol
Epitope AIFQSSMTK
Epitope name Pol347
Subtype A, B, C, D
Immunogen HIV-1 infection
Species (MHC) human, mouse (A3 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope AIFQSSMTK of the HLA-A3 supertype bound most strongly to HLA-A*1101, and -A*0301 and also to -A*6801 but not to -A*3301 or A-*3101. It was conserved 25% in subtype A, 79% in B, 25% in C and 75% in subtype D. 3/23 HLA-A3 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Pol347.

HXB2 Location RT (158–166)
Author Location Pol
Epitope AIFQSSMTK
Epitope name 1339
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A*0301, A*6801, A11, A3, A33)
Donor MHC A02, A03, B08, B51, Cw01, Cw07; A03, A26, B08, B52; A03, A11, B05, B14, Cw08
Country United States
Assay type T-cell Elispot
Keywords binding affinity, supertype, computational epitope prediction, cross-presentation by different HLA
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for AIFQSSMTK: 59% Supertype epitope binding to A03, A3.1, A11, A6801, A33.

HXB2 Location RT (158–166)
Author Location Pol (313–321)
Epitope AIFQSSMTK
Immunogen HIV-1 infection
Species (MHC) human (A11, A3)

CTL CD8+

References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location RT (158–166)
Author Location Pol (325–333)
Epitope AIFQSSMTK
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A11, A3, A33)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- Variants (S/A)IFQSSMTK are specific for the A/B clades.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-A3 women, 2/2 HEPS and 3/3 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in one of the 2/2 HEPS cases and in one of the 3/3 HIV-1 infected women.

HXB2 Location RT (158–166)
Author Location Pol (325–333)
Epitope AIFQSSMTK
Immunogen peptide-HLA interaction
Species (MHC) (A11, A3, A33, A68)
Assay type HLA binding
Keywords binding affinity, immunodominance
References Racape *et al.* 2006

- Interaction between purified HLA-A3 molecules and several dominant CD8 epitopes was characterized. Amplitude, stability, and kinetic parameters of the interaction between HLA-A3, peptides, and anti-HLA mAbs were tested.
- Epitopes tested bound strongly to HLA-A3 and formed very stable complexes.
- Gag epitope RLRPGGKKK and Nef epitope RLAFHHVAR complexes with HLA-A3 were not recognized by the A11.1 mAb specific to HLA-A3 alleles. The proposed explanation was that Arg at position P1 of the peptide may push the α2 helix residue and affect mAb recognition.

HXB2 Location RT (158–166)
Author Location RT (325–333 LAI)
Epitope AIFQSSMTK
Subtype B
Immunogen
Species (MHC) human (A33)
References Rowland-Jones 1995

- Defined as minimal peptide by titration curve, S. Rowland-Jones, pers. comm.

HXB2 Location RT (158–166)
Author Location
Epitope AIFQSSMTK
Immunogen HIV-1 infection
Species (MHC) human (A33)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 1/22 HEPS sex worker controls, ML1668.

HXB2 Location RT (158–166)
Author Location RT
Epitope AIFQCSMTK
Epitope name AK9(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- The tested peptide sequence, QGWKGSPAIFQcSMTKIL, contains a variant, AIFQcSMTK that differs by 1 substitution from the previously described HLA-A3 and HLA-A11 previously described epitope AIFQSSMTK.
- None of the 3 HLA-A3 carriers responded to peptide epitope AIFQcSMTK. 4 of the 16 HLA-A11 carriers responded with average magnitude of CTL response of 183 SFC/million PBMC.

HXB2 Location RT (158–182)
Author Location RT (325–349 PV22)
Epitope AIFQSSMTKILEPFRKQNPDIVIYQ
Immunogen HIV-1 infection
Species (MHC) human (A11)
References Jassoy *et al.* 1993

- HIV-1 specific CTLs release γ-IFN, and α- and β-TNF.

HXB2 Location RT (158–182)
Author Location RT (325–349)
Epitope AIFQSSMTKILEPFRKQNPDIVIYQ
Immunogen HIV-1 infection
Species (MHC) human (A11)
References Price *et al.* 1995

- Study of cytokines released by HIV-1 specific activated CTL.

HXB2 Location RT (159–167)
Author Location RT (C-96BW15C05)
Epitope IFQSSMTKI
Epitope name E
Subtype C
Immunogen vaccine
Vector/Type: DNA, alphavirus replicon *Strain:* C clade C-96BW04.09, C clade C-96BW15C05 *HIV component:* Gag, Gag-Pol, Pol
Species (MHC) mouse (H-2^d)
Assay type Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, vaccine antigen design
References Megede *et al.* 2006

- HIV clade C gag, pol and fusion gagpol vaccines were compared in mice. Breadth of T cell responses was improved in mice immunized with gagpol fusion genes, compared to single antigen constructs. 5 new murine CD8+ T cell epitopes were mapped.
- This is a novel epitope.

HXB2 Location RT (159–167)
Author Location RT Pol
Epitope IFQSSMTKI
Epitope name P
Subtype A, B, C
Immunogen vaccine
Vector/Type: DNA with CMV promotor, modified vaccinia Ankara (MVA), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade, B clade, C clade Du422, Other *HIV component:* Gag, Nef, RT
Species (MHC) mouse (H-$2K^d$)
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords subtype comparisons, vaccine-induced epitopes, variant cross-recognition or cross-neutralization, antagonism
References Larke *et al.* 2007

- Cross-clade vaccine recognition was studied using either single-, multi or several anatomically separated single-clade vaccines. Limited cross-clade response was seen with single-clade administrations. Multi-clade vaccines gave immune interference (antagonism and original antigenic sin), reducing CTL response. Simultaneously administered but anatomically separated vaccines from clades A, B, C decreased antagonism and increased immune responses.
- After immunization with A-clade vaccine, index epitope P, IFQSSMTKI, and variant IFQaSMTKI were recognized. Variant IFQcSMTKI was not recognized.

HXB2 Location RT (164–172)
Author Location RT (1645–172)
Epitope MTKILEPFR
Epitope name MR9
Immunogen
Species (MHC) human (A*0301)
References Zimbwa *et al.* 2007

- E169D is a processing mutation for HLA-B*0702 restricted SPAIFQSSM (SM9) as well as an epitope variation for HLA-A*0301 restricted MTKILEPFR (MR9).
- CTL recognition of MR9 was detected 5 days post-infection with wild type (169E) HIV-1, but not with mutant 169D virus bearing eptiope MTKILdPFR.
- Binding assays found a 44% reduction in binding to HLA-A*0301 by the variant epitope MTKILdPFR.
- Mutation 169D lies within MR9. In vitro proteasome processing assays showed that both wild type or variant 27-mer synthetic peptide QGWKGSPAIFQSSMTKILE(d)PFRKQNPD released appropriate MR9-intermediate peptides within 6 h.

HXB2 Location RT (164–172)
Author Location Pol (343–351)
Epitope MTKILEPFR
Immunogen HIV-1 infection
Species (MHC) human (A3 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 4/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801).

HXB2 Location RT (164–172)
Author Location Pol (319–327)
Epitope MTKILEPFR
Subtype B
Immunogen HIV-1 infection, peptide-HLA interaction
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance
References Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.

CTL CD8+

- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, MTKILEPFR, is similar to human protein Piwi-like 2, sequence MTKILEPc and human protein SON DNA Binding protein, sequence sMTKILdsF.

HXB2 Location RT (173–181)
Author Location RT (173–181 LAI)
Epitope KQNPDIVIY
Subtype B
Immunogen
Species (MHC) human (A*3002)
Keywords optimal epitope
References Goulder *et al.* 2001a; Llano *et al.* 2009

- C. Brander notes this is an A*3002 epitope.

HXB2 Location RT (173–181)
Author Location RT
Epitope KQNPDIVIY
Epitope name KY9 (RT-53)
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
References Goulder *et al.* 2001a

- HLA-A*3002 is very common in African populations, 50% of Zimbabweans express HLA-A30, 44% in African Zulu, so five new HIV epitopes were characterized that are presented by this HLA molecule.
- A rapid method was developed combining ELISPOT with intracellular IFN-γ staining of PBMCs to map optimal epitopes, then HLA presenting molecules were defined – this method was completed within 48 to 72 hours of receipt of blood.
- Two individuals were studied: Subject 199 (HLA A*0201/*3002 B*4402/51 Cw2/5), a Caucasian, and Subject 6007 (HLA A*3002/ B53/*5801 Cw4/7) an African-Caribbean.
- In both HLA-A*3002 individuals the response to RSLYNTVATLY was dominant.
- In subject 199 four additional A*3002 epitopes were identified.
- Three quantitative assays, ELISPOT, precursor frequency and chromium release, confirmed a hierarchy of response: RY11 (p17) > KY9 (gp41) > KY9 (RT-53) > IY9 (gp41)

HXB2 Location RT (173–181)
Author Location (C consensus)
Epitope AQNPEIVIY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location RT (173–181)
Author Location
Epitope KQNPDIVIY
Immunogen HIV-1 infection
Species (MHC) human (A30)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (A30), an additional HLA (A6801) was statistically predicted to be associated with this epitope.

HXB2 Location RT (173–181)
Author Location RT
Epitope KQNPDIVIY
Epitope name KY9(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A30)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide sequences, MTKILEPFRKQNPDIVIY and RKQNPDIVIYQYMDDLYV, contain the exact sequence of a previously described HLA-A30 epitope, KQNPDIVIY, none of the 15 HLA-A30 carriers responded to it.

HXB2 Location RT (173–181)

Author Location RT
Epitope KQNPDIVIY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, rate of progression, immunodominance
References Frahm *et al.* 2006

- CTL responses restricted by HLA-B*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects inspite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominanat CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.
- KQNPDIVIY of clade B is a potential HLA-B*1503-restricted epitope, with epitope KQNPeIVIY found in clade C.

HXB2 Location RT (173–183)
Author Location (C consensus)
Epitope AQNPEIVIYQY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- AQNPEIVIYQY is an optimal epitope.

HXB2 Location RT (175–182)
Author Location RT (329–337)
Epitope NPDVILIQY
Subtype HIV-2
Immunogen HIV-1 or HIV-2 infection
Species (MHC) human (B35)
Country Gambia
Keywords HIV exposed persistently seronegative (HEPS), HIV-2
References Rowland-Jones *et al.* 1995

- HIV-1 infected and HIV-2-infected B35+ subjects recognized both the HIV-1 (HPDIVIYQY) and HIV-2 forms (NPDVILIQY). NPDIVIYQY preferred sequence for some CTL clones.

HXB2 Location RT (175–183)
Author Location (C consensus)
Epitope NPEIVIYQY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*18)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the I4 residue of NPEIVIYQY are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location RT (175–183)
Author Location (C consensus)
Epitope NPEIVIYQY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- NPEIVIYQY is an optimal epitope.

HXB2 Location RT (175–183)
Author Location RT (175–183)
Epitope NPDIVIYQY
Epitope name NY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLAs-B*35-associated substitution within optimally defined epitope NPDIVIYQY is at position D3, NPdIVIYQY.

HXB2 Location RT (175–183)
Author Location RT (328–336 IIIB)
Epitope NPDIVIYQY
Immunogen HIV-1 infection
Species (MHC) human (B*3501)

CTL CD8+

References Tomiyama *et al.* 1997

- A CTL clone responsive to this epitope was obtained.
- 3/7 B35-positive individuals had a CTL response to this epitope.
- D to E, or V to I, substitutions at positions 3 or 5, respectively, reduces CTL activity and binding to B*3501.

HXB2 Location RT (175–183)
Author Location RT (342–350 LAI)
Epitope HPDIVIYQY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*3501 epitope. Variant nPDIVIYQY also noted.

HXB2 Location RT (175–183)
Author Location Pol (330–338)
Epitope NPDIVIYQY
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
References Tomiyama *et al.* 2000a

- CD8+ T-cells that bound one of six HIV-specific B*3501-epitope tetramers did not express CD28 or CD45A.
- A significant increase in CD28-CD45RA- cells and a decrease of CD28+CD45RA+ cells was observed in chronically HIV-1-infected individuals relative to healthy individuals.
- CD28-CD45RA- cells are likely to be effector cells and have high levels of perforin in their cytoplasm.
- The mean percentage of total CD28- CD8+ cells in chronically infected HIV-1-infected patients was 76.6% in comparison to HIV-1-uninfected individuals (40.6%)

HXB2 Location RT (175–183)
Author Location RT (175–183 IIIB)
Epitope NPDIVIYQY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Keywords epitope processing, escape
References Moore *et al.* 2002b

- HIV polymorphisms in the RT protein were examined relation to HLA alleles found in a population of 473 participants in the Western Australian HIV Cohort Study. 64 significant associations between polymorphisms at particular positions and HLA alleles were detected, for HLA-B7, -B12, -B35 and -B15. Fifteen of these were in positions with known epitopes, 4 in anchor residues, 11 in other positions. Six additional polymorphic sites associated with particular HLA molecules flanked known epitopes and may relate to processing.
- NPDIVIYQY was one of two epitopes characterized in detail. D177x substitutions are know to specifically abrogate binding to HLA-B*3501, and not other B*35 subtypes. D177x substitutions were associated with people who carried HLA-B*3501 and not other B*35 subtypes; considering high resolution typing generally strengthened the B*35 associations.

HXB2 Location RT (175–183)
Author Location RT (175–183)
Epitope NPDIVIYQY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Donor MHC A*2301, B*1503, B*3501, Cw2, Cw7
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ INF-γ T-cell responses in 21 men within 15-92days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-γ secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

HXB2 Location RT (175–183)
Author Location Pol (330–338)
Epitope HPDIVIYQY
Epitope name HY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Donor MHC A*0201, A*0301, B*3501, B*51, Cw*04, Cw*06
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords escape, acute/early infection
References Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- The response to this epitope was not detected until month 25.

HXB2 Location RT (175–183)
Author Location
Epitope NPEIVIYQY
Epitope name NY9

CTL CD8+

Immunogen
Species (MHC) human (B18)
Keywords optimal epitope
References Llano *et al.* 2009
- C. Brander notes this is a B18 epitope.

HXB2 Location RT (175–183)
Author Location RT (342–350 LAI)
Epitope HPDIVIYQY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords review
References McMichael & Walker 1994
- Review of HIV CTL epitopes.

HXB2 Location RT (175–183)
Author Location RT (329–337)
Epitope HPDIVIYQY
Subtype B
Immunogen HIV-1 or HIV-2 infection
Species (MHC) human (B35)
Country Gambia
Keywords HIV exposed persistently seronegative (HEPS), HIV-2
References Rowland-Jones *et al.* 1995
- HIV-1 infected and HIV-2-infected B35+ subjects recognized both the HIV-1 (HPDIVIYQY) and HIV-2 forms (NPDVILIQY). NPDIVIYQY preferred sequence for some CTL clones.

HXB2 Location RT (175–183)
Author Location (SF2)
Epitope NPDIVIYQY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords binding affinity, rate of progression, escape
References Kawana *et al.* 1999
- HLA B35 is associated with rapid disease progression.
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals.
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals – only one of these reduced the binding of the peptide to B35 and was shown to be an escape mutation.
- npEiviyqy was found in 8/10 of the B35+ individuals, and two of the B35- individuals—the D–>E substituted peptide had reduced binding affinity to B35 and may be an escape mutant.

HXB2 Location RT (175–183)
Author Location RT (329–337)
Epitope HPDIVIYQY
Immunogen in vitro stimulation or selection
Species (MHC) human (B35)
References Lalvani *et al.* 1997
- A peptide-based protocol was optimized for restimulation of CTLp using optimized peptide and IL-7 concentrations – importantly this protocol does not stimulate a primary response, only secondary – peptide-specific CTLp counts could be obtained via staining with peptide-Class I tetramers.
- This peptide was one of the B35 presented test peptides used in control experiments showing that the assay gave no activity using lymphocytes from 21 healthy B35 seronegative donors.

HXB2 Location RT (175–183)
Author Location RT (328–336 IIIB)
Epitope NPDIVIYQY
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Menendez-Arias *et al.* 1998; Shiga *et al.* 1996
- Binds HLA-B*3501.
- CTL activity to this epitope was originally detected in a long-term survivor, however it has since been found in normal progressors – it is cross-reactive with HIV-2 (HPDILIYQY), but D3E and V5I substitutions reduce binding Menendez-Arias *et al.* [1998]

HXB2 Location RT (175–183)
Author Location RT (328–336 IIIB)
Epitope NPDIVIYQY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords review, escape
References Menendez-Arias *et al.* 1998; Sipsas *et al.* 1997
- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB.
- NPDIIIYQY, a variant found in HIV-1 JRCSF, was also recognized.
- NPEIVIYQY, was also recognized.
- NPDLVIYQY, was also recognized.
- Menendez-Arias *et al.* [1998], in a review, notes that the YXDD motif, highly conserved among polymerases, overlaps this epitope – CTL activity to this epitope was originally detected in a long-term survivor, however it has since been found in normal progressors – it is cross-reactive with HIV-2 (HPDILIYQY), but D3E and V5I substitutions reduce binding.

HXB2 Location RT (175–183)
Author Location RT
Epitope NPDIVIYQY
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B35)
Keywords review, subtype comparisons, HIV exposed persistently seronegative (HEPS)
References Menendez-Arias *et al.* 1998; Rowland-Jones *et al.* 1998a
- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.

CTL CD8+

- The A subtype consensus is HPDIVIYQY.
- The D subtype consensus is NPEIVIYQY.
- Menendez-Arias *et al.* [1998], in a review, notes that the YXDD motif, highly conserved among polymerases, overlaps this epitope – CTL activity to this epitope was originally detected in a long-term survivor, however it has since been found in normal progressors – it is cross-reactive with HIV-2 (HPDILIYQY), but D3E and V5I substitutions reduce binding.

HXB2 Location RT (175–183)
Author Location Pol (subtype B)
Epitope `NPDIVIYQY`
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B35)
Keywords subtype comparisons
References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- Clade A version of epitope HPDIVIYQY, Clade D NPEIVIYQY.

HXB2 Location RT (175–183)
Author Location Pol
Epitope `HPDIVIYQY`
Immunogen
Species (MHC) human (B35)
References Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective.
- HIV-2 version of this epitope is not conserved: NPDVILIQY, but the CTLs are cross-reactive – one of five B35 CTL epitopes that are cross-reactive, see also Rowland-Jones *et al.* [1995]

HXB2 Location RT (175–183)
Author Location
Epitope `HPDIVIYQY`
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords acute/early infection
References Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B2705; and A*0201, A*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK.
- The subject with A*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705.
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

HXB2 Location RT (175–183)
Author Location Pol (subtype A)
Epitope `HPDIVIYQY`
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- HPDIVIYQY or NPDIVIYQY was recognized in 1 of the 6 women (ML857), and the response was present in the last available sample prior to seroconversion, 7 months.
- 20/20 sequences of the infecting strain had three substitutions in this epitope, all 20 were NpQiIiyqy, and this form was not recognized by CTL from ML 857 – this was the only case in the study where a virus carrying an unrecognized form of the epitope broke through.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- NPDIVIYQY was recognized by 1/22 HEPS control sex workers, ML887.

HXB2 Location RT (175–183)
Author Location RT (175–183 SF2)
Epitope `NPDIVIYQY`
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.

- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 1/2 group 1, 0/2 group 2, and 1/1 group 3.

HXB2 Location RT (175–183)
Author Location Pol (342–350)
Epitope HPDIVIYQY
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B35)
Keywords HIV exposed persistently seronegative (HEPS), immunodominance
References Kaul *et al.* 2001a

- Variants (H/N)PDIVIYQY are specific for the A/B clades.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B35 women, 2/3 HEPS and 1/4 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in only one of the 2/3 HEPS cases, and was not to this epitope in the one responsive HIV-1 infected women.
- Subject ML 857 shifted from a A*6802 DTVLEDINL and B35 (H/N)PDIVIYQY response prior to seroconversion to a B35 PPIPVGDIY and B35 VPLRPMTY response post-seroconversion and the loss of the pre-seroconversion response was not due to sequence variation within these epitopes.

HXB2 Location RT (175–183)
Author Location
Epitope HPDIVIYQY
Epitope name Pol-HY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B35, 4/21 (19%) recognized this epitope.

HXB2 Location RT (175–183)
Author Location Pol
Epitope NPDIVIYQY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC A11, A3, B35, B51
Keywords mother-to-infant transmission
References Sabbaj *et al.* 2002

- IFNgamma T-cell responses in breast milk of 5 HIV-1 infected women from the US and 6 from Zambia were tested with using Elispot. 11/11 women responded to Gag, 8/11 responded to Pol, 7/11 women to Nef, and 2/5 women to Env peptide pools. These responses were shown to be primarily due to CD8+ T-cells in one woman, and another woman had cytolytic responses measured by Cr-release.
- T-cells in breast milk from a volunteer who was HLA A3, A11, B35, B51 induced IFNgamma after stimulation with a peptide that carries known B35 epitope NPDIVIYQY.
- The frequencies of responses in the two compartments differed, and 2/4 women that responded to epitopes in Nef 101-205 and Pol 601-710 showed responses in breast milk but no detectable responses in peripheral blood cells.

HXB2 Location RT (175–183)
Author Location Pol
Epitope HPDIVIYQY
Subtype A
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human, macaque (B35)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location RT (175–183)
Author Location Pol (342–350)
Epitope HPDIVIYQY
Subtype B
Immunogen HIV-1 infection

CTL CD8+

Species (MHC) human (B35)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords Th1, characterizing CD8+ T cells
References Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- None of three patients responded to this peptide with GzB producing cells, while one of the patients responded with IFN-gamma producing cells.

HXB2 Location RT (175–183)
Author Location RT Pol (330–338)
Epitope `HPDIVIYQY`
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 5/9 patients recognized this epitope.

HXB2 Location RT (175–183)
Author Location RT
Epitope `NPDIVIYQY`
Epitope name B35-NQY9(RT)
Immunogen HIV-1 infection
Species (MHC) human (B35)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (175–183)
Author Location RT
Epitope `HPDIVIYQY`
Epitope name B35-HY9(RT)
Immunogen HIV-1 infection
Species (MHC) human (B35)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
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- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (175–183)
Author Location
Epitope `NPDIVIYQY`
Immunogen HIV-1 infection
Species (MHC) human (B35)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope NPDIVIYQY elicited a magnitude of response of 180 SFC with a functional avidity of 0.0005nM and binding affinity of 9nM.

HXB2 Location RT (175–183)
Author Location RT
Epitope `NPDIVIYQY`
Epitope name NY9(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B35-restricted epitope NPDIVIYQY elicited an immune response in Chinese HIV-1 positive subjects as part of peptide RKQNPDIVIYQYMDDLYV. This epitope differs from another described epitope, HPDIVIYQY, at 1 residue, nPDIVIYQY.
- 5 of the 12 HLA-B35 carriers responded to NPDIVIYQY-containing peptide with average magnitude of CTL response of 662 SFC/million PBMC (author communication and Fig.1).

HXB2 Location RT (175–184)
Author Location RT (175–184 LAI)
Epitope `NPDIVIYQYM`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
References Samri *et al.* 2000

- This epitope contains the mutation M184V, a frequent mutation induced by nucleoside reverse transcriptase inhibitors.
- Patient 246#1 (B51), was found by ELISPOT to recognize the wild type and the mutated peptide after zidovudine treatment.
- The resistance mutation M184V gave an increased predicted binding score to B51 (`http://bimas.dcrt.nih.gov/molbio/hla_bind`) compared to the wildtype RT sequence and also an increased ELISPOT reactivity.

HXB2 Location RT (175–199)
Author Location RT (342–366 LAI)
Epitope `NPDIVIYQYMDDLYVGSDLEIGQHR`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
References Menendez-Arias *et al.* 1998; Walker *et al.* 1989

- One of five epitopes defined for RT-specific CTL clones in this study.

HXB2 Location RT (179–187)
Author Location RT (179–187)
Epitope `VIYQYMDDL`
Epitope name VL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

HXB2 Location RT (179–187)
Author Location RT (179–187)
Epitope `VIVQYMDDL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, VIVQYMDDL, was detected within overlapping peptide RKQNPDIVIVQYMDDLYV.

HXB2 Location RT (179–187)
Author Location RT
Epitope `VIYQYMDDL`
Immunogen vaccine
Vector/Type: vaccinia
Species (MHC) human (A*0201)
References Hanke *et al.* 1998a; Hanke *et al.* 1998b

- This epitope was shown to be processed and presented to appropriate CTL clones upon infection of human target cells with vaccinia virus Ankara (VVA) carrying 20 HIV-1 epitopes recognized by humans.

HXB2 Location RT (179–187)
Author Location RT
Epitope `VIYQYMDDL`
Immunogen HIV-1 infection

Species (MHC) human (A*0201)
References Tan *et al.* 1999

- Adoptive transfer of two autologous *in vitro*-expanded CTL clones against the A*0201 restricted epitopes SLYNTVATL and VIYQYMDDL were infused into a patient – they were well tolerated, but the SLYNTVATL clone was shown by tetramer staining to be rapidly eliminated through apoptosis, and the treatment had no impact upon viral load and CD4 and CD8 cell counts.
- Tetramer staining failed for the VIYQYMDDL epitope as the tetramer was unstable.

HXB2 Location RT (179–187)
Author Location Pol (346–354)
Epitope `VIYQYMDDL`
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords epitope processing, immunodominance, escape
References Sewell *et al.* 1999

- Proteasome regulation influences epitope processing and could influence patterns of immunodominance.
- The proteasome is inhibited by lactacystin treatment, and gamma IFN induces expression of proteasome subunits, LMP2 and LMP7, which combine with the proteasome to create an immunoproteasome.
- IFN-gamma induction of the immunoproteasome and lactacystin inhibition increases the presentation of the A*0201 VIYQYMDDL epitope, but decreases the presentation of the A*0201 ILKEPVHGV epitope, which is immunodominant within pol proteins, showing the two epitopes are processed by different pathways.
- ILKEPVHGV seems to be processed by the classical proteasome pathway, while VIYQYMDDL appears to be destroyed by this pathway.
- This epitope contains the catalytic site (YMDD) of RT, a conserved sequence in HIV-1 which restricts escape mutants.

HXB2 Location RT (179–187)
Author Location RT (346–354 LAI)
Epitope `VIYQYMDDL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords review
References Harrer *et al.* 1996a; Menendez-Arias *et al.* 1998

- The substitution VIYQYVDDL abrogates CTL response and confers drug resistance.
- Menendez-Arias *et al.* [1998], in a review, notes that this epitope includes catalytic residues (Asp-185 and Asp-186) in the active site of RT.

HXB2 Location RT (179–187)
Author Location RT (346–354 LAI)
Epitope `VIYQYMDDL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*0201 epitope.

HXB2 Location RT (179–187)
Author Location RT (346–354)
Epitope `VIYQYMDDL`
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords review, escape
References Brander *et al.* 1998a; Menendez-Arias *et al.* 1998

- Of 17 infected HLA A*0201 subjects, 13 had CTL responses against the p17 SLYNTVATL epitope, six recognized ILKEPVHGV and five recognized VIYQYMDDL, and there was no correlation between viral load and recognition of a specific epitope or evidence of immune escape.
- Only one subject had CTL against all three epitopes.
- Subjects were part of the San Francisco City Clinic Cohort, the ARIEL project and from the Boston area.
- In the review Menendez-Arias *et al.* [1998] the authors note that substitution of three residues in this epitope can confer resistance to RT inhibitors (1, 3, and 6) – substitutions V1E and M6V abolish CTL activity, and M6V confers resistance to 3TC – substitution Y3C reduces CTL activity and is associated with resistance to non-nucleoside RT inhibitors.

HXB2 Location RT (179–187)
Author Location RT
Epitope `VIYQYMDDL`
Epitope name RT VL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords subtype comparisons, supertype, computational epitope prediction
References Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, including RT VL9, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- RT VL9 was not recognized by any of the 22 HLA-A2 patients with chronic HIV-1 infection or the 13 HLA-A2 patients with acute HIV-1 infection included in this study.

HXB2 Location RT (179–187)
Author Location RT (346–354)
Epitope `VIYQYMDDL`
Epitope name VL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Dela Cruz *et al.* 2000

- Integration of HIV RT CTL epitopes into the N-terminus of the HLA-A2 heavy chain, or tethering the epitopes to the target chain, resulted in epitope-specific lysis by CD8+ CTL.

- These antigens could also be used to stimulate primary responses *in vitro*.

HXB2 Location RT (179–187)
Author Location Pol (346–354)
Epitope VIYQYMDDL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords epitope processing, immunodominance
References Sewell *et al.* 2002

- Epitope processing of three different HLA-A*0201 HIV epitopes was shown to use different pathways, which might influence patterns of immunodominance. .174 cells were used that lack TAP1 and TAP2 genes, as well as the LMP2 and LMP7 genes that encode the beta-subunits of the immunoproteasome. These genes could be added back through transfection to study processing.
- ILKEPVHGV was efficiently presented in TAP-1 and -2 transfected cells while VIYQYMDDL and SLYNTVATL were not. VIYQYMDDL was destroyed by the MB1 subunit of the protease, and could be expressed in the presence of the proteasome inhibitor lactacystin, but SLYNTVATL expression was not restored. SLYNTVATL expression was unaltered by lactacystin in a wild type cell line.

HXB2 Location RT (179–187)
Author Location RT (346–354 LAI)
Epitope VIYQYMDDL
Epitope name LR26
Subtype B
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade LAI *Adjuvant:* Incomplete Freund's Adjuvant (IFA), Montanide (ISA 720), P30, PLG
Species (MHC) mouse (A*0201)
Keywords binding affinity, vaccine-specific epitope characteristics, immunodominance
References Peter *et al.* 2001

- The stability of peptide binding to HLA-A2.1 was determined for six HLA-A2.1 peptides included in this vaccine study – ILKEPVHGV (RT), SLYNTVATL (p17), SLLNATDIAV (gp41) and LLWKGEGAV (RT) all bound with high affinity comparable to a influenza epitope reference (GILGFVFTL), while RGPGRAFVTI and VIYQYMDDL bound with a lower affinity (relative binding activity = 0.01).
- The four high-affinity peptides formed stable complexes with half-lives ranging between 8 and 32 hours, while the low affinity peptides had half lives of less than an hour.
- HLA-A2.1 transgenic mice were immunized with the six HIV-1 peptides and P30, as a universal T-helper epitope, with IFA or Montanide or microspheres as adjuvants.
- All peptides except VIYQYMDDL induced a stong CTL response in Cr-release assays - stronger responses were observed when peptides were delivered alone, indicating immunodominance when the combination was used.

HXB2 Location RT (179–187)
Author Location RT (346–354 LAI)
Epitope VIYQYMDDL
Epitope name LR26
Subtype B
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade LAI *Adjuvant:* Incomplete Freund's Adjuvant (IFA), IL-12, P30
Species (MHC) mouse (A*0201)
Keywords vaccine-specific epitope characteristics, immunodominance
References Peter *et al.* 2002

- When HIV-1 peptides were used to vaccinate HLA-A2.1 transgenic A2-Kb mice, strong responses to five peptides were observed when the peptides were given individually, but immunodominance limited the response to some of the peptides when they were given in combination Peter *et al.* [2001]. IL-12 can counteract immunodominance in BALB/c mice, so it was given with the multiple epitope vaccination, and was instead found to specifically eliminate the HLA-A2.1-epitope CTL responses, but not Kb CTL responses. This was possibly a consequence of transient depletion of T-cells, B cells and macropahges in the spleen.

HXB2 Location RT (179–187)
Author Location Pol
Epitope VIYQYMDDL
Subtype A, B, C, D
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human, macaque (A*0201)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location RT (179–187)
Author Location RT (179–187)
Epitope VIYQYMDDL
Subtype B
Immunogen vaccine

Vector/Type: peptide *HIV component:* RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA), IL-12
Species (MHC) mouse (A*0201)
Donor MHC A2.1
Assay type Cytokine production, Chromium-release assay
Keywords binding affinity, vaccine-induced epitopes
References Okazaki *et al.* 2003

- Alanine substitutions of VIYQYMDDL were tested for importance of each amino acid for HLA-A2.1 binding. Peptide variant (vLyqymddV) showed an 8 fold higher MHC binding affinity than wild type. YLyqymddV had an even higher binding affinity, but the Y at position one blocked TCR recognition. The higher affinity form of vLyqymddV induced CTL *in vivo* that could protect against a vaccinia virus expressing RT and the wild type epitope.

HXB2 Location RT (179–187)
Author Location RT (179–187 MN)
Epitope VIYQYMDDL
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* B clade MN *HIV component:* gp120, Protease, RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) humanized mouse (A*0201)
Assay type CD8 T-cell Elispot - IFNγ
Keywords epitope processing, vaccine-specific epitope characteristics, immunodominance, immunotherapy
References Isaguliants *et al.* 2004

- Immunization of HLA-A*0201-transgenic mice with synthetic genes encoding clusters of human A*0201 CTL epitopes located at the sites of drug resistance mutations, induced RT-specific cellular responses indicating the immunogenicity of these constructs. This vaccine strategy may be a first step towards a therapeutic vaccine against drug-resistant strains.
- This was one of five HLA-A*0201 epitopes from the RT or protease proteins that was included in the polyepitope vaccine. When the transgenic HLA A*0202 mice were vaccinated with the polyepitope construct or with a mixture of RT peptides, a sustained low level CD8+ T-cell gamma IFN response was observed, in contrast to when an intact RT gene was used for vaccination.

HXB2 Location RT (179–187)
Author Location Pol (346–354)
Epitope VIYQYMDDL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords Th1, characterizing CD8+ T cells
References Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- One of seven patients responded to this peptide with GzB producing cells, while none of the patients responded with IFN-gamma producing cells.

HXB2 Location RT (179–187)
Author Location (C consensus)
Epitope VIYQYMDDL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- VIYQYMDDL is an optimal epitope.

HXB2 Location RT (179–187)
Author Location RT (179–187)
Epitope VIYQYMDDL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope VIYQYMDDL was predicted to be restricted by HLA A*0201, A*0205, A*0207, A*0214.

HXB2 Location RT (179–187)
Author Location Pol
Epitope VIYQYMDDL
Subtype B

Immunogen HIV-1 infection
Species (MHC) human (A*0201, A2)
Donor MHC A1, A19, B*3501, B44, Cw16, Cw7; A*0201, A19, B14, B44, Cw16, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
References Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than interperson sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-A2/A*0201 restricted epitope, VIYQYMDDL was mutated to cIYQYMDDL in the daughter D2 isolate.

HXB2 Location RT (179–187)
Author Location RT
Epitope `VIYQYMMDL`
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A2)
Keywords subtype comparisons, HIV exposed persistently seronegative (HEPS)
References Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A and D consensus sequences are both VIYQYMMDL.

HXB2 Location RT (179–187)
Author Location Pol (346–354)
Epitope `VIYQYMDDL`
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost
Species (MHC) human (A2)
References Woodberry *et al.* 1999

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2.
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D^d – this transgene is the only MHC molecule expressed in the mice.
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost.
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFDSRL)
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested.
- VIYQYMDDL was recognized by 3 of the HLA-A2 patients.

HXB2 Location RT (179–187)
Author Location RT (179–187)
Epitope `VIYQYMDDL`
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords escape, immunotherapy
References Schmitt *et al.* 2000

- The mutation M184V confers resistance to lamivudine, and is in the middle of the HLA-A2 epitope VIYQYMDDL.
- 1/28 individuals tested produced HIV-1 RT-specific CTL that recognized the peptide representing the lamivudine escape mutants VIYQYVDDL and VIYQYIDDL, but failed to recognize the wildtype epitope VIYQYMDDL.
- This suggests immunotherapy stimulating anti-VIYQYVDDL responses maybe helpful for reducing lamivudine escape.

HXB2 Location RT (179–187)
Author Location RT (179–187)
Epitope `VIYQYMDDL`
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Haas *et al.* 1998

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)

HXB2 Location RT (179–187)
Author Location Pol (339–347 93TH253 subtype CRF01)
Epitope `VIYQYMDDL`
Epitope name P334-342
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HIV exposed persistently seronegative (HEPS)
References Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.

CTL CD8+

- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was reactive in HIV+ control study subject 144 who carried HLA-A2.

HXB2 Location RT (179–187)
Author Location Pol (339–347 93TH253 subtype CRF01)
Epitope VIYQYMDDL
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords subtype comparisons
References Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- 2/4 tested FSWs recognized the E clade version of this epitope, which is identical to the previously defined B clade version VIYQYMDDL.
- This epitope was conserved in many subtypes, and exact matches were very uncommon.

HXB2 Location RT (179–187)
Author Location RT (179–187)
Epitope VIYQYMDDL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.

HXB2 Location RT (179–187)
Author Location Pol (346–354 LAI)
Epitope VIYQYMDDL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HAART, ART, epitope processing
References Kelleher *et al.* 2001a

- Ritonavir (RTV) inhibits chymotryptic activity in the 20S proteasome *in vitro*, as does Saquinavir (SQV) to a lesser extent; Indinavir (IDV) does not. Thus there is concern protease inhibitors may adversely effect CTL epitope processing, but this paper indicates that processing is not inhibited at therapeutically relevant concentrations of RTV when the proteasome is functioning in an intracellular context.
- RTV did not alter the presentation two RT A2 epitopes processed by distinct pathways: ILKEPVHGV, generated by the constitutive proteasome containing the MB1 beta subunit, and VIYQYMDDL which is dependent on IFNgamma induction of LMP7 which replaces MB1 in the immunoproteasome, and is destroyed by MB1 in the constitutive proteasome.
- RTV did not inhibit the processing and assembly of HLA-B35 or -A2, which are assembled with a rapid and moderate time course, respectively, or of HLA-A3, -B27 and -B39.

HXB2 Location RT (179–187)
Author Location Pol (334–)
Epitope VIYQYMDDL
Epitope name Pol334
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This epitope was one of the previously identified HLA-A2 epitopes studied.
- 1/17 HIV-infected HLA-A2+ people in this study recognized this epitope.

HXB2 Location RT (179–187)
Author Location Pol (334–342)
Epitope VIYQYMDDL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A02, B35, Bw62
Assay type proliferation, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, memory cells, immune dysfunction
References Gamberg *et al.* 2004a

- HAART restores HIV specific immunity after advanced infection by increase of CD4+ and CD8+ T cell numbers after supression of viral replication. However, HIV specific CTLs emerged only with detectable viral replication breakthroughs and were short-lived while CD4+ T-cell responses remained compromised, suggesting failure of generating stable CD8+ memory T-cells in the absence of HIV-specific T-helper responses.

HXB2 Location RT (179–187)
Author Location RT (179–187)
Epitope VIYQYMDDL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Canada

Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords HAART, ART, immunotherapy, variant cross-recognition or cross-neutralization
References Mason *et al.* 2004

- Accumulation of specific antiretroviral drug-resistance mutations in Pol gene was shown to sustain and even enhance the antigenicity and immunogenicity of HIV-1 CTL epitopes in this region. Several different patterns of cross-reactivity and selective recognition of wild-type and variant epitopes were found.
- VIcQYMDDL, VIYQYvDDL and VIcQYvDDL variants are detected due to appearence of Y181C and M184V resistance mutations. The double mutant was the only form recognized in one A02 treated individual, the epitope was not recognized in another.

HXB2 Location RT (179–187)
Author Location RT Pol (334–342)
Epitope `VIYQYNDDL`
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 5/19 patients recognized this epitope.

HXB2 Location RT (179–187)
Author Location Pol
Epitope `VIYQMDDL`
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A2)
Donor MHC A*02, A*30, B*15, B*4402
Assay type Tetramer binding, T-cell Elispot
Keywords HIV exposed persistently seronegative (HEPS)
References Missale *et al.* 2004

- HIV-specific T-cell response was tested in patients exposed to blood from a patient with highly replicating HIV; these patients were nosocomially infected with HBV, but uninfected with HIV. HIV-specific T-cell responses were directed to structural and non-structural HIV proteins in 2 patients, suggesting that the virus replicated in these patients sufficiently to prime a cell-mediated immune response that protected them from HIV infection.
- This patient responded to 4/8 HIV epitopes tested in an IFNgamma EliSpot assay or tetramer assay. Responses were detected 8 and 28 weeks after exposure. No response to this epitope was detected by IFNgamma EliSpot, but a response was detected by tetramer staining.

HXB2 Location RT (179–187)
Author Location RT (179–187)
Epitope `VIYQYMDDL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords acute/early infection, optimal epitope
References Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized in chronic infection.

HXB2 Location RT (179–187)
Author Location RT (179–187 HXB2)
Epitope `VIYQYMDDL`
Epitope name 51F
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* multiple epitope immunogen *HIV component:* p17/p24 Gag, Pol *Adjuvant:* IL-12
Species (MHC) transgenic mouse (A2)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-specific epitope characteristics, vaccine antigen design
References Bolesta *et al.* 2005

- Immunization of transgenic mice with a codon-optimized hGagp17p24-Polp51 DNA plasmid, consisting of clusters of highly conserved CTL epitopes presented by multiple MHC class I alleles, induced 2- to 5-fold higher CD8+ T-cell responses than the corresponding full-length proteins. The modified proteins had the ribosomal frameshift deleted, as well as the potentially immunosuppressive p15, and protease and integrase. This correlated with higher protection against challenge with Gag and Pol expressing recombinant vaccinia virus. Mice immunized with the hGagp17p24-Polp51 also showed an elevated level of type 1 cytokine production as well as an increased titer of p24- and RT-specific IgG2 antibody responses.
- This was 1 of 4 A2 gag/pol epitopes tested. Transgenic mice immunized with the deleted construct induced more potent EliSpot reactions to this epitope than those immunized with full length Gag/Pol.

HXB2 Location RT (179–187)
Author Location RT (346–354)
Epitope `VIYQYMDDL`
Epitope name VL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Germany
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords HAART, ART, optimal epitope
References Schmitt-Haendle *et al.* 2005

CTL CD8+

- CTL responses to 3 HLA-A2-restricted epitopes were investigated in 51 HIV-1 infected HLA-A2+ individuals. The most prevalent response was seen for IV9, followed by SL9. The VL9 epitope was not recognized.

HXB2 Location RT (179–187)
Author Location
Epitope VIYQYMDDL
Epitope name Pol 334
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Control epitope Pol 334, VIYQYMDDL, was found in all 11 patients but only 1 had a CTL immune response to it.

HXB2 Location RT (179–187)
Author Location RT
Epitope VIYQYMDDL
Epitope name VL9(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously desctibedHLA-A2-restricted epitope VIYQYMDDL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide RKQNPDI-VIYQYMDDLYV.
- 4 of the 55 HLA-A2 carriers responded to VIYQYMDDL-containing peptide with average magnitude of CTL response of 252 SFC/million PBMC (author communication and Fig.1).

HXB2 Location RT (179–187)
Author Location Pol (433–)
Epitope VIYQYMDDL
Epitope name Pol334
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Pol control epitope VIYQYMDDL, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients.

HXB2 Location RT (179–187)
Author Location RT
Epitope VIYQYMDDL
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Garrison *et al.* 2007

- The study examined the influence of HIV-1 infection on human endogenous retroviruses (HERVs) activity and explored T cells cross-reactivity in regions of HIV-1/HERV similarity.
- T cell responses to HERV peptides were identified in HIV-1 positive individuals. There was an inverse correlation between anti-HERV T cell responses and HIV-1 viral load.
- Responses to HIV-1 VIYQYMDDL and HERV ILVHYIDDI peptides were compared. This HERV peptide is unique for this study as it shares only 3 amino acids with its closest corresponsing peptide in HIV-1 (VIYQYMDDL). Analysis also included intermediate sequence variant peptides. One individual responded to HERV peptide but not to HIV-1 or intermediate peptides. Two individuals responded to HIV-1 and intermediate peptides but not to HERV peptide.

HXB2 Location RT (179–187)
Author Location Pol (subtype B)
Epitope VIYQYMMDL
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A*0202, A2)
Keywords subtype comparisons
References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.

- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among A, B and D clade viruses.

HXB2 Location RT (180–189)
Author Location RT (LAI)
Epitope IYQYMDDLYV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Menendez-Arias *et al.* 1998; van der Burg *et al.* 1997

- Recognized by CTL from a progressor, spans important RT functional domain.
- A previous study determined that this was an epitope recognized by a long-term survivor.

HXB2 Location RT (181–189)
Author Location RT (181–189)
Epitope YQYMDDLYV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- Two patients developed responses to epitope YQYMDDLYV during primary infection and in early chronic infection.

HXB2 Location RT (181–189)
Author Location RT (181–189 LAI)
Epitope YQYMDDLYV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords binding affinity, computational epitope prediction
References Samri *et al.* 2000

- This epitope contains the mutation M184V, a frequent mutation induced by nucleoside reverse transcriptase inhibitors.
- High levels of recognition by ELISPOT were observed for zidovudine induced mutation YQYVDDLYV and for the wildtype peptide YQYMDDLYV in patient 250#0 (HLA-A*0201), but neither were recognized by patient 201#5 (also HLA-A*0201)
- Both the wild-type and the mutated peptide were computer predicted to have a high binding affinity for A2 (http//bimas.dcrt.nih.gov/molbio/hla_bind)

HXB2 Location RT (181–189)
Author Location RT (181–189)
Epitope YQYMDDLYV
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope YQYMDDLYV was predicted to be restricted by HLA A*0201.

HXB2 Location RT (192–201)
Author Location RT (192–201)
Epitope DLEIGQHRTK
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Haas *et al.* 1998

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules.

HXB2 Location RT (192–201)
Author Location Pol (192–201)
Epitope DLEIGQHRTK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands

CTL CD8+

Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 7 epitopes from this individual that varied over time, although the internal mutations did not become fixed. The dleMgqhrtk variant arose at late time points.

HXB2 Location RT (192–216)
Author Location RT (359–383 HXB2)
Epitope DLEIGQHRTKIEELRQHLLRWGLTT
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B60)
References Menendez-Arias *et al.* 1998; Walker *et al.* 1989

- One of five epitopes defined for RT-specific CTL clones in this study.

HXB2 Location RT (192–216)
Author Location RT (191–215)
Epitope DLEIGQHRTKIEELRQHLLRWGFTT
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, escape
References Haas *et al.* 1997; Menendez-Arias *et al.* 1998

- Polyclonal CTL recognition switched from RT 191-215 to RT 514-524 when AZT therapy selected for the resistance mutation, and presumably the escape variant, RT T215Y.

HXB2 Location RT (198–212)
Author Location RT (SF2)
Epitope HRTKIEELRQHLLRW
Immunogen HIV-1 infection
Species (MHC) human
References Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined.

HXB2 Location RT (201–209)
Author Location RT (201–209)
Epitope KIEELRQHL
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Haas *et al.* 1998

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules.

HXB2 Location RT (201–210)
Author Location Pol
Epitope KIEELRQHLL
Immunogen
Species (MHC) human (B58)
References De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conservered regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFNγ production in an ELISPOT assay.
- KIEELRQHLL was newly identified as a HLA-B58 epitope in this study, it had been previously shown to be presented by HLA-A2 and Bw60.
- KIEELRQHLL did not bind detectably to B7.

HXB2 Location RT (201–219)
Author Location RT
Epitope KIEELRQHLLRWGFTTPDK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This overlapping peptide, KIEELRQHLLRWGFTTPDK, was differentially targeted across ethnic groups and had an overall frequency of recognition of 13.3% - 5.1% AA, 23.1% C, 25%

H, 0% WI (P value = 0.0018). HLA-B44 was the most commonly present HLA allele among individuals with responses to this peptide.

HXB2 Location RT (202–210)
Author Location RT (202–210 LAI)
Epitope IEELRQHLL
Subtype B
Immunogen
Species (MHC) human (B*4001)
Keywords optimal epitope
References Altfeld *et al.* 2000; Llano *et al.* 2009

- C. Brander notes this is a B*4001 epitope.

HXB2 Location RT (202–210)
Author Location Pol (357–365)
Epitope IEELRQHLL
Epitope name IL9
Immunogen HIV-1 infection
Species (MHC) human (B*4001)
Donor MHC A*0201, A*2402, B*4001, B*5001, Cw03, Cw04
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords immunodominance, escape, variant cross-recognition or cross-neutralization
References Draenert *et al.* 2006

- HIV-specific cellular and humoral immune responses were examined in monozygotic male twins infected simultaneously with the same virus. 15 of 17 targeted epitopes were identical in the twins, including two immunodominant responses. 3 of 4 declining responses in the twins showed mutations at the same residue. Evolving antibody responses cross-neutralized the other twin's virus. The results were compared with a third brother, infected by the twins' virus 13 months after their seroconversion. The data show similarity in disease course in persons of identical genetic background infected with the same strain of HIV-1.
- This epitope, IEELRQHLL (IL9) restricted by HLA-B*4001, was one of two immunodominant responses. Variants that arose were vEELReHLL and IEELReHLL.

HXB2 Location RT (202–210)
Author Location RT
Epitope IEELRQHLL
Epitope name B40-IL9(RT)
Immunogen HIV-1 infection
Species (MHC) human (B40)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (202–210)
Author Location Pol
Epitope IEELRQHLL
Epitope name IL-9
Immunogen HIV-1 infection
Species (MHC) human (B40)
Keywords escape, TCR usage, immune evasion
References Yu *et al.* 2007b

- The dependence of TCR clonotype recruitment on genetic background was determined by studying monozygotic twins infected with the same HIV-1 strain. After an early, initial correlation in the magnitude, specificity and immunodominance of CTL response [Draenert et al. J. Exp. Med. 203:529-539(2006)], subsequent disease was mixed with respect to CTL epitopes' mutational escape. TCR alpha and beta chain repertoires were analyzed and it was found that their clonotypes in HIV-specific CTLs were broadly heterogeneous for both concordant and discordant epitope sequence evolution between the twins. Therefore initial TCR recruitment appears to be an entirely random process independent of genetic background of the infected individual.
- This epitope, IL9, showed concordant epitope evolution between the twins, but both alpha and beta TCR chains recruited were entirely different between them.

HXB2 Location RT (202–210)
Author Location
Epitope IEELRQHLL
Immunogen HIV-1 infection
Species (MHC) human (B40)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B40), an additional HLA (B37) was statistically predicted to be associated with this epitope.

HXB2 Location RT (202–210)
Author Location RT
Epitope IEELRQHLL
Epitope name IL9(RT)
Subtype B

Immunogen HIV-1 infection
Species (MHC) human (B40)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B40-restricted epitope IEELRQHLL elicited an immune response in Chinese HIV-1 positive subjects as part of peptides LEIGQHRTKIEELRQHLL and KIEELRQHLLRWGFTTPDK.
- 5 of the 20 HLA-B40 carriers responded to IEELRQHLL-containing peptide #193 with average magnitude of CTL response of 716 SFC/million PBMC (author communication and Fig.1).

HXB2 Location RT (202–210)
Author Location RT (SF2)
Epitope IEELRQHLL
Immunogen HIV-1 infection
Species (MHC) human (B60)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B60+ individuals that had a CTL response to this epitope broken down by group: 0/2 group 1, 1/1 group 2, and 0/0 group 3.

HXB2 Location RT (202–210)
Author Location RT (SF2)
Epitope IEELRQHLL
Immunogen HIV-1 infection
Species (MHC) human (B60)
References Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes.
- B60 is present in 10-20% of the Caucasoid and very common in Asian populations.

HXB2 Location RT (202–210)
Author Location RT
Epitope IEELRQHLL
Epitope name IL9
Immunogen HIV-1 infection
Species (MHC) human (B60)
Donor MHC A2, A24, B38, B60, Cw12, Cw2
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, supervised treatment interruptions (STI), early treatment
References Montefiori *et al.* 2003

- HIV-1 + patient AC10 underwent early HAART treatment, which was discontinued 1.5 years later. At this timepoint potent NAb responses against autologous virus were detected. Treatment interruption initially induced weak CD8+ responses directed against 5 epitopes. By days 873d and 923d the CTL response had broadened to target 22 epitopes; of these six were fully characterized. Eventually the virus escaped the NAb response, but escape was not accompanied by a rise in viral load, and the authors suggest the virus was contained by the CTL response.

HXB2 Location RT (202–210)
Author Location RT (202–210)
Epitope IEELRQHLL
Immunogen HIV-1 infection
Species (MHC) human (B60, B61)
Keywords immunodominance
References Day *et al.* 2001

- No immunodominant responses were detected to five B61-restricted epitopes tested.
- All five B60-restricted epitopes were reactive in another subject, and the B60-restricted responses together contributed over one-third of the total CTL response.

HXB2 Location RT (203–211)
Author Location RT
Epitope EELRQHLLR
Immunogen HIV-1 infection
Species (MHC) human (B44)
Donor MHC A*3101, A68, B*4403, B51
Keywords HAART, ART, supervised treatment interruptions (STI)
References Arnedo-Valero *et al.* 2004

- T cell immune responses following STI were monitored in two chronically HIV-1 infected partners (A and B) who had contracted HIV-1 during 1992. Both were heterozygous for the CCR5 delta32, and had different HLAs and treatment histories. STI induced strong transitory CD4+ and CD8+ T cell responses in both patients. Patient A displayed broad CD8+ T cell responses directed against Env, Pol, Gag, and Nef HIV-1 antigens. CTL responses in patient B were mainly directed against two epitopes: Gag(p24)NANPDSKTI and Pol(RT)EELRQHLLRW.
- Despite the host differences, both patients had similar dynamics of vial evolution and CD4+ T-cells, suggesting that good immune reponses to STI may be more related to the virus than host characteristics in these cases.

HXB2 Location RT (203–212)
Author Location RT
Epitope EELREHLLKW

Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4403)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- EELREHLLKW is a previously described HLA-B*4403-restricted epitope (part of Pol(RT) reacting peptide QHRAKIEELReHLLKWGFTTP) that contains a B*4403-associated reversion at residue E (EELReHLLKW).

HXB2 Location RT (203–212)
Author Location RT (LAI)
Epitope EELRQHLLRW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B44)
References Menendez-Arias *et al.* 1998; van der Burg *et al.* 1997

- The only epitope recognized by CTL from a long-term survivor in two samples taken six years apart.
- Recognized by CTL from a progressor, EILKEPVGHGV and TWETWWTEYW were also recognized.

HXB2 Location RT (203–212)
Author Location RT (203–212)
Epitope EELRQHLLRW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B44)
Country Canada
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords HAART, ART, immunotherapy, variant cross-recognition or cross-neutralization
References Mason *et al.* 2004

- Accumulation of specific antiretroviral drug-resistance mutations in Pol gene was shown to sustain and even enhance the antigenicity and immunogenicity of HIV-1 CTL epitopes in this region. Several different patterns of cross-reactivity and selective recognition of wild-type and variant epitopes were found.
- EELRQHLwRW variant is detected due to appearence of L210W resistance mutation. The in this case, the wild-type epitope was preferentially recognized relative to the L210W variant.

HXB2 Location RT (203–212)
Author Location RT Pol (358–367)
Epitope EELRQHLLRW
Immunogen HIV-1 infection
Species (MHC) human (B44)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 9/11 patients recognized this epitope; of three B*44 eptiopes tested, this was the only one that was recognized by more than 2/11 patients.

HXB2 Location RT (203–212)
Author Location RT
Epitope EELRQHLLRW
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B44)
Donor MHC A01, A03, B39, B44, Cw4, Cw6
Assay type T-cell Elispot
Keywords HIV exposed persistently seronegative (HEPS)
References Missale *et al.* 2004

- HIV-specific T-cell response was tested in patients exposed to blood from a patient with highly replicating HIV; these patients were nosocomially infected with HBV, but uninfected with HIV. HIV-specific T-cell responses were directed to structural and non-structural HIV proteins in 2 patients, suggesting that the virus replicated in these patients sufficiently to prime a cell-mediated immune response that protected them from HIV infection.
- This patient responded to 3/11 HIV epitopes tested in an IFNgamma EliSpot assay. Responses were detected 16 and 20 weeks after exposure, but were lost by week 80.

HXB2 Location RT (203–212)
Author Location p24
Epitope EELRQHLLRW
Immunogen HIV-1 infection
Species (MHC) human (B44)
Donor MHC A01, A32, B*1410, B15; A*3101, A68, B*4403, B51
Country Spain
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, supervised treatment interruptions (STI)
References Arnedo-Valero *et al.* 2004

- T cell immune responses following STI were monitored in two chronically HIV-1 infected partners (A and B) who had contracted HIV-1 during 1992. STI induced strong transitory CD4+ and CD8+ T cell responses in both patients. The viruses remained very closely related over 10 years, despite the two individuals having different HLA types; the authors suggest the maintained similarity does not support a strong role for HLA driven HIV diversity as has been claimed in Moore et al. (Science 2002).

CTL CD8+

- During the second treatment stop, patient A developed a strong proliferative response to p24, and multiple strong CD8+ T cell repsonses to Env, Pol, Gag and Nef. This patient was able to control viral load for two years follow up without therapy. Patient B developed a very weak CD4+ T cell response against p24 during breaks in therapy, and had CD8+ responses to two epitopes. Patient A: A01, A32, B*1410, B15; Patient B: A*3101, A68, B*4403, B51.

HXB2 Location RT (203–212)
Author Location RT (203–212)
Epitope EELRQHLLRW
Immunogen HIV-1 infection
Species (MHC) human (B44)
Country Canada
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords mimics
References Mason *et al.* 2005

- CTL responses against the IP-30 signal peptide associated with autoimmunity were shown to be elicited by stimulation of PBMCs from HIV-1 infected individuals with HIV protease peptide 76-84. In vitro stimulation with HIV PR 76-84 or the IP-30 signal peptide was shown to activate a comparable population of cross-reactive effector cells. None of the peptides activated CTL in non-HIV-infected individuals. IP-30 signal peptide was shown to have lower avidity T-cell interactions than the HIV peptide.
- As a control, responses to A2-restricted HIV epitopes ALVEICTEM, EELRQHLLRW, and LSPRTLNAW were shown not to give IP-30 responses.

HXB2 Location RT (204–212)
Author Location RT (204–212 HXB2)
Epitope ELRQHLLRW
Epitope name EW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2501)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Position 8 in the epitope had potentially experienced positive selection. ELRQHLLkW escape variant was found.

HXB2 Location RT (206–214)
Author Location RT Pol
Epitope RAHLLSWGF
Epitope name RT1
Subtype A, B, C
Immunogen vaccine
Vector/Type: DNA with CMV promotor, modified vaccinia Ankara (MVA), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade, B clade, C clade Du422, Other *HIV component:* Gag, Nef, RT
Species (MHC) mouse (H-2K^d)
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords subtype comparisons, vaccine-induced epitopes, variant cross-recognition or cross-neutralization, antagonism
References Larke *et al.* 2007

- Cross-clade vaccine recognition was studied using either single-, multi or several anatomically separated single-clade vaccines. Limited cross-clade response was seen with single-clade administrations. Multi-clade vaccines gave immune interference (antagonism and original antigenic sin), reducing CTL response. Simultaneously administered but anatomically separated vaccines from clades A, B, C decreased antagonism and increased immune responses.
- After immunization with Clade A vaccine containing RT1, RAHLLSWGF, this index epitope was not recognized. Clade B vaccine containing RQHLLRWGL generated T cells that recognized its index epitope as well as variants RaHLLsWGf (Clade A index), RkHLLkWGf (Clade C index), RaHLLRWGf, RQHLLRWGf, ReHLLkWGf, ReHLLRWGf, RgHLLkWGf, RkHLLsWGf at lower levels. C Clade vaccine with index epitope RKHLLKWGF resulted in T cells that recognized that epitope, and Clade B index epitope RqHLLrWGl, and epitope RKHLLsWGF at 53%.

HXB2 Location RT (209–220)
Author Location RT (209–220)
Epitope LLRWGLTTPDKK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

HXB2 Location RT (209–220)
Author Location RT (209–220 MN)
Epitope LLRWGLTTPDKK
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* B clade MN *HIV component:* gp120, Protease, RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) humanized mouse (A*0201)
Assay type CD8 T-cell Elispot - IFNγ
Keywords epitope processing, vaccine-specific epitope characteristics, immunodominance, immunotherapy
References Isaguliants *et al.* 2004

- Immunization of HLA-A*0201-transgenic mice with synthetic genes encoding clusters of human A*0201 CTL epitopes located at the sites of drug resistance mutations, induced RT-specific cellular responses indicating the immunogenicity of these constructs. This vaccine strategy may be a first step towards a therapeutic vaccine against drug-resistant strains.
- This was one of five HLA-A*0201 epitopes from the RT or protease proteins that was included in the polyepitope vaccine. When the transgenic HLA A*0202 mice were vaccinated with the polyepitope construct or with a mixture of RT peptides, a sustained low level CD8+ T-cell gamma IFN response was observed, in contrast to when an intact RT gene was used for vaccination.

HXB2 Location RT (209–220)
Author Location RT (209–220)
Epitope LLRWGLTTPDKK
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Haas *et al.* 1998

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules.

HXB2 Location RT (210–220)
Author Location Pol (209–220)
Epitope LRWGFCTPDKK
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A2, B44, B57; A2, A29, B57, B62
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords HAART, ART, cross-presentation by different HLA, characterizing CD8+ T cells
References Mason & Grant 2005

- The common form of this epitope, LRWGFTTPDKK is weakly recognized in the context of HLA-A2, and it encompasses several common antiretroviral escape mutations. Responses were tested in 2 siblings.
- T215Y then Y215C antiretroviral therapy-associated mutations within the epitope induced a strong reaction, but changed the restriction of the epitope to HLA-B57. This mutation is thus suggested to potentially enhance CD8 T-cell recognition of HIV.

HXB2 Location RT (214–223)
Author Location Pol
Epitope FTTPDKKHQK
Epitope name 1267
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A11, A68)
Donor MHC A11, A68, B42, B45, Cw16, Cw17
Country United States
Assay type T-cell Elispot
Keywords binding affinity, supertype, computational epitope prediction, cross-presentation by different HLA
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for FTTPDKKHQK:36% Supertype epitope binding to A68 and A11.

HXB2 Location RT (215–224)
Author Location Pol
Epitope TTPDKKHQKE
Epitope name 1281
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A68, B42, B45, Cw16, Cw17; A01, A68, B15, B40, Cw03
Country United States
Assay type T-cell Elispot
Keywords binding affinity, supertype, computational epitope prediction, cross-presentation by different HLA
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for TTPDKKHQKE:60% Supertype epitope binding to A68.

HXB2 Location RT (218–235)
Author Location (C consensus)
Epitope DKKHQKEPPFLWMGYELH
Subtype C
Immunogen HIV-1 infection

CTL CD8+

Species (MHC) human (B*1510)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location RT (240–257)
Author Location (C consensus)
Epitope TVQPIQLPEKDSWTVNDI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location RT (240–257)
Author Location RT (240–257 HXB2)
Epitope TVQPIVLPEKDSWTVNDI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- Responses to this peptide were detected in 16% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location RT (240–257)
Author Location
Epitope TVQPIQLPEKDSWTVNDI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- TVQPIQLPEKDSWTVNDI is of unknown restriction. Response was detected in a rapid progressor 12 weeks post-infection.

HXB2 Location RT (243–252)
Author Location RT (LAI)
Epitope PIVLPEKDSW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
References Menendez-Arias *et al.* 1998; van der Burg *et al.* 1997

- Recognized by CTL from a progressor and a long-term survivor, KITTESIVIW was also recognized.

HXB2 Location RT (243–252)
Author Location RT (LAI)
Epitope PIVLPEKDSW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords binding affinity, escape
References Menendez-Arias *et al.* 1998; van der Burg *et al.* 1997

- Recognized by CTL from long-term survivor, whose CTL response persisted for more than 10 years – the substitution V3M reduced affinity but was well recognized, on the other hand V3T and D8G did not reduce affinity, but abrogated CTL response.

HXB2 Location RT (243–252)
Author Location RT (410–419)
Epitope PIVLPEKDSW
Epitope name PIV
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords HAART, ART, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- None of the 8 study subjects recognized this epitope but none were HLA B57+

HXB2 Location RT (243–252)
Author Location RT
Epitope PIVLPEKDSW
Epitope name PIV
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords HAART, ART, supervised treatment interruptions (STI)
References Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFNgamma Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

HXB2 Location RT (243–252)
Author Location RT Pol (398–407)
Epitope PIVLPEKDSW
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 6/7 patients recognized this epitope.

HXB2 Location RT (244–252)
Author Location
Epitope IVLPEKDSW
Epitope name IW9
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B*57-restricted optimal epitope IVLPEKDSW was tested for immune response.
- No loss of recognition was seen for variants I147L (lVLPEKDSW) and I147M (mVLPEKDSW) in several subjects, none of whom had the I147M mutation.
- I146P variant, iIVLPEKDSW, blocks presentation of epitope IW9.

HXB2 Location RT (244–252)
Author Location RT (244–252)
Epitope IVLPEKDSW
Epitope name rtIW9
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country United Kingdom, Kenya
Assay type CD8 T-cell Elispot - IFNγ
Keywords TCR usage, structure, characterizing CD8+ T cells
References Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B*57-peptide complexes were studied.
- In addition, immunodominancy of the previously mapped B*57 epitopes during chronic infection was assessed. KGFNPEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

HXB2 Location RT (244–252)
Author Location RT (244–252)
Epitope IVLPEKDSW
Epitope name IW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country Australia, Canada, Germany, United States
Keywords escape, variant cross-recognition or cross-neutralization, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.

CTL CD8+

- Escape (and reversion) rates for B*57-restricted epitopes were highest for Gag-TW10 (TSTLQEQIGW) > RT-IW9 (IVLPEKDSW) > Nef-YY9 (YTPGPGIRY) > Nef-HW9 (HTQGYFPDW) > Gag-IW9 (ISPRTLNAW) > Gag-KF11 (KAFSPEVIPMF) .
- HLAs-B*57-associated substitutions within optimally defined epitope IVLPEKDSW are at positions V2 and E4, IvLPeKDSW. IW9 was the 7th most rapidly escaping epitope.

HXB2 Location RT (244–252)
Author Location RT (399–407)
Epitope IVLPEKDSW
Immunogen
Species (MHC) human (B*5701)
Keywords optimal epitope
References Llano *et al.* 2009

- Subtype of B57 not determined.
- C. Brander notes this is a B*5701 epitope.

HXB2 Location RT (244–252)
Author Location RT (244–252 LAI)
Epitope IVLPEKDSW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701, B*5801)
Keywords binding affinity, rate of progression, escape
References Klein *et al.* 1998

- This peptide was defined as the optimal epitope.
- B57 has been associated with long-term non-progression in the Amsterdam cohort.
- The most pronounced CTL responses in HLA B*5701 LTS were to RT and Gag.
- B57 restricted CTL responses are targeted at multiple proteins, but one LTS had a response that was dominated by reactivity to the epitope – two variants were found in this LTS: ITLPEKESW, which bound to B*5701 with similar affinity as the index peptide but was an escape mutant that was not recognized by CTL, and IMLPEKDSW, which bound to B*5701 with reduced affinity but could still be recognized.
- In an additional HIV+ LTS, only the variant IELPEKDSW was found, and this epitope was recognized by CTL but had less affinity for B*5701 than the index peptide.
- This epitope was recognized in the context of both HLA-B*5701 and B*5801.

HXB2 Location RT (244–252)
Author Location Pol (244–252)
Epitope IVLPEKDSW
Immunogen HIV-1 infection
Species (MHC) human (B*5801)
References Appay *et al.* 2000

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α

HXB2 Location RT (244–252)
Author Location RT (399–407)
Epitope IVLPEKDSW
Immunogen
Species (MHC) human (B57)
References van der Burg *et al.* 1997

HXB2 Location RT (244–252)
Author Location RT (244–252)
Epitope IVLPEKDSW
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords early-expressed proteins, kinetics
References Guillon *et al.* 2002b

- An early-expressed Nef protein was modified to contain Env and Pol epitopes to enable the study the effect of expression kinetics on CTL mediated suppression of replication. The "EpiNef" construct was inserted into a recombinant vaccinia virus which was used to infect a target cell line; the target cells were lysed by CTL clones specific for the Env and Pol epitopes indicating that they were properly processed.

HXB2 Location RT (244–252)
Author Location RT (244–252 ACH320.2A.2.1)
Epitope IVLPEKDSW
Subtype B
Immunogen HIV-1 infection
Species (MHC) (B57)
Keywords acute/early infection, early-expressed proteins, kinetics
References van Baalen *et al.* 2002

- Tat, Rev and Nef are the first HIV proteins expressed upon acute infection of T-cells (< 6 hours), and RT is not expressed until after 24 hours. The B14-restricted Rev-SAEPVPLQL specific CD8 T-cell clone TCC108, and the B57-restricted RT-IVLPEKDSW specific CD8 T-cell clone TCL1C11 were co-incubated with CD4+ cultures innoculated with HIV-1 at low MOI. Co-incubation with the Rev-specific CTL resulted in two logs less HIV-1 production in ten days of culture. When the RT epitope was cloned into the Nef gene of the infecting strain, another early expressed protein, it proved as effective as the Rev epitope at inhibiting viral production. A mathematical model of CTL-target interactions suggest early proteins are important for vaccine design.

HXB2 Location RT (244–252)
Author Location Pol
Epitope IVLPEKDSW
Epitope name IW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 2, was found in the most polymorphic residue in the epitope. This was shared between clades B and C. The position 2 mutation was significantly more common among persons expressing HLA-B57.

HXB2 Location RT (244–252)
Author Location RT
Epitope `IVLPEKDSW`
Epitope name B57-IW9(RT)
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (244–252)
Author Location
Epitope `IVLPEKDSW`
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location RT (244–252)
Author Location Gag
Epitope `IVLPEKDSW`
Epitope name IW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Australia, Canada, United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, immune evasion, optimal epitope
References Streeck *et al.* 2007a

- To characterize HIV-1 proteome areas that are targeted in early, effective CTL responses, two cohorts were studied. Responses in early infection were against fewer epitopes and of lower magnitude than during chronic infection. While no region of the proteome was favored, Nef was the predominant target based on length of proteins.
- When based on the expression of protective versus nonprotective HLA I alleles, it was found that HLA-B27 and -57 possessing slow progressors to disease directed the majority of their responses to Gag in early infection, as opposed to those with HLA-B*3501 or B*3502, i.e. rapid progressors to AIDS, who had negligible responses to Gag. As compared with HLA-B57-/B27- subjects and HLA-B35 subjects, HLA-B57+/27+ subjects responded most to the p24 component of Gag. By using overlapping peptides within Gag p24, two were picked as being consistently targeted, and both contained previously described epitopes TSTLQEQIGW and KRWIILGLNK.
- IVLPEKDSW, i.e. epitope IW9 of RT protein was targeted in 62% of B57+ non-progressors to disease.

HXB2 Location RT (244–252)
Author Location
Epitope `IVLPEKDSW`
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B57), an additional HLA (B58) was statistically predicted to be associated with this epitope.

HXB2 Location RT (244–252)
Author Location RT
Epitope `IVLPEKDSW`
Epitope name IW9
Subtype B

Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- IW9(RT), IVLPEKDSW, is a known HLA-B57-restricted epitope used as a positive control for eliciting CTL IFN-gamma response.

HXB2 Location RT (244–252)
Author Location
Epitope IVLPEKDSW
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords responses in children, mother-to-infant transmission, escape
References Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.

HXB2 Location RT (245–252)
Author Location Pol
Epitope IVPEKDSW
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Kostense *et al.* 2001

- HLA tetramers to six epitopes were used to study HLA-A2, B8 and B57 CTL in 54 patients – HIV-specific tetramer positive cells were inversely correlated with viral load in patients with high CD4, but in patients with CD4 T-cells below 400 high tetramer frequencies were found despite high viral load.
- Most patients have high levels of HIV-specific T-cell expansions, but many of these cells aren't functional.
- In 15 of the patients, the proportion of IFN gamma producing tetramer cells correlated with AIDS-free survival.

HXB2 Location RT (246–254)
Author Location Pol
Epitope LPEKDSWTV
Epitope name Pol1145
Subtype C
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Previously published epitope LPEKDSWTV elicits IFN-gamma ELISpot responses in 1/7 subjects; and bound HLA-B7 with low affinity in cell-based assays.

HXB2 Location RT (248–264)
Author Location (C consensus)
Epitope EKDSWTVNDIQKLVGKL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0205)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location RT (259–267)
Author Location Pol (448–)
Epitope KLVGKLNWA
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (A*0201)
Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008

- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location RT (259–267)
Author Location Pol
Epitope KLVGKLNWA

CTL CD8+

Epitope name Pol448
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- KLVGKLNWA is a Pol epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location RT (259–267)
Author Location Pol
Epitope `KLVGKLNWA`
Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind four of the five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802).
- Tetramer staining with A2, beta2microglobulin, and either SLYNTVATL, KLVGKLNWA, or LTFGWCFKL revealed that tetramers detected more HIV-specific sells in LTNP than in progressors, activated effector cells were the minority population, and ELISPOT correlated better with the effector cell subpopulation than the total tetramer stained population.

HXB2 Location RT (259–267)
Author Location Pol
Epitope `KLVGKLNWA`
Epitope name Pol448
Subtype A, B, C, D
Immunogen HIV-1 infection
Species (MHC) human, mouse (A2 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope KLVGKLNWA of the HLA-A2 supertype bound most strongly to HLA-A*0203, -A*0202, -A*0206 and -A*0201, but also to -A*6802. It was conserved 100% in subtype A, 95% in B, 100% in C and 75% in subtype D. 0/22 HLA-A2 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Pol448.

HXB2 Location RT (260–271)
Author Location RT (415–426 IIIB)
Epitope `LVGKLNWASQIY`
Immunogen HIV-1 infection
Species (MHC) human (B*1501)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*1501 epitope.

HXB2 Location RT (260–271)
Author Location Pol (260–271)
Epitope `LVGKLNWASQIY`
Immunogen HIV-1 infection
Species (MHC) human (B15)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 7 epitopes from this individual that varied over time, although the internal mutations did not become fixed. lvgkXnwasqiy variants arose at late time points

HXB2 Location RT (260–271)
Author Location RT
Epitope `LVGKLNWASQIY`
Epitope name B15-LY12(RT)
Immunogen HIV-1 infection
Species (MHC) human (B15)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

CTL CD8+

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (260–271)
Author Location RT
Epitope `LVGKLNWASQIY`
Epitope name LY12(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B15)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B15-restricted epitope LVGKLNWASQIY elicited an immune response in Chinese HIV-1 positive subjects as part of peptide NDIQKLVGKLNWASQIYA.
- 4 of the 21 HLA-B15 carriers responded to LVGKLNWASQIY-containing peptide with average magnitude of CTL response of 350 SFC/million PBMC (author communication and Fig.1).

HXB2 Location RT (260–271)
Author Location RT (415–426 IIIB)
Epitope `LVGKLNWASQIY`
Immunogen HIV-1 infection
Species (MHC) human (B62)
References Brander & Walker 1996; Menendez-Arias *et al.* 1998

- P. Johnson, pers. comm.

HXB2 Location RT (260–271)
Author Location RT (260–271)
Epitope `LVGKLNWASQIY`
Immunogen HIV-1 infection
Species (MHC) human (B62)
Keywords immunodominance
References Day *et al.* 2001

- No immunodominant responses were detected to four B62-restricted epitopes tested.

HXB2 Location RT (260–271)
Author Location Pol (415–426)
Epitope `LVGKLNWASQIY`
Epitope name LY12
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62)
Donor MHC A*01, A*11, B*08, B*15, Cw*04, Cw*07
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords escape, characterizing CD8+ T cells, optimal epitope
References Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- The autologous form of the epitope, LVGKLNWASQIY, matched the B consensus throughout the 5-year period of study, with 1 rare variant at the first time point: LVGKLNWASQIh.

HXB2 Location RT (263–271)
Author Location RT (263–271 LAI)
Epitope `KLNWASQIY`
Subtype B
Immunogen
Species (MHC) human (A*3002)
Keywords optimal epitope
References Goulder *et al.* 2001a; Llano *et al.* 2009

- C. Brander notes this is an A*3002 epitope.

HXB2 Location RT (263–271)
Author Location RT
Epitope `KLNWASQIY`
Epitope name KY9 (RT-35)
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
References Goulder *et al.* 2001a

- HLA-A*3002 is very common in African populations, 50% of Zimbabweans express HLA-A30, 44% in African Zulu, so five new HIV epitopes were characterized that are presented by this HLA molecule.
- A rapid method was developed combining ELISPOT with intracellular IFN-γ staining of PBMCs to map optimal epitopes, then HLA presenting molecules were defined – this method was completed within 48 to 72 hours of receipt of blood.
- Two individuals were studied: Subject 199 (HLA A*0201/*3002 B*4402/51 Cw2/5), a Caucasian, and Subject 6007 (HLA A*3002/ B53/*5801 Cw4/7) an African-Caribbean.

- In both HLA-A*3002 individuals the response to RSLYNTVATLY was dominant.
- In subject 199 four additional A*3002 epitopes were identified.
- Three quantitative assays, ELISPOT, precursor frequency and chromium release, confirmed a hierarchy of response: RY11 (p17) > KY9 (gp41) > KY9 (RT-53) > IY9 (gp41)

HXB2 Location RT (263–271)
Author Location (C consensus)
Epitope KLNWASQIY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location RT (263–271)
Author Location (C consensus)
Epitope KLNWASQIY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- KLNWASQIY is an optimal epitope.

HXB2 Location RT (263–271)
Author Location RT
Epitope KLNWASQIY
Epitope name A30-KY11(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A30)
Donor MHC A30, A32, B18, B27
Keywords HAART, ART, supervised treatment interruptions (STI)
References Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (`http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html`) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient D displayed the greatest response to B27-KK10 (p24), and also responded to A30-RY11(p17), A32-PW10(RT), A30-KY11(RT), A32-RW10(gp120), and B18-YY9(Nef).

HXB2 Location RT (263–271)
Author Location RT
Epitope KLNWASQIY
Epitope name A30-KIY9(RT)
Immunogen HIV-1 infection
Species (MHC) human (A30)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (263–271)
Author Location RT
Epitope KLNWASQIY
Epitope name KY9(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A30)

CTL CD8+

Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A30-restricted epitope KLNWASQIY elicited an immune response in Chinese HIV-1 positive subjects as peptide NDIQKLVGKLNWASQIYA but not as peptide KLNWASQIYAGIKVKQL.
- 1 of the 15 HLA-A30 carriers responded to KLNWASQIY-containing peptide #201 with average magnitude of CTL response of 40 SFC/million PBMC. Although the second tested peptide #202 contains the exact sequence of a previously described HLA-A30 optimal epitope, KLNWASQIY, none of the 15 HLA-A30 carriers responded to it (author communication and Fig.1).

HXB2 Location RT (266–280)
Author Location RT (421–435)
Epitope `WASQIYAGIKVKQLC`
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008

- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.
- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.
- CTL immune response to consensus sequence WASQIYAGIKVKQLC was elicited in subject 00015. Consensus epitope of subjects was the same as Clade B consensus.

HXB2 Location RT (266–285)
Author Location Pol (421–440)
Epitope `WASQIYPGIKVRQLCKLLRG`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location RT (268–282)
Author Location RT (SF2)
Epitope `SQIYPGIKVRQLCKL`
Immunogen HIV-1 infection
Species (MHC) human
References Altfeld *et al.* 2001a

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- RT peptides SQIYPGIKVRQLCKL and WKGSPAIFQSSMTKI were recognized.

HXB2 Location RT (269–277)
Author Location RT (269–277)
Epitope `QIYPGIKVR`
Epitope name QR9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*03)
Country Australia, Canada, Germany, United States
Keywords escape, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-A*03-associated substitution within optimally defined epitope QIYPGIKVR is at position R9, QIYPGIKVr. QR9 exceeded its epitope recognition frequency by its escape frequency which ranked 6th overall. This could be due to an overestimation of escape.

HXB2 Location RT (269–277)
Author Location (LAI)
Epitope `QIYPGIKVR`
Subtype B
Immunogen
Species (MHC) human (A*0301)
Keywords optimal epitope
References Altfeld 2000; Llano *et al.* 2009

HXB2 Location RT (269–277)
Author Location RT (269–277)
Epitope QIYPGIKVR
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Assay type Other
Keywords HLA associated polymorphism
References Boutwell & Essex 2007

- Publicly available HIV-1 subtype C sequences from South Africa and Botswana were analyzed, and 94 HLA-associated amino acid polymorphisms were found. Many polymorphisms were associated with multiple HLA allele classes. 12% associations were negative: association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles accounted for 50% of associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes.
- QIYPGIKVR was a previously defined A*0301 presented epitope that encompassed an A*03-associated polymorphism, QIYPGIKVr|Q ,in the last position. This epitope was embedded in a previoulsy determined CTL immunoreactive region.

HXB2 Location RT (269–277)
Author Location Pol (424–432)
Epitope QIYAGIKVK
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Keywords binding affinity, subtype comparisons
References Fukada *et al.* 2002

- binding affinity, inter-clade comparisons.
- Counterparts for eight known clade B HLA A*1101 epitopes were generated for clade E (CRF01). Three epitopes, identical among clade A-E, were cross-reactive and recognized by clade E infected individuals. The clade E and B analogs to three more HLA A*1101 epitopes was recognized in a clade specific manner. Two other HLA A*1101 clade B defined epitopes were found not to have stimulated a response in clade E infected individuals.
- QIYAGIKVK is commonly found in viruses representing subtypes A, B and E. It was strongly recognized by CTL from 1/5 B clade infected Japanese subjects, and 5/7 E clade infected Thai subjects.
- QIYAGIKVK had the highest A*1101 binding affinity, but qiyagikvR and qiyPgikvR (the most common C and D clade variant both bound to A*1101). QIYAGIKVK and qiyagikvR were both cross-presented by a clone from a B clade infection, but qiyPgikvR was not.

HXB2 Location RT (269–277)
Author Location (B consensus)
Epitope QIYAGIKVK
Epitope name QVK9
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A02, A11, B18, B44, Cw12, Cw5
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location RT (269–277)
Author Location Pol (425–433)
Epitope QIYAGIKVK
Epitope name QK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords optimal epitope
References Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For one of the escape variants, a novel CD8 T-cell response equal in magnitude to the wild type, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wild type.
- This epitope did not vary.

HXB2 Location RT (269–277)
Author Location Pol (425–433)
Epitope QIYAGIKVK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location RT (269–277)
Author Location RT

CTL CD8+

Epitope QIYAGIKVK
Epitope name QK9(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A11-restricted epitope QIYAGIKVK elicited an immune response in Chinese HIV-1 positive subjects as part of peptide KLNWASQIYAGIKVKQL.
- 3 of the 28 HLA-A11 carriers responded to QIYAGIKVK-containing peptide with average magnitude of CTL response of 53 SFC/million PBMC (author communication and Fig.1).

HXB2 Location RT (269–277)
Author Location RT (269–277)
Epitope QIYPGIKVR
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant.

HXB2 Location RT (269–277)
Author Location RT (424–432)
Epitope QIYPGIKVR
Epitope name A3-QR9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 1/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 4/7 individuals began to have detectable responses to this epitope after STI.

HXB2 Location RT (269–277)
Author Location RT (269–277)
Epitope QIYAGIKVK
Epitope name A3-QR9 Pol
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), escape, early treatment, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The second infecting strain had the variant qiyagikvR. The initial CTL response to both variants was strong but eventually declined, particularly to the variant in the second strain. .

HXB2 Location RT (269–277)
Author Location RT (269–277)
Epitope QIYPGIKVR
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these eptiopes, but this increased over time.

HXB2 Location RT (269–277)
Author Location Pol
Epitope QIYPGIKVK
Epitope name QK9

Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 9, qiypgikvR, was found not to correspond to the most polymorphic residues in the epitope.

HXB2 Location RT (269–277)
Author Location RT
Epitope `QIYPGIKVR`
Epitope name A3-QR9(RT)
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (269–277)
Author Location RT
Epitope `QIYPGIKVR`
Epitope name QR9(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords non-susceptible form
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- The tested peptide sequence, KLNWASQIYaGIKVkQL, contains a variant, QIYaGIKVk that differs by 2 substitutions from the previously described HLA-A3 epitope QIYPGIKVR. None of the 18 HLA-A3 carriers responded to the variant QIYaGIKVk.

HXB2 Location RT (271–279)
Author Location RT (271–279)
Epitope `YPGIKVRQL`
Epitope name YL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*42)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLAs-B*42-associated substitutions within optimally defined epitope YPGIKVRQL are at positions P2 and Q8, YpGIKVRqL.

HXB2 Location RT (271–279)
Author Location (LAI)
Epitope `YPGIKVRQL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*4201 epitope.

HXB2 Location RT (271–279)
Author Location (C consensus)
Epitope `YPGIKVRQL`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

CTL CD8+

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location RT (271–279)
Author Location (C consensus)
Epitope YPIGKVRQL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the L9 residue of YPIGKVRQL are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location RT (271–279)
Author Location RT (271–279)
Epitope YPGIKVRQL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Assay type Other
Keywords HLA associated polymorphism
References Boutwell & Essex 2007

- Publicly available HIV-1 subtype C sequences from South Africa and Botswana were analyzed, and 94 HLA-associated amino acid polymorphisms were found. Many polymorphisms were associated with multiple HLA allele classes. 12% associations were negative: association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles accounted for 50% of associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes.
- YPGIKVRQL was a previously defined B*4201 presented epitope that encompassed an B*42 associated polymorphism, YpGIKVRQL,in the second position. This epitope was found embedded in a previously determined immunoreactive region.

HXB2 Location RT (271–279)
Author Location
Epitope YPGIKVKQL
Epitope name YL9
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type proliferation, Tetramer binding, Intracellular cytokine staining
References Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

HXB2 Location RT (271–279)
Author Location
Epitope YPGIKVRQL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Donor MHC A*2301, A*2902, B*4101, B*4201, Cw*1701
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- Known epitope YPGIKVRQL is HLA-B*4201-restricted. Response to a peptide containing this epitope was detected in a rapid progressor 12 weeks post-infection.

HXB2 Location RT (271–279)
Author Location RT
Epitope YPGIKVRQL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- YPGIKVRQL is a previously described HLA-B*4201-restricted epitope (part of Pol(RT) reacting peptide GKLNWASQIYpGIKVRQLCKL) that contains a B*4201-associated reversion at residue P (YpGIKVRQL).

HXB2 Location RT (271–279)
Author Location (C consensus)
Epitope YPIGKVRQL

Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4202)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the L9 residue of YPIGKVRQL are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location RT (271–279)
Author Location RT (438–446 IIIB)
Epitope `YPGIKVRQL`
Immunogen HIV-1 infection
Species (MHC) human (B42)
Keywords responses in children, mother-to-infant transmission
References Menendez-Arias *et al.* 1998; Wilson *et al.* 1996

- YAGIKVRQL and YPGIKVKQL are naturally occurring variants that are both reactive.
- YHKIKVRQL is a naturally occurring variant that has not been tested.
- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.

HXB2 Location RT (271–279)
Author Location Pol (438–446 IIIB)
Epitope `YPGIKVRQL`
Immunogen HIV-1 infection
Species (MHC) human (B42)
Keywords mother-to-infant transmission, escape
References Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- An additional variant that gave a positive CTL response: YPGIKVKQL, YAGIKVRQL.
- YHGIKVRQL was an escape mutant.

HXB2 Location RT (271–279)
Author Location
Epitope `YPGIKVRQL`
Epitope name YL9 ?
Immunogen HIV-1 infection
Species (MHC) human (B42)
Country United States, South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords memory cells
References Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

HXB2 Location RT (271–279)
Author Location Pol
Epitope `YPGIKVKQL`
Epitope name Pol1153
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Novel Pol epitope YPGIKVKQL elicits IFN-gamma ELISpot responses in 1/7 subjects; and bound HLA-B7 with low and high affinities in soluble and cell-based assays respectively.

HXB2 Location RT (271–279)
Author Location RT (271–279)
Epitope `YPGIKVRQL`
Epitope name YL9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Other
Keywords supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism
References Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alelles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Statistically significant associations between numbers of HLA-4201 expressing subjects and epitope YPGIKVRQL were found.

CTL CD8+

- A strong association between B*4201 and variation in epitope YL9 was found.

HXB2 Location RT (271–279)
Author Location
Epitope YPGIKVRQL
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost, polyepitope *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human
Donor MHC A*3001, A*3002; B*4201/02, B*4403/26/30
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location RT (271–279)
Author Location RT
Epitope YPGIKVRQL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords HLA associated polymorphism
References Rousseau *et al.* 2008

- 3 phylogenetic correction methods—MLL (maximum likelihood character state analysis followed by likelihood ratio test), MLF (maximum likelihood character state analysis followed by Fisher test), and parsimony character state analysis were used to identify points in the HIV-1 subtype C proteome that conferred susceptibility or resistance to CTLs. Associations of HLA-epitope combinations that were inferred to be susceptible or resistant were organized into immunological sets that would help identify the best residues and genes as candidates for vaccines. While all proteins were interrogated, Gag, Pol, Env and Nef were focused upon. Amino acid changes were evaluated for association with plasma viral load.
- Proteome maps may be seen at `http://www.hiv.lanl.gov/content/immunology/hlatem/study5/index.html` with information showing single or multiple sites involving escape and reversion.
- HLA- B and -C alleles associated more with aa changes than HLA-A, suggesting that the former two are more important in driving viral evolution.
- The ratio of susceptible to resistant residues in HIV proteins was in descending order, Vpr>Gag>Rev>Pol>Nef>Vif>Tat>Env>Vpu, showing that epitopes from the earlier proteins are more conserved owing to viral fitness cost upon mutation.
- This Pol HLA-B*42-restricted epitope, YPGIKVRQL, lies within a set of 6 immunological associations, experiencing conflicting selective pressures.

HXB2 Location RT (293–301)
Author Location RT (448–456 SF2)
Epitope IPLTEEAEL
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
References Menendez-Arias *et al.* 1998; Tomiyama *et al.* 1997

- A CTL clone responsive to this epitope was obtained.
- Only 1/7 B35-positive individuals had a CTL response to this epitope.
- An E to K substitution at position 5 abrogates specific lysis, but not binding to B*3501.
- An I to V substitution at position 1, P to Q at position 2, and E to K at 5, abrogates specific lysis and binding to B*3501.
- An I to V substitution at position 1 did not alter reactivity.
- Reviewed in Menendez-Arias *et al.* [1998], this epitope lies in the thumb region of RT.

HXB2 Location RT (293–301)
Author Location Pol (HXB2, LAI)
Epitope IPLTEEAEL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Donor MHC A*2402, A*2601, B*3501, B*5101
Country Japan
Assay type Cytokine production, Tetramer binding, Chromium-release assay
Keywords binding affinity, kinetics, TCR usage, characterizing CD8+ T cells, immune dysfunction
References Ueno *et al.* 2004b

- Two different clonotypes of CD8+ T-cells with specificity for this epitope were isolated from a chronic HIV+ patient. The clonotype with the relatively high affinity TCR had no cytolytic activity, cytokine production or proliferation in response to HIV-infected cells, while the moderate affinity clonotype had strong reactions. More than 3-fold increased duration in tetramer 1/2 life was observed with the defective clonotype. The TCRs from the two clonotypes preserved the phenotype when transduced into primary CD8+ T cells, suggesting the TCR with higher affinity was directly associated with impaired T-cell reactivity of the cells.
- The high affinity impared TCR was Valpha1.1/Vbeta13.3, the moderate affinity active TCR was Valpha12.1/Vbeta5.6.

HXB2 Location RT (293–301)
Author Location Pol (HXB2, LAI)
Epitope IPLTEEAEL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1501, B*3501)

Donor MHC A*2402, A*2601, B*3501, B*5101
Country Japan
Assay type Cytokine production, Tetramer binding, Chromium-release assay
Keywords binding affinity, cross-presentation by different HLA, immunotherapy, TCR usage, characterizing CD8+ T cells
References Ueno *et al.* 2004a

- This paper described the transduction of HIV specific clone TCR genes Valpha12.1/Vbeta5.6 into primary CD8+ T cells. Epitope fine specificity and appropriate effector functions were observed in the transduced cells, although functional avidity could change due to different densities of TCR on the surface of the transduced cells. No allogenic responses were detected. This methodology could have immunotherapeutic applications.

HXB2 Location RT (293–301)
Author Location Pol (448–456 SF2-24)
Epitope IPLTEEAEL
Epitope name HIV-B35-SF2-24
Immunogen HIV-1 infection
Species (MHC) human (B*3501, B*5101)
References Tomiyama *et al.* 2000b

- This epitope is naturally processed and presented by both HLA-B*3501 and HLA-B*5101 and is cross-recognized by a single CTL clone.
- IPLTEEAEL binds approximately four times more tightly to HLA-B*3501 than HLA-B*5101.

HXB2 Location RT (293–301)
Author Location Pol (489–456)
Epitope IPLTEEAEL
Immunogen HIV-1 infection
Species (MHC) human (B*0702, B*3501, B*5101, B*5301)
Donor MHC A24, A26, B35, B51, Cw3
Keywords supertype, cross-presentation by different HLA, TCR usage
References Ueno *et al.* 2002

- The IPLTEEAEL epitope was known to be presented by both HLA-B*3501 and -B*5101 to a dual specific CTL clone. A single TCR complex bearing Valpha12.1 and Vβ5.6 was shown recognize the epitope in either HLA-B*3501 and -B*5101. Furthermore, this TCR also recognized the peptide presented by B*5301 and B*0702 in cytolytic CTL assays, demonstrating that this single TCR complex recognizes the same peptide presented by a range of HLA class I molecules.

HXB2 Location RT (293–301)
Author Location (SF2)
Epitope IPLTEEAEL
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords rate of progression
References Kawana *et al.* 1999

- HLA B35 is associated with rapid disease progression.
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals.
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals but this was one of the six that had no B35 associated pattern of mutation.

HXB2 Location RT (293–301)
Author Location RT (448–456 SF2)
Epitope IPLTEEAEL
Immunogen HIV-1 infection
Species (MHC) human (B35, B51)
References Menendez-Arias *et al.* 1998; Shiga *et al.* 1996

- Binds HLA-B*3501 and B*5101.
- Reviewed in Menendez-Arias *et al.* [1998], this epitope lies in the thumb region of RT.

HXB2 Location RT (293–301)
Author Location Pol (447–455)
Epitope IPLTEEAEL
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B51)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location RT (293–301)
Author Location RT (293–301)
Epitope IPLTEEAEL
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these eptiopes, but this increased over time.

HXB2 Location RT (293–301)
Author Location RT (293–301)
Epitope VPLTREAEL
Epitope name VL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)

Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-B51-restricted autologous epitope VPLTREAEL elicited increasing CTL responses at the last 2 time points. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location RT (293–301)
Author Location RT Pol (286–294)
Epitope IPLTEEAEL
Epitope name IPL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A2, A68.1, B*07, B*3503, Cw*0401, Cw*0702, DQ2, DQ6, DR15, DR17, DR51, DR52
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, CD4 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, escape
References Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses,and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relatively efficiency of the variant eptiopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- The IPL epitope was found to be under positive selection for escape mutations and it was replaced by first variant between days 297 and 369, ipltGeael. This new variant was subsequently replaced by 2 further variants, that were even more resistent to CD8+ T cell recognition between days 369 and 635, ipltAeael and ipltVeael.

HXB2 Location RT (293–301)
Author Location RT
Epitope IPLTEEAEL
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Garrison *et al.* 2007

- The study examined the influence of HIV-1 infection on human endogenous retroviruses (HERVs) activity and explored T cells cross-reactivity in regions of HIV-1/HERV similarity.
- T cell responses to HERV peptides were identified in HIV-1 positive individuals. There was an inverse correlation between anti-HERV T cell responses and HIV-1 viral load.
- HIV-1 epitope LSHFLKEKGGLEG has a corresponding HERV peptide LDLLTAEKGGLCI. These 2 peptides were used in measuring IFN-γ ELISPOT responses in HIV-1-positive and -negative individuals.

HXB2 Location RT (294–318)
Author Location RT (461–485 HXB2)
Epitope PLTEEAELELAENREILKEPVHGVY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Menendez-Arias *et al.* 1998; Walker *et al.* 1989

- One of five epitopes defined for RT-specific CTL clones in this study.

HXB2 Location RT (298–312)
Author Location RT (291–305)
Epitope EAELELAENREILKE
Epitope name EAE
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A2, A68.1, B*07, B*3503, Cw*0401, Cw*0702, DQ2, DQ6, DR15, DR17, DR51, DR52
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ
Keywords rate of progression, escape
References Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses,and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relatively efficiency of the variant eptiopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- This was one of 8 reactive peptides found not to vary over time. It was one of four epitopes that were not precisely defined.

HXB2 Location RT (302–319)
Author Location (C consensus)
Epitope ELAENREILKEPVHGVYY

CTL CD8+

Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0202)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location RT (302–319)
Author Location RT
Epitope `ELAENREILKEPVHGVYY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This overlapping peptide, ASRELERFAVNPGLL, was differentially targeted across ethnic groups and had an overall frequency of recognition of 13.3% - 6.8% AA, 26.9% C, 20.5% H, 0% WI (P value = 0.0028). HLA-A2 was the most commonly present HLA allele among individuals with responses to this peptide.

HXB2 Location RT (308–317)
Author Location RT (LAI)
Epitope `EILKEPVGHV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Menendez-Arias *et al.* 1998; van der Burg *et al.* 1997

- Recognized by CTL from a long-term survivor, SPIETVPVKL was also recognized.
- Recognized by CTL from a progressor, EELRQHLLRW and TWETWWTEYW were also recognized.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope `ILKEPVHGV`
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Keywords HAART, ART
References Huang *et al.* 2000

- The single cell ELISPOT assay was optimized and highly specific, and found to work well even after the primary cells had been frozen and thawed.
- Increases in gamma interferon producing cells were observed in response to anti-retroviral therapy using single cell IFN-gamma-production ELISPOT.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope `ILKEPVHGV`
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Keywords HAART, ART
References Rinaldo *et al.* 2000

- Administration of triple-drug antiretroviral therapy (IDV, 3TC and ZDV) sometimes showed a transient increase and other times failed to increase CTL responses in patients with advanced HIV disease, but there is a stable population of tetramer stained HIV-specific CD8+ CD45RO+ cells that persist after therapy and long periods of virus being below the level of detection.

HXB2 Location RT (309–317)
Author Location RT
Epitope `ILKEPVHGV`
Epitope name IV9
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Keywords HAART, ART, immunodominance
References Scott-Algara *et al.* 2001

- This study examined with CTL response in HLA A*02+ children by tetramer staining for HLA-A2 immunodominant epitopes SLYNTVATL and ILKEPVHGV.
- 71% of the 28 HIV-1 infected HLA-A*02 positive children recognized both epitopes, with cells from 26 children stained positive by the gag tetramer (SLYNTVATL) and 21 children by the pol tetramer (ILKEPVHGV)
- There were no differences observed in children that had therapy versus those that did not.
- Tetramer-binding cells were memory activated CD28-, CD45RO+, CD45RA- HLADR+, CD69-, CD8+ T-cells.

HXB2 Location RT (309–317)
Author Location RT
Epitope ILKEPVHGV
Epitope name POL
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country France
Assay type Cytokine production, Tetramer binding, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords responses in children, characterizing CD8+ T cells
References Scott-Algara *et al.* 2005

- Only a fraction of HIV-1-specific CD8 T-cells detected in the PBMC of 17 infected children (ages 2-18) were able to produce cytokines (IFN-gamma, TNF-alpha) or chemokines (CCL4, CCL5) after stimulation with the cognate peptide. A negative correlation was found between the plasma viral load and the precentage of CD8+ Gag-specific T-cells secreting IFN-gamma. Tetramers used in this study were SLYNTVATL-HLA-A*02 and ILKEPVHGV-HLA-A*02.

HXB2 Location RT (309–317)
Author Location RT (309–317)
Epitope ILKEPVHGV
Epitope name IV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- Responses to epitope IV9 were seen in early chronic infection.

HXB2 Location RT (309–317)
Author Location RT (309–317)
Epitope ILKEPVHGV
Epitope name IV9
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Assay type CTL suppression of replication
Keywords class I down-regulation by Nef
References Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Late protein RT epitope ILKEPVHGV-recognizing CTLs were affected by Nef.

HXB2 Location RT (309–317)
Author Location Protease-RT (476–484)
Epitope ILKEPVHGV
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human (A*02)
Assay type Other
Keywords kinetics
References Wick *et al.* 2005

- Experimental and mathematical models were used to estimate the number of HIV-infected cells that can be killed by CD8+ T-cells. On average, CTLs can kill from 0.7 to 3.0 cells/day.
- CTL clone 68A62 recognizes epitope ILKEPVHGV and was used to study the inhibition of HIV-1 replication in acutely infected cells in vitro.

HXB2 Location RT (309–317)
Author Location
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords acute/early infection
References Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T cells and viral load.
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B2705; and A*0201, A*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK.
- The subject with A*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705.
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

HXB2 Location RT (309–317)
Author Location Pol (476–484)
Epitope ILKEPVHGV

Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Spiegel *et al.* 2000

- High levels of CD8+ HIV-1 specific and cytomegalovirus specific CTL were detected by HLA-A*0201-peptide tetramers in 3 infected subjects with very low CD4 counts, but CD8 T cell mediated effector activity was not seen.
- Thus HIV-1 specific CD8+ cells may be present but may lack direct effector activity in late disease, suggesting that overcoming antigen unresponsiveness may be a useful therapeutic strategy.

HXB2 Location RT (309–317)
Author Location Pol (476–484)
Epitope `ILKEPVHGV`
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords epitope processing, immunodominance
References Sewell *et al.* 1999

- Proteasome regulation influences epitope processing and could influence immunodominance.
- The proteasome is inhibited by lactacystin treatment, and gamma IFN induces expression of proteasome subunits, LMP2 and LMP7, which combine with the proteasome to create an immunoproteasome.
- IFN-gamma induction of the immunoproteasome and lactacystin inhibition increases the presentation of the A*0201 VIYQYMDDL epitope, but decreases the presentation of the A*0201 ILKEPVHGV epitope, which is immunodominant within pol proteins, showing the two epitopes are processed by different pathways.
- ILKEPVHGV seems to be processed by the classical proteasome pathway, while VIYQYMDDL appears to be destroyed by this pathway.
- This epitope contains the catalytic site (YMDD) of RT, a conserved sequence in HIV-1 which restricts escape mutants.

HXB2 Location RT (309–317)
Author Location Pol (476–484)
Epitope `ILKEPVHGV`
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords epitope processing
References Loing *et al.* 2000

- The ILKEPVHGV was modified by the addition of an N-palmitoyl-lysine residue at the P0, P1 or P10 positions of the parent peptide to create a lipopeptide for direct antigen delivery to the cytoplasm for processing.
- The N-terminal modification increased the life span for functional CTL recognition up to 48 hours in comparison to the parent peptide.

HXB2 Location RT (309–317)
Author Location Pol (510–518)
Epitope `ILKEPVHGV`
Immunogen vaccine
Vector/Type: canarypox, vaccinia *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human (A*0201)
References Larsson *et al.* 1999

- ELISPOT was used to assay the CD8 T cell response to the HIV-1 proteins Gag, Pol, Nef or Env expressed in vaccinia or canarypox vectors in 19 HIV+ people.
- The highest CTL frequency was directed at epitopes in Pol.
- In A*0201 individuals, higher numbers of spot-forming T cells were directed against HIV-1 proteins expressed in vaccinia than to peptides SLYNTVATL and ILKEPVHGV presented by A2.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope `ILKEPVHGV`
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords TCR usage
References Wilson *et al.* 1998a

- HIV+ individuals were followed longitudinally using MHC tetramers in combination with 14 anti-BV chain MAbs, and clonal expansion of HIV-specific T cells was followed *in vivo*.
- Seven HIV+ people were studied, and all showed expansions of particular TCR BV clones, often several, relative to uninfected controls.
- Three patients were followed in detail, TCR VB expansions persisted for 2 to 3 years, with occasional transient increases.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope `ILKEPVHGV`
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 2/11 of the A2+ individuals responded to ILKEPVHGV, and neither of these two responded to SLYNTVATL.

HXB2 Location RT (309–317)
Author Location Pol
Epitope `ILKEPVHGV`
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords HAART, ART
References Gray *et al.* 1999

- Administration of highly active antiretroviral therapy (HAART) reduced CD8+ cell frequency, and the CD8+ cells detected by tetramer staining were likely to be memory cells, indicating that persistently replicating viral populations are needed to maintain high frequencies of HIV-1 specific CTL.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope `ILKEPVHGV`
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Menendez-Arias *et al.* 1998; Ogg *et al.* 1998b

- HLA-tetrameric complexes were used in a cross-sectional study of 14 untreated HLA A*0201 positive individuals, revealing an inverse relationship between HIV Gag and Pol specific CTL effector cells (CTLe) and viral load.
- Inclusion of both the p17 SLYNTVATL and RT ILKEPVHGV epitopes gives a good representation of HLA A*0201-restricted activity.
- No correlation was observed between the CTLe and CD4 count or clearance rate of productively infected cells.

HXB2 Location RT (309–317)
Author Location RT
Epitope ILKEPVHGV
Immunogen vaccine
Vector/Type: vaccinia
Species (MHC) human (A*0201)
References Hanke *et al.* 1998a; Hanke *et al.* 1998b
- This epitope was shown to be processed and presented to appropriate CTL clones upon infection of human target cells with vaccinia virus Ankara (VVA) carrying 20 HIV-1 epitopes recognized by humans.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope ILKEPVHGV
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Keywords binding affinity
References Konya *et al.* 1997; Menendez-Arias *et al.* 1998
- This epitope was included as a positive control.
- Binding affinity to A*0201 was measured, $C_{1/2\ max}$ μM =12.

HXB2 Location RT (309–317)
Author Location RT (468–476)
Epitope ILKEPVHGV
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
References van der Burg *et al.* 1996
- Immunogenic in humans, slow dissociation rate, and associated with immunogenicity in transgenic HLA-A*0201/K^b mice.
- CTL generated by *in vitro* stimulation of PBMC derived from uninfected individual.

HXB2 Location RT (309–317)
Author Location RT (468–476)
Epitope ILKEPVHGV
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
References van der Burg *et al.* 1995
- Binds HLA-A*0201 – CTL generated by *in vitro* stimulation of PBMC from an HIV negative donor.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Menendez-Arias *et al.* 1998; Pogue *et al.* 1995
- Mutational study: position 1 I to Y increases complex stability with HLA-A*0201.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords review, escape
References Goulder *et al.* 1997e; Goulder *et al.* 1997a; Menendez-Arias *et al.* 1998
- HLA-identical sibling hemophiliac brothers were both infected with the same batch of factor VIII.
- One had a response to gag A2 epitope SLYNTVATL, the other to pol A2 epitope ILKEPVHGV. They were tested 6-8 years after infection.
- Viral sequencing from the twin that had no response to SLYNTVATL indicated his virus had the substituted form SLHNAVAVL.
- 71% of an additional set of 22 HIV-1 infected HLA-A*0201 positive donors preferentially responded to gag SLYNTVATL.
- Those individuals with a pol ILKEPVHGV response tended to have mutations in or around SLYNTVATL.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

HXB2 Location RT (309–317)
Author Location RT (309–317)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Altman *et al.* 1996
- This paper introduces the tetramer methodology which permits quantification of specific CTL based on expression of specific TCRs—HLA-A2 tetramers were prepared that can stain CTL lines specific for ILKEPVHGV and SLYNTVATL, and can quantify HIV-specific CD8+ cell lines in freshly isolated PBMCs.
- Three patients only stained the Gag epitope SLYNTVATL, one patient had the highest frequency of tetramer staining to the Pol epitope (0.77%), less to the Gag epitope (0.28%)
- The A2-Pol CD8+ clones were CD45RO positive and HLA-DR and CD38 negative, suggesting a memory rather than effector phenotype.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope ILKEPVHGV
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Keywords epitope processing
References Menendez-Arias *et al.* 1998; Walter *et al.* 1997
- HLA-A2 heavy chain and β2-microglobulin expressed in E. coli were refolded in the presence of this peptide.
- The HLA-A2-peptide complex elicited HLA-A2 peptide-specific CTL response in cells lacking HLA-A2.

- Suggests that preformed HLA-peptide complexes could provide an alternate to intracellular processing for immunogens.

HXB2 Location RT (309–317)
Author Location RT (464–472)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords HAART, ART
References Gray *et al.* 1999

- Peptide-tetramer complexes of A*0201 and SLYNTVATL or ILKEPVHGV were used to study individuals receiving HAART to determine the frequency of Class I HLA-restricted anti-HIV CD8+ T cells.
- 17/18 asymptomatic patients had a CTL response to one or both epitopes – 72% had a CTL response to SLYNTVATL.
- After HAART, the majority of the epitope-specific CTL were apparently memory cells.

HXB2 Location RT (309–317)
Author Location Pol
Epitope ILKEPVHGV
Immunogen vaccine
Vector/Type: DNA
Species (MHC) transgenic mouse (A*0201)
References Ishioka *et al.* 1999

- A minigene vaccine construct encoding 6 HLA 2.1 and 3 HLA A11 restricted CTL epitopes, the universal Th cell epitope PADRE (pan-DR epitope) and an ER translocating signal sequence was constructed.
- The epitopes were chosen for dominant recognition by CTLs during HBV and HIV infections in humans.
- HLA transgenic mice were used for quantitating *in vivo* immunogenicity of DNA vaccines encoding HLA-restricted CTL epitopes – strong responses were observed to all nine epitopes, and CTL memory persisted up to four months after a single injection.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords escape
References Brander *et al.* 1998a

- Of 17 infected HLA A*0201 subjects, 13 had CTL responses against the p17 SLYNTVATL epitope, six recognized ILKEPVHGV and five recognized VIYQYMDDL, and there was no correlation between viral load and recognition of a specific epitope or evidence of immune escape.
- Only one subject had CTL against all three epitopes.
- Subjects were part of the San Francisco City Clinic Cohort, the ARIEL project and from the Boston area.
- C. Brander notes this is an A*0201 epitope.

HXB2 Location RT (309–317)
Author Location Pol (476–484)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords HAART, ART
References Ogg *et al.* 1999

- CTL effector levels were measured after potent ARV therapy using HLA-tetramer complexes for the A*0201 epitopes SYLVTVATL and ILKEPVHGV in seven patients, and the B*3501 epitope DPNPQEVVL in one additional patient.
- Levels of CTL effectors typically decline for 5-7 days and then rebound, fluctuating during the first two weeks of therapy.
- After the early fluctuation, there was a steady exponential decay with a median half-life of 45 days.

HXB2 Location RT (309–317)
Author Location RT (476–484 LAI)
Epitope ILKEPVHGV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a A*0201 epitope.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope ILKEPVHGV
Epitope name IV9
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human (A*0201)
References Dela Cruz *et al.* 2000

- Integration of HIV RT CTL epitopes into the N-terminus of the HLA-A2 heavy chain, or tethering the epitopes to the target chain, resulted in epitope-specific lysis by CD8+ CTL.
- These antigens could also be used to stimulate primary responses *in vitro*.

HXB2 Location RT (309–317)
Author Location RT (309–317)
Epitope ILKEPVHGV
Epitope name P1
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords HAART, ART, escape
References Samri *et al.* 2000

- The epitope was recognized by patient 250#0 but not in another A*0201+ patient, 201#5, in a study of the effects of therapy escape mutations on CTL recognition.

HXB2 Location RT (309–317)
Author Location Pol (LAI)
Epitope ILKEPVHGV
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Keywords dendritic cells
References Engelmayer *et al.* 2001

- Recombinant canarypox virus vector containing HIV-1 sequences, upon infection of mature dendritic cells, can trigger specific lysis through *in vitro* by T-cells from HIV-1 infected individuals at levels comparable to the response seen to HIV carried in vaccinia vectors.

CTL CD8+

- Recombinant canarypox virus vector containing HIV-1 sequences can also stimulate HIV-specific CD4+ helper T-cell responses.

HXB2 Location RT (309–317)
Author Location Pol
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Gea-Banacloche *et al.* 2000

- In a study including many long-term non-progressors, no correlation between plasma virus levels and number of HIV-specific CD8+ T-cells was found.
- High frequencies of circulating CD8+ T-cells were HIV-1 specific, and the majority of these responses were to gag-pol gene products.
- 4/21 subjects were HLA-(A*0201), and of these only 2 subjects (patient 3 and 19) tested positive to this epitope.

HXB2 Location RT (309–317)
Author Location Pol (476–484)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords HAART, ART, rate of progression
References Jin *et al.* 2000a

- The CTL effector levels (CTLe) were compared in long term non-progressors (LTNP) with low viral load and in patients whose virus was well-suppressed by therapy, using a tetramer assay.
- LTNPs have high memory CTLe numbers and low viral load, while HAART patients had low CTLe numbers and low viral load.

HXB2 Location RT (309–317)
Author Location Pol (476–484)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Appay *et al.* 2000

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α

HXB2 Location RT (309–317)
Author Location Pol
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords dendritic cells
References Ostrowski *et al.* 2000

- The role of CD4+ T-cell help in expansion of virus-specific memory CTL was studied through co-culture *ex vivo*
- Optimal expansion of HIV-1-specific memory CTL depended on CD4+ T cell help in 9 of 10 patients – CD40 ligand trimer (CD40LT) could enhance CTL in the absence of CD4+ T cell help to a variable degree in most of patients.
- Those CTL that didn't respond to CD40LT could expand with IL2 present, and IL15 produced by dendritic cells also contributes.
- The T-helper epitope used for CD4+ T cell stimulation was the universal tetanus helper epitope TET830-843 (QYIKANSKFIGITE)

HXB2 Location RT (309–317)
Author Location RT (309–317)
Epitope ILKEPVHGV
Epitope name RT2
Immunogen vaccine
Vector/Type: HIV-1 peptide in filamentous bacteriophage major coat protein *HIV component:* RT
Species (MHC) human, transgenic mouse (A*0201)
References Guardiola *et al.* 2001

- HLA-A2 transgenic mice were injected with bacteriophage antigens expressing a Th epitope and the HIV CTL epitope ILKEPVHGV, and epitope-specific cytotoxic activity was induced.

HXB2 Location RT (309–317)
Author Location Pol (476–484)
Epitope ILKEPVHGV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords epitope processing, immunodominance
References Sewell *et al.* 2002

- Epitope processing of three different HLA-A*0201 HIV epitopes was shown to use different pathways, which might influence patterns of immunodominance. .174 cells were used that lack TAP1 and TAP2 genes, as well as the LMP2 and LMP7 genes that encode the beta-subunits of the immunoproteasome. These genes could be added back through transfection to study processing.
- ILKEPVHGV was efficiently presented in TAP-1 and -2 transfected cells while VIYQYMDDL and SLYNTVATL were not. VIYQYMDDL was destroyed by the MB1 subunit of the protease, and could be expressed in the presence of the proteasome inhibitor lactacystin, but SLYNTVATL expression was not restored. SLYNTVATL expression was unaltered by lactacystin in a wild type cell line.

HXB2 Location RT (309–317)
Author Location Pol
Epitope ILKEPVHGV
Epitope name IL-9
Immunogen HIV-1 infected monocyte-derived
Species (MHC) mouse (A*0201)
References Poluektova *et al.* 2002

- Nonobese diabetic NOD-C.B-17 SCID mice were reconstituted with HLA-A*0201 positive human PBL and injected with HIV-1 infected monocyte-derived macrophages MDM in the basal ganglia to provide a mouse model of HIV-1 encephalitis.
- HLA-A*0201 CTL responses were detected by tetramer staining in the spleen in seven days, increased through day 14, and the numbers of productively infected were reduced >85% in the second week.

HXB2 Location RT (309–317)
Author Location RT (476–484 LAI)
Epitope ILKEPVHGV
Epitope name LR22
Subtype B
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade LAI *Adjuvant:* Incomplete Freund's Adjuvant (IFA), Montanide (ISA 720), P30, PLG
Species (MHC) mouse (A*0201)
Keywords binding affinity, vaccine-specific epitope characteristics, immunodominance
References Peter *et al.* 2001

- The stability of peptide binding to HLA-A2.1 was determined for six HLA-A2.1 peptides included in this vaccine study – ILKEPVHGV (RT), SLYNTVATL (p17), SLLNATDIAV (gp41) and LLWKGEGAV (RT) all bound with high affinity comparable to a influenza epitope reference (GILGFVFTL), while RGPGRAFVTI and VIYQYMDDL bound with a lower affinity (relative binding activity = 0.01).
- The four high-affinity peptides formed stable complexes with half-lives ranging between 8 and 32 hours, while the low affinity peptides had half lives of less than an hour.
- HLA-A2.1 transgenic mice were immunized with the six HIV-1 peptides and P30, as a universal T-helper epitope, with IFA or Montanide or microspheres as adjuvants.
- All peptides except VIYQYMDDL induced a stong CTL response in Cr-release assays - stronger responses were observed when peptides were delivered alone, indicating immunodominance when the combination was used.

HXB2 Location RT (309–317)
Author Location RT (476–484 LAI)
Epitope ILKEPVHGV
Epitope name LR22
Subtype B
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade LAI *Adjuvant:* Incomplete Freund's Adjuvant (IFA), IL-12, P30
Species (MHC) mouse (A*0201)
Keywords vaccine-specific epitope characteristics, immunodominance
References Peter *et al.* 2002

- When HIV-1 peptides were used to vaccinate HLA-A2.1 transgenic A2-Kb mice, strong responses to five peptides were observed when the peptides were given individually, but immunodominance limited the response to some of the peptides when they were given in combination Peter *et al.* [2001]. IL-12 can counteract immunodominance in BALB/c mice, so it was given with the multiple epitope vaccination, and was instead found to specifically eliminate the HLA-A2.1-epitope CTL responses, but not Kb CTL responses. This was possibly a consequence of transient depletion of T-cells, B cells and macropahges in the spleen.

HXB2 Location RT (309–317)
Author Location RT (309–317)
Epitope ILKEPVHGV
Subtype B
Immunogen vaccine
Vector/Type: peptide *HIV component:* RT *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) transgenic mouse (A*0201)
Keywords binding affinity, vaccine-specific epitope characteristics
References Boissonnas *et al.* 2002

- Ten naturally occurring variants of the Nef epitope VLMWQFDSRL were tested for their affinity to HLA-A*0201 and for their ability to induce gamma-IFN and cytotoxic functions through vaccination of HLA-A*0201 transgenic mice.
- ILKEPVHGV could induce HLA-A*0201 vaccine responses, and was a positive control.

HXB2 Location RT (309–317)
Author Location Pol (468–476)
Epitope ILKEPVHGV
Immunogen vaccine
Vector/Type: DNA *HIV component:* HIV-1
Species (MHC) mouse (A*0201)
Keywords epitope processing, vaccine-specific epitope characteristics, immunodominance
References Singh *et al.* 2002; Sykes & Johnston 1999

- C3H (H-2k) transgenic mice carrying a fused HLA-A*0201 alpha1 and alpha2 and H-2Dk alpha3 hybrid class I molecule were immunized using an epidermal gene gun with an ubiquitin expression library of 32 plasmids that spanned the HIV-1 genome. Ubiquitin targets the expressed HIV-1 peptides to the proteasome.
- A single immunization with the UB-HIV-1 library vaccine induced potent, stable and multivalent CTL responses against all library members.
- Immunodominant epitopes SLYNTVATL (Gag), ILKEPVHGV (Pol), RIQRGPGRAFVTIGK (Env) and AFHHVAREK (Nef) elicited strong CD8+/IFN- responses and stimulated CTL that were functional in a Cr-release assay and against wild type antigen.
- The presence of multiple plasmids HLA-A*0201-restricted CTL epitopes did not decrease CTL immunogenicity, and CTL responses to single peptide immunizations were comparable to responses based on mixtures of either 16 or 32 peptides.

HXB2 Location RT (309–317)
Author Location Pol
Epitope ILKEPVHGV
Subtype A, B, C, D
Immunogen HIV-1 infection, vaccine

CTL CD8+

Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human, macaque (A*0201)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location RT (309–317)
Author Location Pol (476–484)
Epitope ILKEPVHGV
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Keywords epitope processing, dendritic cells
References Andrieu *et al.* 2003

- This study demonstrates that lipopeptides carrying epitopes can be taken up by human dendritic cells, processed using different pathways, and recognized by epitope-specific CD8+ T-cells originally derived from HIV+ individuals. The RT ILKEPVHGV peptide was embedded in a longer peptide fragment in the lipopeptide, and was internalized by endocytosis and processed in the cytosol by proteasomal cleavage by following an endosome-to-cytosol pathway for processing and presentation. Administration of epoxomycin, a proteasome inhibitor, completely abrogated epitope presentation to a CD8+ T-cell line, while monensin, an inhibitor of acid-dependent endosomal enzyme activity did not.
- In contrast to the RT epitope, dendritic cell presentation of the Nef epitope QVPLRPMTYK embedded in a longer peptide in a lipopeptide was not inhibited by epoxomycin, but was inhibited by monensin, indicative of endocytolitic epitope processing.

HXB2 Location RT (309–317)
Author Location
Epitope ILKEPVHGV
Epitope name IV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Assay type Cytokine production, proliferation, Tetramer binding, Intracellular cytokine staining, Chromium-release assay
References Dagarag *et al.* 2003

- Telomer length is short in the CD8+ T-cell compartment of HIV-1 infected people, indicating excessive CTL activation and premature senescense. Here human telomerase RT (hTERT) transduction of HIV-1-specific CTL was used to study the functional impact of telomerase. Telomerase expression enhanced proliferative capacity, as well as cytolytic and antiviral capabilities; cytokine production was unchanged. hTERT transduced CTLs were 10-fold more efficient in controlling HIV-1 replication in culture. Thus telomerase transduction can restore CTL mediated cytolysis, and may have therapeutic potential.
- Three polyclonal CD8+ T-cell lines derived from an HIV-1, HLA A*0201 positive patient were used in this study, including one specific for this epitope. An IV9-specific monoclonal cell line, 68A62 was also generated.

HXB2 Location RT (309–317)
Author Location Pol (464–472)
Epitope ILKEPVHGV
Epitope name I9V
Subtype B
Immunogen vaccine
Vector/Type: peptide *HIV component:* RT *Adjuvant:* CpG immunostimulatory sequence (ISS)
Species (MHC) transgenic mouse (A*0201)
Donor MHC H-A2/Kb
Assay type Cytokine production, Tetramer binding, Intracellular cytokine staining, Chromium-release assay
References Daftarian *et al.* 2003

- HLA-A*0201 transgenic mice were immunized with a Th-CTL-fusion peptide composed of the I9V CTL epitope linked to the promiscuous PADRE Th epitope. The peptide only when given in combination with CpG elicited strong I9V-CTL responses.
- The peptide-CpG vaccinated mice, when challenged with pol embedded in vaccinia (pol-vv), could clear the virus from the ovaries. Additionally, intranasal immunized mice given an intranasal pol-vv challenge reduced virus in the lungs.

HXB2 Location RT (309–317)
Author Location Pol (476–484)
Epitope ILKEPVHGV
Epitope name IV9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Assay type Tetramer binding
Keywords genital and mucosal immunity
References Shacklett *et al.* 2003

- Lymphocytes from rectal biopsies were used to characterize the CD8+ T cell response to HIV in GALT, Gut-associated lymphoid tissues. Patients were selected on the basis of being HLA-A2+ and having detectable SLYNTVATL and ILKEPVHGV tetramer responses in PBMC. SLYNTVATL

CTL CD8+

frequency was increased in GALT relative to PBMC in 6/7 patients studied, while a control response to a CMV-peptide was diminished in GALT. Only two patients had ILKEPVHGV CD8+ T cell responses, and both had slightly higher frequencies in GALT than PBMC.
- HIV may perturb lymphocyte retention in GALT, suggested by an overall reduction of GALT CD8+ cells expressing alphaEbeta7. GALT HIV-specific CD8+ T cells expressed alphaEbeta7, suggesting mucosal priming.

HXB2 Location RT (309–317)
Author Location RT (309–317 MN)
Epitope ILKEPVHGV
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* B clade MN *HIV component:* gp120, Protease, RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) humanized mouse (A*0201)
Assay type CD8 T-cell Elispot - IFNγ
Keywords epitope processing, vaccine-specific epitope characteristics, immunodominance, immunotherapy
References Isaguliants *et al.* 2004
- Immunization of HLA-A*0201-transgenic mice with synthetic genes encoding clusters of human A*0201 CTL epitopes located at the sites of drug resistance mutations, induced RT-specific cellular responses indicating the immunogenicity of these constructs. This vaccine strategy may be a first step towards a therapeutic vaccine against drug-resistant strains.
- This was one of five HLA-A*0201 epitopes from the RT or protease proteins that was included in the polyepitope vaccine. When the transgenic HLA A*0202 mice were vaccinated with the polyepitope construct or with a mixture of RT peptides, a sustained low level CD8+ T-cell gamma IFN response was observed, in contrast to when an intact RT gene was used for vaccination.

HXB2 Location RT (309–317)
Author Location
Epitope ILKEPVHGV
Epitope name IV9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, T-cell Elispot, Flow cytometric T-cell cytokine assay
Keywords epitope processing, escape, kinetics, variant cross-recognition or cross-neutralization
References Jamieson *et al.* 2003
- Epitope escape mutations in chronically infected individuals developed over several years indicating slight selective advantage of escape mutants. The maturation state of CTLs appear to affect the rate of epitope mutation and CTL decay.
- In two patients, IV9 mutations preceded the loss of IV9-specific CD8+ T-cells. In a third patient, escape mutations were coincident with IV9-specific CD8+ T-cell loss. One patient was infected with a ilepvhgA variant, and transiently reverted to the consensus form at year 3. One patient never made a response to IV9 despite being infected with the consensus form of the epitope.

HXB2 Location RT (309–317)
Author Location Gag
Epitope ILKEPVHGV
Epitope name IV9
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Assay type Tetramer binding, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords epitope processing, rate of progression, immunodominance, acute/early infection, dendritic cells, TCR usage, memory cells
References Kan-Mitchell *et al.* 2004
- In contrast to IV9-CTLs, SL9-CTLs were shown to be primed by immature DCs and to be independent of help from CD4+ or exogenous IL2 and sensitive to paracrine IL-2-induced apoptosis.

HXB2 Location RT (309–317)
Author Location Pol (468–476 IIIB)
Epitope ILKEPVHGV
Epitope name pol468-476
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* Gag-Pol
Species (MHC) humanized mouse (A*0201)
Assay type Intracellular cytokine staining
Keywords epitope processing, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization, vaccine antigen design
References Singh & Barry 2004
- When A*0201-C3H/J transgenic mice were immunized with plasmids encoding wild-type gag-pol, codon-optimized (CO) gag-pol, and an expression library vaccine expressing 16 fragments of gag-pol fused with ubiquitin for proteosome targeting (ELI), the ELI vaccine produced up to 10-fold higher CD8 T-cell responses than the other two vaccines. In contrast to the wt and CO vaccines, which tended to augment only immunodominant responses, boosting with the ELI vaccine resulted in many CD8 responses against variant epitopes from different HIV-1 clades, and against drug-resistant variants.
- This epitope was recognized in transgenic mice vaccinated with all three vaccine constructs, but the most intense responses were to the ELI vaccine.

HXB2 Location RT (309–317)
Author Location Pol (464–472)
Epitope ILKEPVHGV
Epitope name IV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Donor MHC A*0201, A*0301, B*3501, B*51, Cw*04, Cw*06
Country United States

CTL CD8+

Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords escape, acute/early infection
References Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- The response to this epitope was not detected until month 25 and increased over time.

HXB2 Location RT (309–317)
Author Location Pol
Epitope `ILKEPVHGV`
Epitope name I9V
Immunogen vaccine
Vector/Type: measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140ΔV3
Species (MHC) transgenic mouse (A*0201)
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells
References Lorin *et al.* 2005a

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

HXB2 Location RT (309–317)
Author Location RT
Epitope `ILKEPVHGV`
Epitope name IV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords HAART, ART, responses in children, dendritic cells
References Zhang *et al.* 2006b

- Immune responses in HIV-1 infected children either undregoing HAART or not were analysed. HIV-specific CTLs were lower in children responding to HAART than in non-responders and HAART-naive children. CTL frequency was correlated with myeloid DC frequency in treatment-naive patients, and inversely correlated with duration of virus supression following treatment.
- 11 of the 22 children had significant responses to SL9.

HXB2 Location RT (309–317)
Author Location Pol (476–484)
Epitope `ILKEPVHGV`
Epitope name IV9
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords binding affinity, immunodominance, dendritic cells
References Schaubert *et al.* 2007

- CTL responses to the rarely recognized, subdominant HLA-A2-restricted Gag p24 epitope TLNAWKVV (TV9) were studied since its functional sensitivity and viral suppression is relatively high compared to other, dominant HLA-A2-restricted HIV-1 epitopes. Subdominant CTL responses to TV9 were not related to immunogenicity, availability of cognate TCR repertoires or HLA-epitope binding avidity.
- HLA-A2 restricted epitope IV9 of Pol was able to stimulate a clone of TV9-specific CTLs that had been pre-primed by Gag+Pol transduced DCs, to produce IFN-gamma.

HXB2 Location RT (309–317)
Author Location Pol
Epitope `ILKEPVHGV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Country Canada, United States
Assay type proliferation, Tetramer binding, Intracellular cytokine staining, Other
Keywords characterizing CD8+ T cells
References Jones *et al.* 2008

- Tim-3+ T cells form a novel population of dysfunctional CTLs in chronic progressors of HIV infection. Tim-3 surface levels correlate positively with viral load and CD38 expression, but correlates inversely with CD4 T-cell counts.
- Tim-3 expressing CTLs have impaired cytokine production and proliferation in response to antigen, which is restored by blocking Tim-3 signaling pathways.
- Tim-3 expressing CTLs are a distinct population from PD-1 expressing CTLs.
- CTLs specific for HLA-A*0201 restricted Pol epitope ILKEPVHGV were used to follow immune response.

HXB2 Location RT (309–317)
Author Location RT
Epitope `ILKEPVHGV`
Epitope name IV9
Immunogen virus
Species (MHC) human (A*0201)
Keywords immunotherapy, TCR usage
References Joseph *et al.* 2008

- To circumvent failed adoptive transfer of ex-vivo expanded autologous HIV-1-specific CTLs, the authors use autologous peripheral CTLs with redirected antigen specificities instead. CTLs were transduced with lentiviral vectors encoding TCR-alpha and TCR-beta specific for a control, immunodominant Gag epitope, SL9. Potent and specific in vitro and in vivo activity of the transduced CTLs against SL9-presenting cells was seen.

- IV9 epitope was used as a control to show that while IFN-gamma production was induced by the addition of SL9 to transduced CTLs, no cytokine production was induced by addition of IV9 peptide.

HXB2 Location RT (309–317)
Author Location Pol (498–)
Epitope ILKEPVHGV
Immunogen
Species (MHC)
References

HXB2 Location RT (309–317)
Author Location Pol (498–)
Epitope ILKEPVHGV
Immunogen
Species (MHC)
References

HXB2 Location RT (309–317)
Author Location Pol (498–)
Epitope ILKEPVHGV
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (A*0201)
Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008

- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location RT (309–317)
Author Location RT (476–484 LAI)
Epitope ILKEPVHGV
Epitope name P1
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201, A*0205)
Keywords HAART, ART
References Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using tetramer staining or CD8+ cell IFNgamma production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

HXB2 Location RT (309–317)
Author Location RT (309–317)
Epitope ILKEPVHGV
Epitope name IV9
Immunogen HIV-1 infection
Species (MHC) human (A02)
Assay type Chromium-release assay, Other
Keywords binding affinity
References Bennett *et al.* 2007

- Standard assays like ELISpot, ICS and tetramer staining do not measure antiviral activity of HIV-infected CTLs, but use exogenous synthetic peptides on uninfected cells, or HLA tetramers. Similarly, functional avidity assesses CTL activity against uninfected target cells. Here functional avidity is compared to the efficiency of actual infected cells' recognition and killing, revealing a sharp threshold between CTL immune antiviral activity and lack of infected cell recognition.
- As previously shown, epitopes and their variants spanned orders of magnitude of SD50. Likewise, CTL clearance of infected cells varied from 0 to 100% with epitope sequence variation. Moreover, direct suppression of HIV-1 replication by CTLs also varied with epitope variant.
- When killing efficiency (KE) using virus-infected cells was compared to functional avidity using synthetic peptides, there was a narrow threshold separating maximal killing from almost none. Since different SL9-specific clones had similar KEs, which were vastly different from RL10-specific CTL KEs, it was obvious that KEs varied with epitope sequence too. Finally, a strong correlation between KE and inhibition of viral replication was also seen.
- This epitope, ILKEPVHGV, showed marked differences in its functional avidity as well as killing efficiency, when compared to its variants ILKdPVHGV, ILKnPVHGV, ILKdPVHGa, ILKtPVHGV, ILrEPVHGV, ILKEsVHGV, ILKEtVHGV, ILKEPVHGa, ILKEPVHeV, ILKqPVHGV, IiKEPVHGV, ILrtPVHGV, ILKEPVHrV, ILKEPlHGV, kLKEPVHGV and ILKElVHGV.

HXB2 Location RT (309–317)
Author Location
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A02)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the

CTL CD8+

responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope ILKEPVHGV elicited a magnitude of response of 110 SFC with a functional avidity of 0.01nM.

HXB2 Location RT (309–317)
Author Location Pol
Epitope ILKEPVHGV
Subtype B
Immunogen peptide-HLA interaction
Species (MHC) human (A02)
Assay type Chromium-release assay, Other
Keywords TCR usage
References Hofmann *et al.* 2008

- Unlike LTNPs, most patients cannot produce enough conserved-epitope-recognizing, HIV-specific CTLs to curtail infection. Here, primary CTLs are reprogrammed by RNA electroporation of epitope-specific TCRs to produce proinflammatory cytokines and to lyse target cells presenting the appropriate epitope. For the first time functional transfer of epitope-specific TCRs is shown to be feasible.
- T2 cells loaded with epitope ILKEPVHGV, were lysed upon contact with the their corresponding TCRs inserted into CTL clones by RNA electroporation.

HXB2 Location RT (309–317)
Author Location Pol (476–484)
Epitope ILKEPVHGV
Immunogen vaccine
Vector/Type: vaccinia
Species (MHC) human (A2)
References Woodberry *et al.* 1999

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2.
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D^d – this transgene is the only MHC molecule expressed in the mice.
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost.
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFDSRL)
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested.
- ILKEPVHGV was recognized by 2 of the patients.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords subtype comparisons, TCR usage
References Kolowos *et al.* 1999

- TCR usage in CTL specific for this epitope was examined in three patients and identical Vβ6.1 and Valpha2.5 gene segments were used and two of the patients had very similar complementarity-determining regions – clonal expansion of RT-HIV-specific CTL can contribute to the skewed TCR repertoire in HIV-1 infected patients.
- CTL clones from all three patients showed similar sensitivity to mutation in the epitope, ilkepvhEv was well recognized (the sequence from SF2), ilkDpvhgv was not (the common A clade form)

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Collins *et al.* 1998

- Nef down-regulates MHC class I molecules, which inhibits CTL killing of HIV-infected targets.
- The anti-RT CTL clone killed Nef- cells less efficiently than anti-gag clones, correlated with the reduced expression of RT.

HXB2 Location RT (309–317)
Author Location RT (476–484 LAI)
Epitope ILKEPVHGV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords dendritic cells
References Fan *et al.* 1997

- The capacity of dendritic cells to process and present antigen and stimulate anti-HIV-1 CTL memory responses was studied.

HXB2 Location RT (309–317)
Author Location RT (464–472)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords dendritic cells
References Kundu *et al.* 1998b

- Allogeneic dendritic cells (DCs) were obtained from HLA-identical siblings, pulsed with rgp160 MN or A2-restricted HIV-1 epitope peptides, and infused monthly into six HIV-infected patients.
- 1/6 showed increased env-specific CTL and increased lymphoproliferative responses, 2/6 showed increase only in proliferative responses, and 3/6 showed no change – pulsed DCs were well tolerated.

- ILKEPVHGV is a conserved HLA-A2 epitope included in this study – 5/6 patients had this sequence as their HIV direct sequence, and these had a detectable CTL response– one person carried the form ILREPVHGV and had no detectable CTL.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Menendez-Arias *et al.* 1998; Tsomides *et al.* 1994

- CTL clones recognize naturally processed peptide – peptide abundance corresponded to level of CTL killing.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope ILKEPVHGV
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A2)
Keywords subtype comparisons, HIV exposed persistently seronegative (HEPS)
References Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A subtype consensus is ILKDPVHGV.
- The D subtype consensus is identical to the epitope ILKEPVHGV.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords subtype comparisons
References Cao *et al.* 1997a; Menendez-Arias *et al.* 1998

- The consensus peptides of B and D clade viruses and some As have the sequence ILKEPVHGV.
- The consensus peptide of a subset of A clade viruses, ILKDPVHGV, is not cross-reactive.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Menendez-Arias *et al.* 1998; Yang *et al.* 1996

- CD4+ cell lines acutely infected with HIV were studied to determine their susceptibility to lysis by CTL.
- Clones specific for RT lysed HIV-1 infected cells at lower levels than Env or Gag specific clones.
- The distinction was thought to be due to lower expression of RT relative to Env and Gag.
- CTL can lyse infected cells early after infection, possibly prior to viral production.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CTL suppression of replication
References Yang *et al.* 1997a

- CTL inhibit HIV-1 replication at effector cell concentrations comparable to those found *in vivo*.
- CTL produced HIV-1-suppressive soluble factors – MIP-1α, MIP-1β, RANTES, after antigen-specific activation.
- CTL suppress HIV replication more efficiently in HLA-matched cells.

HXB2 Location RT (309–317)
Author Location RT (309–317)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords TCR usage
References Menendez-Arias *et al.* 1998; Moss *et al.* 1995

- Two clones were obtained with different TCR usage, $V_\beta 1$ and $V_\beta 21$.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Menendez-Arias *et al.* 1998; Musey *et al.* 1997

- Cervical CTL clones from an HIV-infected woman recognized this epitope.

HXB2 Location RT (309–317)
Author Location RT (476–484 LAI)
Epitope ILKEPVHGV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Menendez-Arias *et al.* 1998; Tsomides *et al.* 1991

- Precise identification of the nonamer that binds to A2.

HXB2 Location RT (309–317)
Author Location RT (476–484 LAI)
Epitope ILKEPVHGV
Subtype B
Immunogen peptide-HLA interaction
Species (MHC) human (A2)
References Connan *et al.* 1994; Menendez-Arias *et al.* 1998

- Promotes assembly of HLA-A2 molecules in T2 cell lysates.

HXB2 Location RT (309–317)
Author Location RT (510–518)
Epitope ILKEPVHGV
Immunogen in vitro stimulation or selection
Species (MHC) human (A2)
References Parker *et al.* 1992

- Studied in the context of HLA-A2 peptide binding.

CTL CD8+

HXB2 Location RT (309–317)
Author Location Pol (476–484)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Dyer *et al.* 1999

- CTL specific responses were measured over a 1.3 to 1.5 year period in members of the Sydney Blood Bank Cohort (SBBC) who had been infected with a natural attenuated strain of HIV-1 which was Nef-defective.
- Some of these patients had prolonged high levels of CTL effector and memory cells despite low viral load.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope ILKEPVHGV
Immunogen in vitro stimulation or selection
Species (MHC) human (A2)
Keywords dendritic cells
References Zarling *et al.* 1999

- This study compares the ability of macrophages and dendritic cells to stimulate primary responses in CD8+ lymphocytes isolated from HLA-appropriate HIV-uninfected donors using peptide-pulsed APC – the dendritic cells performed better as APC for the stimulation of primary responses.
- Strong CTL responses were elicited by the epitopes DRFYKTLRA and GEIYKRWII when presented by either immature or mature dendritic cells – macrophages were not able to prime a CTL response against DRFYKTLRA.
- A weak response to KLTPLCVSL was stimulated using macrophages as the APC.
- No detectable response was observed for the following previously-defined HIV epitopes: KIRLRPGGK, ILKEPVHGV, IRLRPGGK, GPKVKQWPL.

HXB2 Location RT (309–317)
Author Location RT (480–)
Epitope ILKEPVHGV
Immunogen computer prediction
Species (MHC) (A2)
Keywords subtype comparisons
References Schafer *et al.* 1998

- This study uses EpiMatrix for T cell epitope prediction to identify possible HLA-B27 and A-2 CTL epitopes in HIV.
- Based on EpiMatrix predictions, 28 peptides were synthesized and tested using T2 binding assays for potential HLA A2 or B27 binding, and 12 of these were shown to bind to the predicted HLA molecule.
- Two of these 12 peptides had been previously identified as CTL epitopes: HLA-B27 KRWILGLNK and HLA-A2 ILKEPVHGV.
- This sequence is not conserved between clades, but is found only in a small number of B clade isolates.

HXB2 Location RT (309–317)
Author Location RT
Epitope ILKEPVHGV
Epitope name RT IV9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords binding affinity, subtype comparisons, supertype, computational epitope prediction
References Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- This peptide binds to four HLA-A2 supertype alleles: A*0201, A*0202, A*0206 (highest affinity) and A*6802.
- RT IV9 was recognized in 7/22 patients with chronic HIV-1 infection.
- 1/13 patients with acute HIV-1 infection recognized RT IV9.

HXB2 Location RT (309–317)
Author Location Pol (subtype A)
Epitope ILKDPVHGV
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HIV exposed persistently seronegative (HEPS), escape
References Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- ILKDPVHGV or ILKEPVHGV was recognized in 1 of the 6 women (ML1760), and the response was present in the last available sample prior to seroconversion, 12 months.
- 20/20 sequences of the infecting strain had no substitutions in this epitope, all were ILKDPVHGV, so there was no evidence for escape.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized by 4/22 HEPS control sex workers: ML887, ML1192, ML1250, and ML1749.

HXB2 Location RT (309–317)
Author Location RT (309–317)
Epitope ILKEPVHGV
Epitope name RT2
Immunogen vaccine, in vitro stimulation or selection
Vector/Type: HIV-1 peptide in filamentous bacteriophage major coat protein *HIV component:* RT
Species (MHC) human, transgenic mouse (A2)
Keywords epitope processing
References De Berardinis *et al.* 2000

- Phage display of the CTL epitope, ILKEPVHGV coupled with T helper epitope KDSWTVNDIQKLVGK, elicited specific CTL responses *in vitro* in PBMC from HIV negative individuals and *in vivo* in immunization of HLA-A2 transgenic mice.
- Bacteriophage presentation of peptides is generally used for stimulation of antibodies, and this novel discovery of CTL epitope processing and presentation suggests new possibilities for these vectors.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope ILKEPVHGV
Epitope name ILK
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HAART, ART, supervised treatment interruptions (STI), immunodominance, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- One of the 2/8 HLA-A2+ study subjects recognized this CTL epitope.
- Patient SC9 (HLA A1/2, B8/13, Cw0/0701, DR2/11, DQ6/7) had a CTL response against epitopes FLKEKGGL, ILKEPVHGV, SQRRQDILDLWIYHTQGYFPDWQNY, and GEIYKRWII peptides and all responses declined during therapy initiated at day 390 but were restored when therapy become intermittent.

HXB2 Location RT (309–317)
Author Location Pol
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Kostense *et al.* 2001

- HLA tetramers to six epitopes were used to study HLA-A2, B8 and B57 CTL in 54 patients – HIV-specific tetramer positive cells were inversely correlated with viral load in patients with high CD4, but in patients with CD4 T-cells below 400 high tetramer frequencies were found despite high viral load.
- Most patients have high levels of HIV-specific T-cell expansions, but many of these cells aren't functional.
- In 15 of the patients, the proportion of IFN gamma producing tetramer cells correlated with AIDS-free survival.

HXB2 Location RT (309–317)
Author Location Pol
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HAART, ART, immunodominance
References Seth *et al.* 2001

- CTL responses were studied by tetramer staining in 41 patients with combination therapy – activated CD8+ T-cells decline as the viral load drops in response to therapy, but the overall level of antigen-specific cells capable of differentiating into effectors stays constant and new epitopes may be recognized.
- 6/10 A*0201+ individuals had HIV-specific tetramer staining cells, and 5 of these declined upon successful therapy.
- 3/10 A*0201+ individuals with chronic HIV-1 infection recognized this epitope.
- Prior to therapy, the mean percentage of CD8+ cells that recognized theimmunodominant epitope SLYNTVATL was six-fold greater than the percentage recognizing the epitope ILKEPVHGV.

HXB2 Location RT (309–317)
Author Location RT (476–484 SF2)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with preseroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A2+ individuals that had a CTL response to this epitope broken down by group: 1/10 group 1, 0/6 group 2, and 3/4 group 3.

HXB2 Location RT (309–317)
Author Location Pol (476–484)
Epitope ILKDPVHGV
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A2)
Keywords subtype comparisons, HIV exposed persistently seronegative (HEPS), immunodominance
References Kaul *et al.* 2001a

- Variants ILK(D/E)PVHGV are A/B clade specific.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.

CTL CD8+

- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-A2 women, 7/10 HEPS and 14/26 HIV-1 infected women recognized this epitope, and ILK(D/E)PVHGV tended to be more reactive in HEPS women, SL(F/Y)NTVATL in infected women.
- The dominant response to this HLA allele was to this epitope in all 7/10 HEPS cases but in only 5 of the 14/26 HIV-1 infected women.
- Four epitopes were considered to be "resistant epitopes", as they were preferentially reactive in HEPS women and so may confer resistance, and these were found in three different proteins: A2 ILK(D/E)PVHGV in RT, A*6802 DTVLEDINL in Protease, B14 DLN(M/T)LN(I/V)V in p24 and B18 FRDYVDRF(Y/F)K also in p24.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.
- Subject ML 1250 had an A2 response to ILK(D/E)PVHGV prior to seroconversion, which switched to SL(F/Y)NTVATL post-seroconversion.
- Subject ML 1760 had an A2 response to ILK(D/E)PVHGV prior to seroconversion, and gained responses to epitopes A2 SL(F/Y)NTVATL and B27 KRWII(L/M)GLNK post-seroconversion.

HXB2 Location RT (309–317)
Author Location Pol (93TH253 subtype CRF01)
Epitope ILRIPVHGV
Epitope name P464-472
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HIV exposed persistently seronegative (HEPS)
References Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was reactive in HIV+ control study subject 144 who carried HLA-A2.

HXB2 Location RT (309–317)
Author Location Pol (93TH253 subtype CRF01)
Epitope ILRIPVHGV
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords subtype comparisons
References Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- 1/4 tested FSWs recognized the E clade version of this epitope, which differs from the previously defined B clade version by two amino acids: ILKEPVHGV.
- This epitope was not conserved in many subtypes, and exact matches were very rare.

HXB2 Location RT (309–317)
Author Location RT (309–317)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.

HXB2 Location RT (309–317)
Author Location
Epitope ILKEPVHGV
Epitope name Pol-IV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A02, 9/29 (31%) recognized this epitope.

HXB2 Location RT (309–317)
Author Location Pol (476–484 LAI)
Epitope ILKEPVHGV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HAART, ART, epitope processing
References Kelleher *et al.* 2001a

- Ritonavir (RTV) inhibits chymotryptic activity in the 20S proteasome *in vitro*, as does Saquinavir (SQV) to a lesser extent; Indinavir (IDV) does not. Thus there is concern protease inhibitors may adversely effect CTL epitope processing, but this paper indicates that processing is not inhibited at therapeutically relevant concentrations of RTV when the proteasome is functioning in in an intracellular context.
- RTV did not alter the presentation two RT A2 epitopes processed by distinct pathways: ILKEPVHGV, generated by the constitutive proteasome containing the MB1 beta subunit, and VIYQYMDDL which is dependent on IFNgamma induction of LMP7 which replaces MB1 in the immunoproteasome, and is destroyed by MB1 in the constitutive proteasome.
- RTV did not inhibit the processing and assembly of HLA-B35 or -A2, which are assembled with a rapid and moderate time course, respectively, or of HLA-A3, -B27 and -B39.

HXB2 Location RT (309–317)
Author Location Pol
Epitope ILKDPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2002

- Neisseria gonorrhea cervititis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
- Ghonorrhea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

HXB2 Location RT (309–317)
Author Location RT (476–484 NL43)
Epitope ILKEPVHGV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords class I down-regulation by Nef
References Yang *et al.* 2002

- Nef down-modulates class I protein expression, and this study demonstrates directly that Nef-deleted HIV-1 NL-43 can be more effectively killed *in vitro* than NL-43 with an intact Nef. The effect was shown to be specific for class I presentation of epitopes, and unlike Nef, deleting Vpr did not alter CTL susceptibility of NL-43 infected cells. The CTL clone 68A62, specific for the class I A2 presented ILKEPVHGV epitope, was one of four used in this study.

HXB2 Location RT (309–317)
Author Location RT (476–484 BRU)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2
Keywords epitope processing
References Cohen *et al.* 2002

- The antigen presentation of two A2-restricted epitopes was compared, SLYNTVATL (p17) and ILKEPVHGV (RT). HIV-1 infected cells were more sensitive to lysis by SLYNTVATL-specific CTL than by ILKEPVHGV-specific CTL, because of a higher density of SLYNTVATL-A2 resulting from differences in processing.
- Incubation with a T1-cell proteolytic extract showed that by four hours, 25% of a p17 peptide had a C-term Leu-85 and were SLYNTVATL-precursors, while ILKEPVHGV-precursors were far less frequent (6.8%) even with four times more proteolytic extract after 30 hours.
- p17 was preferentially cleaved between Leu85 and Tyr86, while appropriate Val484 and Tyr485 cleavage was minor for RT.
- In a competition experiment, RSLYNTVATL bound TAP 3.7-fold more efficiently than RT peptides.
- No difference in CTL avidity was detected in six patients with HLA-A2-restricted responses to these epitopes.
- No significant difference in HLA-A2 binding of to p17 or RT epitopes was observed.

HXB2 Location RT (309–317)
Author Location Pol (476–484)
Epitope ILKEPVHGV
Epitope name p9
Immunogen vaccine
Vector/Type: peptide *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (A2)
References De Lucca *et al.* 2002

- BALB/c mice immunized with the p9 peptide, ILKEPVHGV, elicited specific lymphocyte proliferation activity.
- Exposure of lymphocytes from HIV-negative, HLA-A2 positive people to p9-RNA stimulated lymphocyte proliferation activity to p9. Anti-p9 CTL activity in human lymphocytes incubated with RNA extracted from lymphoid organs of p9-vaccinated mice could be more intensely stimulated.
- This murine RNA also mediated RNA-dependent protein kinase (PKR) and NFkappaB activation in the human lymphocytes, which may be driving the enhanced CTL stimulation in the human cells.

HXB2 Location RT (309–317)
Author Location RT
Epitope ILKEPVHGV
Epitope name ILK
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HAART, ART, supervised treatment interruptions (STI)
References Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFNgamma Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

HXB2 Location RT (309–317)
Author Location p51 (476–484)
Epitope ILKEPVHGV
Immunogen vaccine
Strain: B clade IIIB *HIV component:* Gag, Pol *Adjuvant:* IL-12
Species (MHC) mouse (A2)
Donor MHC H2-K^b
References Kmieciak *et al.* 2001

- Transgenic mice expressing a HLA-A2/Kb chimeric protein were vaccinated with either a p17-p24-p51 fusion protein (vG/P-92) or the Gag-Pol precursor protein (vVK1).
- Compared to vVK1, vG/P-92 induced a significant increase in Gag and Pol induced IFNgamma production and CTL responses, and to the epitopes SLYNTVATL and ILKEPVHGV, as determined by Elispot and 51Cr-release assays.

CTL CD8+

HXB2 Location RT (309–317)
Author Location RT (309–317 NL-43)
Epitope ILKEPVHGV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords class I down-regulation by Nef, escape
References Ali *et al.* 2003

- NL43 was passaged in the presence of Nef KEKGGLEGL-specific CTL clones STD11 and KM3, giving rise to rapid selection of escape mutations, including E93G, E93K, K94N+G99R, G95R+G99R, E98K, E98D, G99R, G99E, L100P, and L100I; insertions, deletions, frameshifts and an early stop codon. 34/36 (94%) of sequences carried mutations in the epitope by seven days, 36/36 (100%) by 14 days.
- Several mutations selected by KEKGGLEGL-specific CTL were shown to impair the down regulation of class I MHC by Nef, in particular E93G, E93K, and a truncation mutation at position 51.
- Nef deletion mutants increased 100-fold NL-43 susceptibility to inhibition by CTL specific for epitopes in other proteins, the A2 epitopes ILKEPVHGV in RT and SLYNTVATL in p17 Gag.

HXB2 Location RT (309–317)
Author Location Pol (476–)
Epitope ILKEPVHGV
Epitope name Pol476
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This epitope was one of the previously identified HLA-A2 epitopes studied.
- 9/17 HIV-infected HLA-A2+ people recognized this epitope.

HXB2 Location RT (309–317)
Author Location RT (309–317)
Epitope ILKEPVHGV
Epitope name RT2
Subtype B
Immunogen vaccine, in vitro stimulation or selection
Vector/Type: peptide *HIV component:* RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) transgenic mouse (A2)
References Domingo *et al.* 2003

- A virus-like protein scaffold, called E2DISP, derived from pyruvate dehydrogenase multienzyme from Bacillus stearothermophilus has been engineered to display 60 copies of one or more epitopes on a single molecule.
- The E2DISP scaffold displaying pep23 is able to stimulate a Th responses, and peptide RT2, which is a CTL epitope from HIV-1 RT, was able to elicit a CD8+ T cell response *in vitro* and in a vaccinated HLA-A2 transgenic mouse. Thus the E2DISP scaffold allows cell-entry and access to the class I and class II processing pathways.

HXB2 Location RT (309–317)
Author Location Pol (476–484)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords responses in children
References Sandberg *et al.* 2003

- 65 vertically HIV-1 infected children, ages 1-16, the majority undergoing ART, were analyzed in regard to their plasma viremia and CD4+ and CD8+ T cell counts, and CD8+ T cell responses.
- Using vaccina expressed Gag, Pol, Env, Rev, Nef in target cells in an Elispot assay, 85% of the children recognized at least one HIV antigen. The strong CD8+ T cell responses were directed against Pol, followed by Gag and Nef. Children younger than 4 had significantly weaker responses (7/14 had no reponse) than older children (only 1/32 had no response, and responses were greater in magnitude).
- SLYNTVATL and ILKEPVHGV tetramers were used to quantitate specific responses. 49 chlidren in an expanded cohort carried HLA-A2. 1/11 children under 3 years of age had detectable CD8+ T-cell responses to SLYNTVATL, 2/11 to ILKEPVHGV. Among children over 3, 11/38 recognized SLYNTVATL and 9/38 recognized ILKEPVHGV.
- Older children that maintained a CD4 count greater than 400 cells/ul tended to have stronger CTL reponses.

HXB2 Location RT (309–317)
Author Location RT (309–317)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) (A2)
Donor MHC A2, A3, B27, B51; A2, A3, B27, B57; A2, A23, B57
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining
Keywords assay standardization/improvement, memory cells
References Sun *et al.* 2003

- This study compares assay methods for testing CTL responses using samples from 20 HIV+ patients. The study compares ELISpot, tetramer-binding, and intracellular IFN-γ. Tetramer-bidning analysis was performed with Gag (SLYNTVATL) or Pol (ILKEPVHGV) tetramers. Antigen presentation using recombinant vaccinia viruses (rVVs) encoding HIV-LAI Gag, Pol, Env, Nef, Tat and Vif proteins was compared to peptide panels. HIV antigen recognition in memory CTLs was measured by chronium release assay and compared to effector/memory CD8+ T cells in an IFN-γ ELISpot assay.

- Results: IFN-γ Elispot and flow cytometry gave similar frequencies of HIV specific CD8+ Tcells. Tetramer-binding analysis was most sensitive. Pools of peptides and the sum of frequencies of individual peptides were comparable. Elispot assays using peptides were more sensitive than assays using vaccinia expressed proteins. Cr release and Elispot against rVVs gave comparable memory cell responses 2/3s of the time.
- 3/7 HLA-A2+ patients recognized this epitope.

HXB2 Location RT (309–317)
Author Location RT (309–317 NL43)
Epitope ILKEPVHGV
Epitope name IV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type Chromium-release assay, CTL suppression of replication
Keywords escape
References Yang *et al.* 2003a

- Virus was cultured in the presence of CTL lines specific for 4 different epitopes (SLYNTVATL, ILKEPVHGV, IEIKDTKEAL, and KEKGGLEGL) to study the emergence of escape mutations. Escape varied between clones for the same epitope, and between different epitopes. Gag and RT epitope escape, if it occurred at all, tended to be monoclonal and within the epitope, indicating strong fitness constraints, while the Nef epitope escape was rapid, polyconal, and sometimes the result of upstream frameshifts.
- There was one cloned cell line that recognized ILKEPVHGV, 68A62. After 2 weeks of passaging HIV-1 in the presence of 68A62, the mutated epitope ilkeLvhgv was found in 6/12 sequences.

HXB2 Location RT (309–317)
Author Location Pol
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords HIV exposed persistently seronegative (HEPS)
References Koning *et al.* 2004

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A*11, A*31 and Cw*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
- 2/11 HLA A2+ infection-resistant men, compared to 1/9 preseroconversion men who went on to become infected, reacted to this epitope.

HXB2 Location RT (309–317)
Author Location RT Pol (464–472)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 9/19 patients recognized this epitope.

HXB2 Location RT (309–317)
Author Location RT (309–317)
Epitope ILKEPVHGV
Epitope name RT-IV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type Chromium-release assay
Keywords binding affinity, TCR usage, characterizing CD8+ T cells
References Yang *et al.* 2003b

- Killing efficiency of CTLs and their ability to suppress viral replication is shown to depend more on epitope specificity than to antigenic avidity. Different clones recognizing the same epitope had similar killing efficiency despite their variation in avidity. Nef specific CTL clones tended to be most inhibitory, followed by Gag, then by RT specific clones, regardless of avidity.
- 2/14 CTL T-cell clones tested were specific for RT/IV9. Under conditions of excess peptide (100ug/ml), there was no difference in their lytic potential; all possessed similar effector capacity. Avidity was measured as the sensitizing dose of peptide required for 50% of maximal killing (SD50), which varied from 20 pg/ml to 100 ng/ml, over four orders of magnitude for all 14 epitopes. The SD50 values for the two RT/IV9 clones were very different, 50 and 20,000 pg/ml.

HXB2 Location RT (309–317)
Author Location (B consensus)
Epitope ILKEPVHGV
Epitope name IV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A02, A03, B08, B62, Cw10, Cw7
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells

CTL CD8+

References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location RT (309–317)
Author Location RT (309–317)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type Chromium-release assay
Keywords assay standardization/improvement
References Lubong *et al.* 2004

- Using IL7 or IL15 in culturing of HIV-1-specific CTL clones was inferior to using IL-2 alone; the addition of these cytokines to IL-2 did not show any advantage. Neither proliferation, survival, nor lytic capacity of HIV-1-specific CTLs was significantly enhanced by addition of IL7 or IL15.

HXB2 Location RT (309–317)
Author Location Pol
Epitope ILKEPVHGV
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A2)
Donor MHC A*02, A*30, B*15, B*4402
Assay type Tetramer binding, T-cell Elispot
Keywords HIV exposed persistently seronegative (HEPS)
References Missale *et al.* 2004

- HIV-specific T-cell response was tested in patients exposed to blood from a patient with highly replicating HIV; these patients were nosocomially infected with HBV, but uninfected with HIV. HIV-specific T-cell responses were directed to structural and non-structural HIV proteins in 2 patients, suggesting that the virus replicated in these patients sufficiently to prime a cell-mediated immune response that protected them from HIV infection.
- This patient responded to 4/8 HIV epitopes tested in an IFNgamma EliSpot assay or tetramer assay. Responses were detected 8 and 28 weeks after exposure. A response to ILKEPVHGV was detected by both assays.

HXB2 Location RT (309–317)
Author Location Pol
Epitope ILKEPVHGV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United Kingdom
Assay type Tetramer binding, T-cell Elispot, Intracellular cytokine staining
Keywords rate of progression, acute/early infection, characterizing CD8+ T cells, immune dysfunction
References Papagno *et al.* 2004

- Acute HIV-1 infection induces massive activation of HIV-specific and non-HIV-specific CD8+ T-cells resulting in differentiation of these cells. High differentiation of CD8+ T-cells is correlated with disease progression. Differentiation is a natural process but it can be driven by elevated immune activation, such as in HIV infection.

HXB2 Location RT (309–317)
Author Location (309–317)
Epitope ILKEPVHGV
Epitope name RT2
Immunogen vaccine
Vector/Type: bacteriophage coat protein, dihydrolipoyl acetyltransferase E2 protein, of Bacillus stearothermophilus *HIV component:* RT
Species (MHC) transgenic mouse (A2)
Assay type Chromium-release assay
Keywords vaccine antigen design
References De Berardinis *et al.* 2003

- An RT T-helper (KDSWTVNDIQKLVGK) that can be promiscuously presented by multiple HLA-DR molecules, and an RT CTL epitope (ILKEPVHGV) presented by HLA-A2, were displayed using two different antigen presentation systems, bacteriophage virions or E2 protein scaffolds. Both systems enabled display of the epitopes in a mouse model system to the immune system. CTL responses were detected in immunized mice, and were processed correctly for both class I and class II presentation.

HXB2 Location RT (309–317)
Author Location Pol
Epitope ILKEPVHGV
Epitope name IV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Two escape mutations, at positions 3 ilRepvhgv, and 9 ilkepvhgA, were found not to correspond to the most polymorphic residues in the epitope.

HXB2 Location RT (309–317)
Author Location RT (309–317)
Epitope ILKEPVHGV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States

Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords acute/early infection, optimal epitope
References Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection.
- ILKEPVHGV was targeted in 54% of 74 A2+ chronically infected individuals, but only 1/14 acutely infected A2+ individuals.

HXB2 Location RT (309–317)
Author Location
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, variant cross-recognition or cross-neutralization, optimal epitope
References Harrer *et al.* 2005

- An HLA-B13-restricted optimal epitope was defined in Nef, RI9. The frequency of CTLs specific for this epitope in B13-positive patients exceeded the number of CTLs against other epitopes, indicating that this is a dominant epitope in B13-positive subjects. Three B13-positive patients who had an immunodominant response to this epitope were good controllers of their infection, with low viral loads over long periods.
- 5 HLA A2+ B13+ patients were found to make an immunodominant response to the B13 epitope RI9. 0/5 recognized the A2 epitope ILKEPVHGV, and only 1/5 recognized the A2 epitope SLYNTAVTL, with a much lower frequency than the B13 response.

HXB2 Location RT (309–317)
Author Location Pol (476–484 BRU)
Epitope ILKEPVHGV
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 2/9 CRF02_AG-infected Ivorians, and 1/9 B-infected French subjects.

HXB2 Location RT (309–317)
Author Location RT (77–85)
Epitope ILKEPVHGV
Epitope name IL9
Subtype B
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A2)
Country Canada
Assay type CD8 T-cell Elispot - IFNγ
Keywords HIV exposed persistently seronegative (HEPS), immunodominance, genital and mucosal immunity, characterizing CD8+ T cells
References Makedonas *et al.* 2005

- CD8 T-cell responses were studied in individuals who remained seronegative in spite of being mucosally (group 1) or intravenously (group 2) exposed to HIV-1. A similar proportion of subjects from each group recognized at least 1 HIV peptide, and they recognized peptides with similar cumulative intensity. The proportion of responding individuals in both groups was significantly greater than in a low-risk, negative control group. One exposed uninfected subject recognized 7 epitopes.
- HLA-A*0201 epitopes that are immunodominant in chronically infected individuals were rarely stimulatory in exposed uninfected individuals. SLYNTVATL was recognized by one HLA A2+ individual in each group (1/11 vs 1/5), while none of the exposed uninfected individuals tested responded to ILKEPVHGV. In contrast, chronically infected subjects recognized these epitopes at a frequency of 69% and 31%, respectively.

HXB2 Location RT (309–317)
Author Location RT (476–484)
Epitope ILKEPVHGV
Epitope name IV9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Germany
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords HAART, ART, TCR usage, characterizing CD8+ T cells, optimal epitope
References Schmitt-Haendle *et al.* 2005

- CTL responses to 3 HLA-A2-restricted epitopes were investigated in 51 HIV-1 infected HLA-A2+ individuals. The most prevalent response was seen for IV9, followed by SL9. The VL9 epitope was not recognized. There was a significant correlation of CTL activity to the CD8 counts in peripheral blood, but no correlation to CD4 counts, viral load, or antiviral therapy.
- 37.3% of the individuals recognized ILKEPVHGV.
- All analyzed mutations for RT-IV9 epitope could decrease or abrogate CTL recognition dependent on the CTL clones tested, but all were fully immunogenic for other CTL clones. The ilkDpvhgv, ilkepvhEv, Rlkepvhgv and ilRepvhgv variants were tested.

HXB2 Location RT (309–317)
Author Location RT
Epitope ILKEPVHGV
Epitope name A2-IV9(RT)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins

CTL CD8+

References Altfeld *et al.* 2006
- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (309–317)
Author Location
Epitope ILKEPVHGV
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a
- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location RT (309–317)
Author Location
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining
Keywords responses in children, rate of progression
References Chakraborty *et al.* 2005
- A study of long-term surviving children in Kenya revealed CD8 T-cell responses in all progression groups. The most striking atttribute of long term surviving children was strong CD4 T-cell responses, which may be significant in delaying disease progression.
- Response detected in 1 LTNP child and 1 early non-progressive child.

HXB2 Location RT (309–317)
Author Location
Epitope ILKEPVHGV
Epitope name Pol 476
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords immunodominance
References Thorn *et al.* 2007
- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Immunodominant control epitope Pol 476, ILKEPVHGV, was found in 9 patients but only 4 had CTL immune responses to it.

HXB2 Location RT (309–317)
Author Location Pol
Epitope ILKEPVHGV
Epitope name Pol498
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008
- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- ILKEPVHGV is a Pol epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location RT (309–317)
Author Location RT (464–472)
Epitope ILKEPVHGV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Switzerland
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords HAART, ART
References Rehr *et al.* 2008
- By following T-cell function in ART-regimented patients over time, it was shown that ART resulted in reduced viral replication and the restoration of CTLs to polyfunctionality. It is concluded that in vivo antigenic exposure during declining viremia has a positive influence on CTL function.

- Epitope ILKEPVHGV was used to interrogate CTL function in 37 chronically infected HIV-1 positive subjects, with respect to cytokine production.

HXB2 Location RT (309–317)
Author Location RT
Epitope `ILKEPVHGV`
Epitope name IV9(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A2-restricted epitope ILKEPVHGV elicited an immune response in Chinese HIV-1 positive subjects as part of peptide ELAENREILKEPVHGVYY.
- 5 of the 55 HLA-A2 carriers responded to ILKEPVHGV-containing peptide with average magnitude of CTL response of 189 SFC/million PBMC (author communication and Fig.1).

HXB2 Location RT (309–317)
Author Location Pol (476–)
Epitope `ILKEPVHGV`
Epitope name Pol476
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- DK1 responded to HLA-A02-restricted Pol control epitope ILKEPVHGV. ILKEPVHGV also elicited response in a cohort of 11 other HIV-1 + HLA-A2+ patients.

HXB2 Location RT (309–317)
Author Location RT (309–317)
Epitope `ILKEPVHGV`
Epitope name IV9
Subtype B
Immunogen vaccine, in vitro stimulation or selection
Vector/Type: peptide *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords variant cross-recognition or cross-neutralization
References Blondelle *et al.* 2008

- To identify immunogenically optimized peptide epitopes for use in vaccines, two strategies were used. The first studied rare mutant epitopes that were effective in generating a cross-reactive immune response against a range of mutants. The second method was to use a synthetic combinatorial library of peptides and screen for highly effective responses against one epitope (TV9, TLNAWVKVV) and its mutants. Candidate epitopes were tested in HLA-A2 transgenic mice as well as ex vivo human lymphocytes.
- Mutants of epitope IV9 when tested in transgenic mice, showed that the consensus was strongly immunogenic, but the most common mutant, ILKdPVHGV was not especially immunogenic or cross-reactive. Rare mutant, ILKEPVHrV, was highly immunogenic, and cross-reactive to the consensus. Sequences ILrEPiHGV and ILKEPVHGi were also cross-reactive to the consensus. Other mutants were ILKEPVHGa, ILrtPVHGV, IiKEPVHGV, ILrkPVHeV and ILKdPVHkV.

HXB2 Location RT (309–317)
Author Location Pol (476–484)
Epitope `ILKEPVHGV`
Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind three of the five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802).

HXB2 Location RT (309–317)
Author Location Pol
Epitope `ILKEPVHGV`
Epitope name Pol498
Subtype A, B, C, D
Immunogen HIV-1 infection
Species (MHC) human, mouse (A2 supertype)

CTL CD8+

Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope ILKEPVHGV of the HLA-A2 supertype bound most strongly to HLA-A*0203, -A*6802, -A*0201 and also to -A*0202, but not to -A*0206. It was conserved 25% in subtype A, 79% in B, 88% in C and 50% in subtype D. 7/22 HLA-A2 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Pol498.

HXB2 Location RT (309–317)
Author Location Pol (464–472)
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human (A*0201, A2)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location RT (309–317)
Author Location Pol (subtype B)
Epitope ILKEPVHGV
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A*0202, A2)
Keywords subtype comparisons
References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among B and D clade viruses.
- Clade A version of the epitope, ILKDPVHGV, was preferentially recognized by CTL.

HXB2 Location RT (309–317)
Author Location RT (476–484 LAI)
Epitope ILKEPVHGV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0201
Keywords HAART, ART, responses in children
References Luzuriaga *et al.* 2000

- Longitudinal study of 8 infants with prolonged viral suppression due to combination antiretroviral therapy showed no HIV-1 specific CTL responses in peripheral blood cells. 6/8 were studied using a Chromium release assay and no response was detected using Gag expressed in vaccinia in the target cells. Three HLA-A*0201 children were tested using SLYNTVATL or ILKEPVHGV HLA A*0201 tetramers and again no HIV-specific response was detected, either using PBMC specimens, or PBMC which had been stimulated *in vitro* for a week.
- In contrast, one of the children with suppressed HIV viral replication who was co-infected with HIV and EBV, while HIV-tetramer negative, had EBV-tetramer staining cells at a frequency of 0.14% in the PBMC.

HXB2 Location RT (309–317)
Author Location
Epitope ILKEPVHGV
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords binding affinity, acute/early infection
References Lichterfeld *et al.* 2007b

- Differences in early versus chronic AIDS include a decline in CTL number accompanied by a reducing viremia. Comparative analysis of such CTLs in this study show that early infection is characterized by a different clonotypic composition and higher functional avidity of CTLs followed by their selective depletion during transition to chronic disease. The total magnitude of CTL cytokine production is lower in early infection. Intraindividual, early CTLs' functional avidity for the same epitope decreases concomitantly with a reduction in clonotypic TCR repertoire especially of strongly activated and CD127lo, CD38+, Ki-67hi CTLs while progressing to chronic infection states.
- None of the target epitopes, including this epitope ILKEPVHGV seen in 1 patient, underwent sequence changes.

HXB2 Location RT (309–317)
Author Location Pol
Epitope ILKEPVHGV
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.

- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- Epitope ILKEPVHGV was unable to elicit cross-clade recognition. It is predicted to be restricted by HLA supertype A2. It was recognized by at least 4 patients with restricting HLA supertype who were infected with different HIV subtypes.

HXB2 Location RT (309–318)
Author Location Pol
Epitope ILKEPVHGVY
Epitope name 1249
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A02, A30, B39; A02, A03, B44, Cw05, Cw07; A02, A30, B35, B49, Cw04, Cw07
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for ILKEPVHGVY: 96% Promiscuous epitope binding to A02 and Bw62.

HXB2 Location RT (309–318)
Author Location RT (309–318)
Epitope ILKEPVHGVY
Epitope name IY10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*15)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLAs-B*15-associated substitution within optimally defined epitope ILKEPVHGVY is at position V9, ILKEPVHGvY.

HXB2 Location RT (309–318)
Author Location RT (476–485 LAI)
Epitope ILKEPVHGVY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1501)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*1501 epitope.

HXB2 Location RT (309–318)
Author Location RT (309–317)
Epitope ILKEPVHGVY
Immunogen HIV-1 infection
Species (MHC) human (B15)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these eptiopes, but this increased over time.

HXB2 Location RT (309–318)
Author Location RT
Epitope IKLEPVHGVY
Epitope name B15-IY10(RT)
Immunogen HIV-1 infection
Species (MHC) human (B15)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.

- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (309–318)
Author Location RT
Epitope ILKEPVHGVY
Epitope name IY10(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B15)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B15-restricted epitope ILKEPVHGVY elicited an immune response in Chinese HIV-1 positive subjects as part of peptide ELAENREILKEPVHGVYY.
- 4 of the 21 HLA-B15 carriers responded to ILKEPVHGVY-containing peptide with average magnitude of CTL response of 410 SFC/million PBMC (author communication and Fig.1).

HXB2 Location RT (309–318)
Author Location RT (476–485 LAI)
Epitope ILKEPVHGVY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62)
Keywords review
References McMichael & Walker 1994; Menendez-Arias *et al.* 1998

- Review of HIV CTL epitopes.

HXB2 Location RT (309–318)
Author Location RT (309–318)
Epitope IKLEPVHGVY
Immunogen HIV-1 infection
Species (MHC) human (B62)
Keywords immunodominance
References Day *et al.* 2001

- No immunodominant responses were detected to four B62-restricted epitopes tested.

HXB2 Location RT (309–318)
Author Location Pol
Epitope ILKEPVHGVY
Subtype A, B, D
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human (B62)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location RT (317–325)
Author Location Pol (484–492)
Epitope VYYDPSKDL
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (A24)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance, characterizing CD8+ T cells
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 1/9 CRF02_AG-infected Ivorians, and 0/9 B-infected French subjects.

HXB2 Location RT (317–326)
Author Location
Epitope VYYDPSKDIA
Subtype C
Immunogen vaccine
Vector/Type: DNA, DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* C clade Du422, C clade Du151 *HIV component:* Gag, gp160 deletions, Nef, RT, Tat
Species (MHC) mouse (H-2^{kd})
Country South Africa

Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, Th1
References Shephard *et al.* 2008

- A DNA (SAAVI DNA-C) and MVA (SAAVI MVA-C) vaccines vaccines were tested in BALB/c mice. Combining the vaccines in a DNA prime and MVA boost regimen increased the cumulative peptide response compared to the DNA vaccine alone 10-fold.
- Th1 cytokine IFN-γ and TNF-α levels from HIV-specific CD8 and CD4 T cells increased 20- and 8- fold respectively, with a SAAVI MVA-C boost.
- Effector and effector memory RT- and Env-epsific memory CD8 T cell subsets were boosted after MVA immunizations.
- CD8 epitope VYYDPSKDIA was used for detection of IFN-γ-secreting cells.

HXB2 Location RT (317–326)
Author Location RT Pol
Epitope VYYDPSKDLI
Epitope name RT2
Subtype A, B, C
Immunogen vaccine
Vector/Type: DNA with CMV promotor, modified vaccinia Ankara (MVA), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade, B clade, C clade Du422, Other *HIV component:* Gag, Nef, RT
Species (MHC) mouse (H-2K^{d})
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords subtype comparisons, vaccine-induced epitopes, variant cross-recognition or cross-neutralization, antagonism
References Larke *et al.* 2007

- Cross-clade vaccine recognition was studied using either single-, multi or several anatomically separated single-clade vaccines. Limited cross-clade response was seen with single-clade administrations. Multi-clade vaccines gave immune interference (antagonism and original antigenic sin), reducing CTL response. Simultaneously administered but anatomically separated vaccines from clades A, B, C decreased antagonism and increased immune responses.
- After immunization with any clade vaccine, index epitope RT2, VYYDPSKDLI, was recognized, as well as 2 variants at >70% levels, viz. VYYDPSKDLv and VYYDPtKDLI. Variants VYYDPSKeLI, aYYDPSKeLI, VYYePSKeLI were not recognized.

HXB2 Location RT (328–352)
Author Location RT (495–515 LAI)
Epitope EIQKQGQGQWTYQIYQEPFKNLKTG
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
References Menendez-Arias *et al.* 1998; Walker *et al.* 1989

- One of five epitopes defined for RT-specific CTL clones in this study.

HXB2 Location RT (330–344)
Author Location
Epitope QKQGQGQWTYQIYQE
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A*2501, A*3002; B*0702, B*1801
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location RT (333–341)
Author Location Pol (488–496)
Epitope GQGQWTYQI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*13)
Donor MHC A*0301, A*3001, B*1301, B*1402, Cw*0602, Cw*0802
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords epitope processing, immune evasion, viral fitness and reversion, HLA associated polymorphism
References Honeyborne *et al.* 2007

- To determine whether HLA-B*13-restricted CTL responses could partially explain low viremic loads in patients, a cohort of chronic C-clade infected subjects was studied. 6 novel B*13-restricted CTL epitopes were defined from both C- and B-clade viruses, 3 of which were within Gag. B*13-restricted CTL responses correlated with lower viremia, with most immunity targeted against Gag epitopes (p15, p17, p24). Gag epitope escape variants may exact a high viral fitness cost, mutations being seen within and around the optimal epitope.

HXB2 Location RT (333–341)
Author Location
Epitope GQGQWTYQI
Epitope name GI9
Immunogen

CTL CD8+

Species (MHC) human (B13)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B13 epitope.

HXB2 Location RT (333–341)
Author Location RT
Epitope GQGQWTYQI
Epitope name GI9(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B13)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B13-restricted epitope GQGQWTYQI elicited an immune response in Chinese HIV-1 positive subjects as part of peptide GQGQWTYQIYQEPFKNLK.
- >2 of the 29 HLA-B13 carriers responded to GQGQWTYQI-containing peptide with average magnitude of CTL response of 160 SFC/million PBMC (author communication and Fig.1).

HXB2 Location RT (340–350)
Author Location Pol (487–497 93TH253 subtype CRF01)
Epitope QIYQEPFKNLK
Epitope name P495-505
Subtype CRF01_AE
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A11)
Keywords HIV exposed persistently seronegative (HEPS)
References Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was weakly reactive in the HEPS study subject 128 who was HLA A11/A33.
- This epitope was reactive in HIV+ study subjects 053 and 184 who carried HLA-A11.

HXB2 Location RT (340–350)
Author Location Pol (487–497 93TH253 subtype CRF01)
Epitope QIYQEPFKNLK
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords subtype comparisons
References Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This epitope was not predicted by the EpiMatrix method to be likely to bind to A11, though it served as an epitope in the FSWs, and it was one of the six A11 epitopes that had been previously defined.
- 5/8 tested FSWs recognized this epitope.
- This epitope was highly conserved in other subtypes, although exact matches were not very common.

HXB2 Location RT (340–350)
Author Location RT (507–516)
Epitope QIYQEPFKNLK
Immunogen HIV-1 infection
Species (MHC) human
References Menendez-Arias *et al.* 1998; Price *et al.* 1995

- Study of cytokines released by HIV-1 specific activated CTL.

HXB2 Location RT (340–352)
Author Location RT (507–519 LAI)
Epitope QIYQEPFKNLKTG
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords review
References Johnson & Walker 1994; Menendez-Arias *et al.* 1998

- This epitope was listed in a review.

HXB2 Location RT (340–352)
Author Location Pol (495–507)
Epitope QIYQEPFKNLKTG
Immunogen HIV-1 infection
Species (MHC) human (A11)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location RT (341–349)
Author Location (C consensus)
Epitope IYQEPFKNL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location RT (341–349)
Author Location (C consensus)
Epitope IYQEPFKNL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- IYQEPFKNL is an optimal epitope for both A*2301 and A*2402.

HXB2 Location RT (341–349)
Author Location
Epitope IYQEPFKNL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2301, A*2402)
Donor MHC A*2301, B*0801, B*1510, Cw*0701, Cw*1601
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- Known epitope IYQEPFKNLK is HLA_A*2301 and -A*2402-restricted. Response to a peptide containing this epitope was detected in a rapid progressor 12 weeks post-infection.

HXB2 Location RT (341–349)
Author Location (C consensus)
Epitope IYQEPFKNL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- IYQEPFKNL is an optimal epitope for both A*2301 and A*2402.

HXB2 Location RT (341–350)
Author Location RT (341–350)
Epitope IYQEPFKNLK
Epitope name IK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*11)
Country Australia, Canada, Germany, United States
Keywords escape, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLAs-A*11-associated substitution within optimally defined epitope IYQEPFKNLK is at position P5, IYQEpFKNLK. IK10 has a low recognition frequency and escaped once, very early post-infection.

HXB2 Location RT (341–350)
Author Location RT (508–516)
Epitope IYQEPFKNLK
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
References Culmann 1998

- C. Brander notes that this is an A*1101 epitope in the 1999 database.

HXB2 Location RT (341–350)
Author Location RT (508–517 LAI)
Epitope IYQEPFKNLK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*1101 epitope.

CTL CD8+

HXB2 Location RT (341–350)
Author Location (C consensus)
Epitope IYQEPFKNLK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- IYQEPFKNLK is an optimal epitope.

HXB2 Location RT (341–350)
Author Location RT (508–517 SF2)
Epitope IYQEPFKNLK
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A11+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 0/0 group 2, and 1/2 group 3.

HXB2 Location RT (341–350)
Author Location Pol (508–516)
Epitope IYQEPFKNLK
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A11)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location RT (341–350)
Author Location Pol (497–506)
Epitope IYQEPFKNLK
Epitope name IK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords optimal epitope
References Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- This epitope did not vary.

HXB2 Location RT (341–350)
Author Location Pol (497–506)
Epitope IYQEPFKNLK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location RT (341–350)
Author Location RT
Epitope IYQEPFKNLK
Epitope name IK10(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A11-restricted epitope IYQEPFKNLK elicited an immune response in Chinese HIV-1 positive subjects as part of peptide GQGQWTYQIYQEPFKNLK.

- 6 of the 28 HLA-A11 carriers responded to IYQEPFKNLK-containing peptide with average magnitude of CTL response of 316 SFC/million PBMC (author communication and Fig.1).

HXB2 Location RT (346–354)
Author Location Pol (501–508)
Epitope FKNLKTGKY
Subtype B
Immunogen HIV-1 infection, peptide-HLA interaction
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance
References Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, FKNLKTGKY, is similar to human protein Str Spe Recognition protein, sequence FKNsKTG.

HXB2 Location RT (349–366)
Author Location (C consensus)
Epitope LKTGKYAKMRTAHTNDVK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0602)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location RT (356–365)
Author Location
Epitope RMRGAHTNDV
Epitope name Pol-RV10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Donor MHC A*2904, A*3002, B*1503, B*5802, Cw*0202, Cw*0602
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Subject 01RCH50 also recognized the epitope WRFDSRLAF, Nef(183-191), B*1503.
- Among HIV+ individuals who carried HLA A30, 5/16 (31%) recognized this epitope.

HXB2 Location RT (356–365)
Author Location RT (356–365)
Epitope RMRGAHTNDV
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location RT (356–365)
Author Location RT
Epitope RMRGAHTNDV
Epitope name RV10(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A30)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A30-restricted epitope RMRGAHTNDV elicited an immune response in Chinese HIV-1 positive subjects LKTGKYARMRGAHTNDVK.
- 1 of the 15 HLA-A30 carriers responded to RMRGAHTNDV-containing peptide with average magnitude of CTL response of 90 SFC/million PBMC (author communication and Fig.1).

HXB2 Location RT (356–366)
Author Location RT (356–366)
Epitope RMRGAHTNDVK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location RT (356–366)
Author Location RT (15–26)
Epitope RMRGAHTNDVK
Epitope name A3-RK11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)

Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 5/7 individuals began to have detectable responses to this epitope after STI.

HXB2 Location RT (356–366)
Author Location RT (356–366)
Epitope RTRGAHTNDVK
Epitope name A3-RK11 Pol
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), escape, early treatment, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The second infecting strain had the variant rtrgahtndvR. The CTL response to both variants declined over time, and the response to the second variant was lower than to the first throughout.

HXB2 Location RT (356–366)
Author Location (B consensus)
Epitope RMRGAHTNDVK
Epitope name RK11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A02, A03, B08, B62, Cw10, Cw7
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location RT (356–366)
Author Location Pol (512–522)
Epitope RMRGAHTNDVK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location RT (356–366)
Author Location RT
Epitope RMRGAHTNDVK
Epitope name A3-RK11(RT)
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (356–366)
Author Location RT
Epitope RMRGAHTNDVK
Epitope name RK11(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A3-restricted epitope RMRGAHTNDVK elicited no immune response in Chinese HIV-1 positive subjects as part of peptide LKTGKYARMRGAHTNDVK.
- Although the tested peptide sequence contains the exact sequence of a previously described HLA-A3 optimal epitope, RMRGAHTNDVK, none of the 3 HLA-A3 carriers responded to it (author communication and Fig.1).

HXB2 Location RT (364–372)
Author Location RT (518–526 U455)
Epitope DVKQLTEVV
Immunogen
Species (MHC) human (A*6802, A28)
Keywords subtype comparisons
References Dong 1998; Menendez-Arias *et al.* 1998

- Predicted on binding motif, no truncations analyzed.
- Reacts with clade A consensus (U455), and with the peptide DVKQLAEAV, from the D clade.

HXB2 Location RT (364–372)
Author Location RT (470–478 subtype A)
Epitope DVKQLTEVV
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (B70)
Keywords subtype comparisons
References Dorrell *et al.* 1999

- CTL responses in three individuals with non-clade B infections were studied, 2 with subtype A infections, 1 with subtype C – their infections all originated in East Africa.
- This CTL response was defined in a patient with an A subtype infection.
- Bulk cultures from this patient gave a CTL response that could recognize the subtype D form of this epitope, with two substitutions (DVKQLAEAV), though a CTL line from these cultures didn't recognize the B clade variant (DVKQLTEAV)

HXB2 Location RT (366–385)
Author Location Pol (521–540)
Epitope KQLTEAVOKIAMESIVIWGK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location RT (367–375)
Author Location Pol
Epitope QLTEAVQKI
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- Epitope QLTEAVQKI is predicted to be restricted by HLA supertype A2. It was recognized by at least 4 patients with restricting HLA supertype who were infected with several different HIV subtypes.

HXB2 Location RT (370–384)
Author Location Pol (525–539)
Epitope EAVQKIATESIVIWG
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Supresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the Progressor, who had I530V, A531T, V536I substitutions.

CTL CD8+

HXB2 Location RT (373–390)
Author Location RT (373–390 HXB2)
Epitope QKIATESIVIWGKTPKFK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 21% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location RT (373–390)
Author Location Pol
Epitope QKIATESIVIWGKTPKFK
Epitope name POL-72
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, QKIAtESIVIWGKTPKFk differs from the consensus C sequence QKIAmESIVIWGKTPKFr at 2 amino acid positions, i.e. by 10.5%.

HXB2 Location RT (373–390)
Author Location RT
Epitope QKIATESIVIWGKTPKFK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, QKIATESIVIWGKTPKFK, had an overall frequency of recognition of 16% - 22% AA, 15.4% C, 9.1% H, 14.3% WI.

HXB2 Location RT (374–383)
Author Location
Epitope KITTESIVIW
Epitope name KW10
Immunogen HIV-1 infection
Species (MHC) human (B*57)

CTL CD8+

Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B*57-restricted optimal epitope KITTESIVIW was tested for immune response.

HXB2 Location RT (374–383)
Author Location RT (374–383)
Epitope KIATESIVIW
Epitope name KW10
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CTL suppression of replication
Keywords class I down-regulation by Nef
References Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Late protein RT epitope KIATESIVIW-recognizing CTLs were affected by Nef.

HXB2 Location RT (374–383)
Author Location RT
Epitope KITTESIVIW
Epitope name rtKW9
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country United Kingdom, Kenya
Assay type CD8 T-cell Elispot - IFNγ
Keywords TCR usage, structure, characterizing CD8+ T cells
References Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B*57-peptide complexes were studied.
- In addition, immunodominancy of the previously mapped B*57 epitopes during chronic infection was assessed. KGFNPEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

HXB2 Location RT (374–383)
Author Location RT (LAI)
Epitope KITTESIVIW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords rate of progression
References Menendez-Arias *et al.* 1998; van der Burg *et al.* 1997

- Patients studied were from the Amsterdam cohort.
- CTL epitopes of 3 rapid progressors were compared to 4 long-term survivors (LTS); no differences could be found in the degree of conservation between them.
- Epitope recognized by LTS and by a progressor.

HXB2 Location RT (374–383)
Author Location RT (LAI)
Epitope KITTESIVIW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
References van der Burg *et al.* 1997

- Recognized by CTL from a progressor and a long-term survivor, PIVLPEKDSW was also recognized.

HXB2 Location RT (374–383)
Author Location RT Pol (529–538)
Epitope KITTESIVIW
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 7 patients recognized this epitope.

HXB2 Location RT (374–388)
Author Location Pol (529–543)
Epitope KIATESIVIWGKTPK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.

- This epitope elicited IFN-γ response in the Progressor, who had I530V, A531T, V536I, T541I substitutions. The ES had K540R, T541I substitutions.

HXB2 Location RT (375–383)
Author Location RT (375–383 LAI)
Epitope ITTESIVIW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701, B*5801)
Keywords rate of progression
References Klein *et al.* 1998

- Another patient recognized the ten-mer version of this epitope, KITTESIVIW van der Burg *et al.* [1997]
- B57 has been associated with long-term non-progression in the Amsterdam cohort.
- The most pronounced CTL responses in HLA B*5701 LTS were to RT and Gag.
- The patient that recognized ITTESIVIW also recognized IVLPEKDSW.

HXB2 Location RT (375–383)
Author Location (C consensus)
Epitope IAMESIVIW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5703)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- IAMESIVIW is an optimal epitope for both B*5801 and B*5703

HXB2 Location RT (375–383)
Author Location RT (375–383)
Epitope IAMESIVIW
Epitope name IW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*58)
Country Australia, Canada, Germany, United States
Keywords escape, viral fitness and reversion, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- Escape (and reversion) rates for B*57-restricted epitopes were highest for Gag-TW10 (TSTLQEQIGW) > RT-IW9 (IVLPEKDSW) > Nef-YY9 (YTPGPGIRY) > Nef-HW9 (HTQGYFPDW) > Gag-IW9 (ISPRTLNAW) > Gag-KF11 (KAFSPEVIPMF) .
- HLAs-B*58-associated substitutions within optimally defined epitope IAMESIVIW are at positions A2 and S5, IaMEsIVIW.

HXB2 Location RT (375–383)
Author Location RT (375–383)
Epitope IAMESIVIW
Immunogen
Species (MHC) human (B*5801)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location RT (375–383)
Author Location (C consensus)
Epitope IAMESIVIW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the S5 residue of IAMESIVIW are associated with the presence of the HLA presenting molecule in the host.
- IAMESIVIW is an optimal epitope for both B*5801 and B*5703

HXB2 Location RT (375–383)
Author Location (C consensus)
Epitope IAMESIVIW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*57, B*5801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords cross-presentation by different HLA, characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.

- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location RT (375–383)
Author Location RT (375–383 SF2)
Epitope ITTESIVIW
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with preseroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B57+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/0 group 2, and 1/2 group 3.

HXB2 Location RT (375–383)
Author Location Pol
Epitope IATESIVIW
Epitope name IW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- IW9(Pol), IATESIVIW, is a novel HLA-B57-restricted epitope that elicits a CTL IFN-gamma response in the same range as Los Alamos database peptides.

HXB2 Location RT (375–383)
Author Location RT
Epitope IATESIVIW
Epitope name IW9(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- IATESIVIW, elicited an immune response in Chinese HIV-1 positive subjects as a part of peptide QKIATESIVIWGK-TPKFK. This epitope differs from the previously described HLA-B58-restricted epitope IAMESIVIW, at 1 residue, IAtESIVIW.
- 8 of the 14 HLA-B58 carriers responded to IAtESIVIW-containing peptide with average magnitude of CTL response of 455 SFC/million PBMC (author communication and Fig.1).

HXB2 Location RT (390–398)
Author Location Pol
Epitope KLPIWKETW
Epitope name KW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- KW9, KLPIWKETW, is a novel HLA-B57-restricted epitope that elicits a CTL IFN-gamma response in the same range as Los Alamos database peptides.

HXB2 Location RT (390–404)
Author Location RT (545–559)
Epitope KLPIQKETWEAWWTE
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate

Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008

- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.
- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.
- CTL immune response to consensus sequence KLPIQKETWEAWWTE was elicited in subject 00016. Consensus epitope of subjects was rLPIQKETWEAWWmE.

HXB2 Location RT (392–401)
Author Location RT (559–568 LAI)
Epitope PIQKETWETW
Subtype B
Immunogen
Species (MHC) human (A*3201)
References Harrer *et al.* 1996b; Menendez-Arias *et al.* 1998

- Reviewed in Menendez-Arias *et al.* [1998], suggest the epitope is HLA B53/Cw2.
- C. Brander notes that this is an A*3201 epitope in the 1999 database.

HXB2 Location RT (392–401)
Author Location RT (559–568 LAI)
Epitope PIQKETWETW
Subtype B
Immunogen
Species (MHC) human (A*3201)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*3201 epitope.

HXB2 Location RT (392–401)
Author Location
Epitope PIQKETWETW
Epitope name Pol-PW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*3201)
Donor MHC 01RCH59: A*0201, A*3201, B*4002, B*5301, Cw*0202, Cw*0401
Keywords HAART, ART
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previou.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated.
- Subject 01RCH59 was Hispanic, was not on HAART, viral load 5100, CD4 count 349, and she also recognized QASQEVKNW, p24(176-184), B*5301.
- Among HIV+ individuals who carried HLA A32, 1/2 (50%) recognized this epitope.

HXB2 Location RT (392–401)
Author Location RT (559–568 SF2)
Epitope PIQKETWETW
Immunogen HIV-1 infection
Species (MHC) human (A32)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A32+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 1/1 group 2, and 0/0 group 3.

HXB2 Location RT (392–401)
Author Location RT
Epitope PIQKETWETW
Epitope name A32-PW10(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A32)
Donor MHC A32, B14, B7; A32, B44; A30, A32, B18, B27
Keywords HAART, ART, supervised treatment interruptions (STI)
References Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (`http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html`) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope

responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient A displayed the greatest response to epitope B14-EL9(gp41), a strong response to B7-TL9(p24), and responses to B7-TM9(Nef) and A32-PW10(RT). Patient B displayed the greatest response to epitope B44-AW11(p24) and also responded to A32-PW10(RT) in both PB and LN samples, while a third response against epitope A32-RW10(gp120) was only detected in the LN sample. Patient D displayed the greatest response to B27-KK10 (p24), and also responded to A30-RY11(p17), A32-PW10(RT), A30-KY11(RT), A32-RW10(gp120), and B18-YY9(Nef).

HXB2 Location RT (392–401)
Author Location
Epitope PIQKETWETW
Immunogen HIV-1 infection
Species (MHC) human (A32)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006
- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope PIQKETWETW elicited a magnitude of response of 88 SFC with a functional avidity of 1nM.

HXB2 Location RT (392–401)
Author Location
Epitope PIQKETWETW
Immunogen HIV-1 infection
Species (MHC) human (A32)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b
- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (A32), an additional HLA (A24) was statistically predicted to be associated with this epitope.

HXB2 Location RT (392–401)
Author Location RT
Epitope PIQKETWEAW
Epitope name PW10(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008
- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope PIQKETWEAW elicited an immune response in Chinese HIV-1 positive subjects as part of peptide FKLPIQKETWEAWWTEYW. This epitope differs from the previously described HLA-A32-restricted epitope, PIQKETWETW, at 1 residue, PIQKETWEaW.

HXB2 Location RT (397–406)
Author Location RT (LAI)
Epitope TWETWWTEYW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B44)
References Menendez-Arias *et al.* 1998; van der Burg *et al.* 1997
- Recognized by CTL from two progressors, EILKEPVGHGV and EELRQHLLRW were also recognized by one, and RETKLGKAGY was also recognized by the other.

HXB2 Location RT (397–406)
Author Location RT Pol (552–561)
Epitope TWETWWTEYW
Immunogen HIV-1 infection
Species (MHC) human (B44)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004
- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.

CTL CD8+

- Less than 2 of 11 patients recognized this epitope.

HXB2 Location RT (407–416)
Author Location (C consensus)
Epitope QATWIPEWEF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5702)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- QATWIPEWEF is an optimal epitope for both B*5702 and B*5703.

HXB2 Location RT (407–416)
Author Location RT
Epitope QATWIPEWEF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5702)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- QATWIPEWEF is a previously described HLA-B*5702-restricted epitope (part of Pol(RT) reacting peptide TDYWQATWIPeWEFVNTPPLV) that contains a B*5702-associated sequence polymorphism at residue E (QATWIPeWEF).

HXB2 Location RT (407–416)
Author Location (C consensus)
Epitope QATWIPEWEF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5703)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- QATWIPEWEF is an optimal epitope for both B*5702 and B*5703.

HXB2 Location RT (407–416)
Author Location (C consensus)
Epitope QATWIPEWEF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location RT (413–429)
Author Location (C consensus)
Epitope EWEFVNRPPLVKLWYQL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location RT (416–423)
Author Location Pol (571–)
Epitope FVNTPPLV
Epitope name Pol571
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.

- This peptide was a good A2 binder, and induced a CTL responses 1/6 transgenic mice. Responses to the peptide were not detected in 17 HIV+ HLA-A2 subjects.

HXB2 Location RT (416–423)
Author Location
Epitope FVNTPPLV
Epitope name Pol 571
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Pol 571 FVNTPPLV epitope was found in 10 patients but none had CTL immune responses to it. It was however targeted by an HLA-A2- patient.

HXB2 Location RT (416–424)
Author Location RT (416–424)
Epitope FVNTPPLVK
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope FVNTPPLVK was predicted to be restricted by HLA A*1101.

HXB2 Location RT (416–424)
Author Location Pol (563–571 93TH253 subtype CRF01)
Epitope FVNTPPLVK
Epitope name P571-579
Subtype CRF01_AE
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A11)
Keywords HIV exposed persistently seronegative (HEPS)
References Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was weakly reactive in the HEPS study subject 128 who was HLA A11/A33.

HXB2 Location RT (416–424)
Author Location Pol (563–571 93TH253 subtype CRF01)
Epitope FVNTPPLVK
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords subtype comparisons
References Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This is one of the new A11 epitopes identified through the streamlined EpiMatrix method, and 1/8 tested FSWs recognized it.
- This epitope was conserved many subtypes (but not subtype H), but exact matches were not very common.

HXB2 Location RT (416–425)
Author Location Pol
Epitope FVNTPPLVKL
Epitope name Pol1152
Subtype C
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Epitope FVNTPPLVKL elicits IFN-gamma ELISpot responses in 2/7 subjects; and bound HLA-B7 with low affinity in cell-based assays. Previously published HLA restrictions of this epitope include DRB1*0101, DRB1*0401, DRB1*0405, DRB1*0701, DRB1*0802, DRB1*0901, DRB1*1101,

CTL CD8+

DRB1*1302, DRB1*1501, DRB5*0101 (Immune Epitope Database).

HXB2 Location RT (419–429)
Author Location RT (419–429)
Epitope TPPLVKLWYQL
Epitope name TL11
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Other
Keywords supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism
References Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alelles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Statistically significant associations between numbers of HLA-8101 expressing subjects and epitope TPPLVKLWYQL were found.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope RT TL11 restriction.

HXB2 Location RT (421–429)
Author Location Pol
Epitope PLVKLWYQL
Epitope name P9L
Immunogen vaccine
Vector/Type: measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140ΔV3
Species (MHC) transgenic mouse (A*0201)
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells
References Lorin *et al.* 2005a

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

HXB2 Location RT (421–429)
Author Location RT (421–429)
Epitope PLVKLWYQL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope PLVKLWYQL was predicted to be restricted by HLA A*0201, A*0202 and A*0203.

HXB2 Location RT (421–429)
Author Location RT (421–429)
Epitope PLVKLWYQL
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Haas *et al.* 1998

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules.

HXB2 Location RT (428–445)
Author Location RT
Epitope QLEKEPIVGAETFYVDGA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV

sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, QLEKEPIVGAETFYVDGA, had an overall frequency of recognition of 15.3% - 22% AA, 11.5% C, 4.5% H, 23.8% WI.

HXB2 Location RT (432–440)
Author Location RT (587–597 SF2)
Epitope `EPIVGAETF`
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Keywords review
References Menendez-Arias *et al.* 1998; Tomiyama *et al.* 1997
- A CTL clone responsive to this epitope was obtained.
- 5/7 B35-positive individuals had a CTL response to this epitope.
- An E to D substitution at position 1, and V to I at position 4, reduces activity but not binding to B*3501.
- Menendez-Arias *et al.* [1998] note in their review that this epitope is near the protease cleavage site and conservation of this region is important for proper viral maturation.

HXB2 Location RT (432–440)
Author Location Pol (587–595)
Epitope `EPIVGAETF`
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
References Tomiyama *et al.* 2000a
- CD8+ T-cells that bound one of six HIV-specific B*3501-epitope tetramers did not express CD28 or CD45A.
- A significant increase in CD28-CD45RA- cells and a decrease of CD28+CD45RA+ cells was observed in chronically HIV-1-infected individuals relative to healthy individuals.
- CD28-CD45RA- cells are likely to be effector cells and have high levels of perforin in their cytoplasm.
- The mean percentage of total CD28- CD8+ cells in chronically infected HIV-1-infected patients was 76.6% in comparison to HIV-1-uninfected individuals (40.6%)

HXB2 Location RT (432–440)
Author Location
Epitope `EPIVGAETF`
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords acute/early infection
References Wilson *et al.* 2000a
- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B2705; and A*0201, A*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK.
- The subject with A*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705.
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

HXB2 Location RT (432–440)
Author Location Pol (587–595)
Epitope `EPIVGAETF`
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Dyer *et al.* 1999
- CTL specific responses were measured over a 1.3 to 1.5 year period in members of the Sydney Blood Bank Cohort (SBBC) who had been infected with a natural attenuated strain of HIV-1 which was Nef-defective.
- Some of these patients had prolonged high levels of CTL effector and memory cells despite low viral load.

HXB2 Location RT (432–440)
Author Location Pol
Epitope `EPIVGAETF`
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords HIV exposed persistently seronegative (HEPS)
References Koning *et al.* 2004
- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A*11, A*31 and Cw*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.

CTL CD8+

- No one, 0/3 HLA B35+ infection-resistant men, and 0/5 pre-seroconversion men who went on to become infected, reacted to this epitope.

HXB2 Location RT (432–440)
Author Location RT (587–596 SF2)
Epitope EPIVGAETF
Immunogen HIV-1 infection
Species (MHC) human (B35, B51)
References Shiga *et al.* 1996

- Binds HLA-B*3501, and is also presented by B51 – but CTL could not kill RT-vaccinia virus infected cells that expressed B51.

HXB2 Location RT (432–440)
Author Location Pol (587–595)
Epitope EPIVGAETF
Immunogen HIV-1 infection
Species (MHC) human (B35, B51)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location RT (432–440)
Author Location RT (432–440)
Epitope EPIVGAETF
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these eptiopes, but this increased over time.

HXB2 Location RT (432–441)
Author Location Pol (587–596)
Epitope EPIVGAETFY
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
References Tomiyama *et al.* 2000a

- CD8+ T-cells that bound one of six HIV-specific B*3501-epitope tetramers did not express CD28 or CD45A.
- A significant increase in CD28-CD45RA- cells and a decrease of CD28+CD45RA+ cells was observed in chronically HIV-1-infected individuals relative to healthy individuals.
- CD28-CD45RA- cells are likely to be effector cells and have high levels of perforin in their cytoplasm.
- The mean percentage of total CD28- CD8+ cells in chronically infected HIV-1-infected patients was 76.6% in comparison to HIV-1-uninfected individuals (40.6%)

HXB2 Location RT (432–441)
Author Location RT (587–597 SF2)
Epitope EPIVGAETFY
Immunogen HIV-1 infection
Species (MHC) mouse (B35)
Keywords review
References Menendez-Arias *et al.* 1998; Shiga *et al.* 1996

- Binds HLA-B*3501, but not presented by B51, in contrast to the peptide EPIVGAETF.
- Menendez-Arias *et al.* [1998] note in their review that this epitope is located near the protease cleavage site and conservation of this region is important for viral maturation.
- This epitope spans the Pol p66 RT – p15 (RNAse) domain.

HXB2 Location RT (432–441)
Author Location RT (587–597 SF2)
Epitope EPIVGAETFY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords rate of progression
References Kawana *et al.* 1999

- HLA B35 is associated with rapid disease progression.
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals.
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals, but this was one of the six that had no B35 associated pattern of mutation.

HXB2 Location RT (432–441)
Author Location Pol (587–596)
Epitope EPIVGAETFY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35, B51)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords characterizing CD8+ T cells
References Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- None of seven patients responded to this peptide with GzB producing cells, while two of the patients responded with IFN-gamma producing cells.

HXB2 Location RT (434–447)
Author Location RT (LAI)
Epitope IVGAETFYVDGAAS

Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*6802)
References Menendez-Arias *et al.* 1998; van der Burg *et al.* 1997

- Recognized by CTL from a long-term survivor that recognized a set of 5 overlapping peptides spanning IVGAETFYVDGAAS as well as PIVLPEKDSW and KITTESIVIW.
- A*6802 is a subset of HLA-A28.
- This epitope spans the Pol p66 RT – p15 (RNAse) domain.

HXB2 Location RT (434–448)
Author Location Pol (589–603)
Epitope `IVGAETFYVDGAANR`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the Progressor. Both patients had V590I substitutions.

HXB2 Location RT (436–445)
Author Location (C consensus)
Epitope `GAETFYVDGA`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*6802)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- GAETFYVDGA is an optimal epitope.

HXB2 Location RT (436–445)
Author Location RT (436–445)
Epitope `GAETFYVDGA`
Immunogen
Species (MHC) human (A*6802)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an A*6802 epitope.

HXB2 Location RT (436–445)
Author Location
Epitope `GAETFYVDGA`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*6802)
Donor MHC A*2301, A*6802, B*1510, B*5802, Cw*0511, Cw*0611
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- Known epitope GAETFYVDGA is HLA-A*6802-restricted. Response to a peptide containing this epitope was detected in a rapid progressor 12 weeks post-infection.

HXB2 Location RT (436–445)
Author Location RT
Epitope `GAETFYVDGA`
Epitope name GA10(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A68)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A68-restricted epitope GAETFYVDGA elicited an immune response in Chinese HIV-1 positive subjects as part of peptides QLEKEPIEGAETFYVDGA and GAETFYVDGAANRETKL.

HXB2 Location RT (436–445)
Author Location RT (591–600 IIIB)
Epitope `GAETFYVDGA`
Immunogen HIV-1 infection
Species (MHC) human (B45)
References Menendez-Arias *et al.* 1998

- This epitope spans the Pol p66 RT – p15 (RNAse) domain.

HXB2 Location RT (436–445)
Author Location Pol (591–600 IIIB)

CTL CD8+

Epitope GVETFYVDGA
Immunogen HIV-1 infection
Species (MHC) human (B45)
Keywords responses in children, mother-to-infant transmission, escape
References Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- No variants of this epitope were found in a non-transmitting mother who had a CTL response to it.
- This epitope spans the Pol p66 RT – p15 (RNAse) domain.

HXB2 Location RT (436–452)
Author Location (C consensus)
Epitope GAETFYVDGAANRETKI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*3402)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location RT (436–452)
Author Location (C consensus)
Epitope GAETFYVDGAANRETKI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*6801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location RT (436–452)
Author Location RT
Epitope GAETFYVDGAANRETKL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, GAETFYVDGAANRETKL, had an overall frequency of recognition of 18% - 20.3% AA, 11.5% C, 18.2% H, 19% WI.

HXB2 Location RT (437–445)
Author Location
Epitope AETFYVDGA
Epitope name Pol-AA9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*4501)
Donor MHC A*3002, A*3201, B*4501, B*5301, Cw*0401, Cw*1202
Keywords HAART, ART
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Subject 00RCH33 was on HAART had a viral load of 2900 and CD4 count of 727 and also recognized the epitopes YPLTFGWCY, Nef(135-143), HLA B*5301; RSLYNTVATLY, p17(76-86), HLA A*3002; and HIGPGRAFY, gp160(310-318), HLA A*3002.
- Among HIV+ individuals who carried HLA B45, 3/9 (33%) recognized this epitope.

HXB2 Location RT (437–447)
Author Location RT (592–602 LAI)

Epitope AETFYVDGAAN
Subtype B
Immunogen
Species (MHC) human (A28)
References Brander & Walker 1996; Menendez-Arias *et al.* 1998

- P. Johnson, pers. comm.
- This epitope spans the Pol p66 RT – p15 (RNAse) domain.

HXB2 Location RT (437–447)
Author Location Pol (592–602)
Epitope AETFYVDGAAN
Immunogen HIV-1 infection
Species (MHC) human (A28)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location RT (438–448)
Author Location (C consensus)
Epitope ETFYVDGAANR
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*66)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- ETFYVDGAANR is an optimal epitope.

HXB2 Location RT (438–448)
Author Location RT (593–603 IIIB)
Epitope ETFYVDGAANR
Immunogen HIV-1 infection
Species (MHC) human (A26)
References Menendez-Arias *et al.* 1998

- This epitope spans the Pol p66 RT – p15 (RNAse) domain.

HXB2 Location RT (438–448)
Author Location Pol (593–603 IIIB)
Epitope ETFYVDGAANR
Immunogen HIV-1 infection
Species (MHC) human (A26)
Keywords responses in children, mother-to-infant transmission, escape
References Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- One other variant was found that gave a positive, though reduced, CTL response: ETYYVNGAANR.
- This epitope spans the Pol p66 RT – p15 (RNAse) domain.

HXB2 Location RT (438–448)
Author Location RT
Epitope ETFYVDGAANR
Epitope name A26-ER11(RT)
Immunogen HIV-1 infection
Species (MHC) human (A26)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (438–448)
Author Location RT
Epitope ETFYVDGAANR
Epitope name ER11(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A26)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A26-restricted epitope ETFYVDGAANR elicited an immune response in Chinese HIV-1 positive subjects as part of peptide GAETFYVDGAANRETKL.
- 1 of the 8 HLA-A26 carriers responded to ETFYVDGAANR-containing peptide with a magnitude of CTL response of 220 SFC/million PBMC (author communication and Fig.1).

HXB2 Location RT (438–448)
Author Location
Epitope ETFYVDGAANR
Epitope name ER11
Immunogen
Species (MHC) human (A66)
Keywords optimal epitope

References Llano *et al.* 2009
- C. Brander notes this is a A66 epitope.

HXB2 Location RT (438–452)
Author Location Pol (593–607)
Epitope ETFYVDGAANRETKL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008
- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the Progressor, who had K606R substitution.

HXB2 Location RT (440–448)
Author Location Pol (594–602 SF2)
Epitope FYVDGAANR
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (A*3303)
Assay type Chromium-release assay
Keywords binding affinity, computational epitope prediction
References Hossain *et al.* 2003
- HLA-A*3303 is a common HLA allele in east and southeast Asia. Pol, Gag and Nef SF2 proteins were scanned for potential A*3303 epitopes. 99 potential epitopes were synthesized, and 52/99 bound to A*3303. Six of these served as peptide-targets for lysis by PBMC from infected individual, and clones derived from 4 of these 6 could lyse HIV-vaccinia infected target cells, indicating proper processing.
- This epitope is one of the 4 that are properly processed.

HXB2 Location RT (448–457)
Author Location RT
Epitope RETKLGKAGY
Immunogen HIV-1 infection
Species (MHC) human (A29)
Keywords rate of progression
References van der Burg *et al.* 1997
- Patients studied were from the Amsterdam cohort.
- CTL epitopes of 3 rapid progressors were compared to 4 long-term survivors (LTS) and no differences could be found in the degree of conservation between them.
- Epitope recognized by a LTS.
- This epitope occurs in the p15 (RNAse) domain of Pol p66 RT.

HXB2 Location RT (449–457)
Author Location
Epitope ETKLGKAGY
Epitope name Pol-EY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2601)
Donor MHC A*2601, A*3303, B*5801, B*8201, Cw*0302, Cw*0701
Keywords HAART, ART
References Sabbaj *et al.* 2003
- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Subject 03RCH40 was African American, had a viral load of 2500, CD4 count of 372, was not on HAART, and also recognized the epitope DILDLWIY, Nef(108-115), HLA Cw*0701.
- Among HIV+ individuals who carried HLA A26, 2/8 (25%) recognized this epitope.

HXB2 Location RT (449–457)
Author Location Pol (604–612)
Epitope ETKLGKAGY
Immunogen HIV-1 infection
Species (MHC) human (A*2601)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location RT (449–457)
Author Location Pol (604–612)
Epitope ETKLGKAGY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2601)
Country Japan
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay, Other, HLA binding
Keywords immunodominance, characterizing CD8+ T cells, optimal epitope
References Satoh *et al.* 2005
- Reverse immunogenetics was used to identify HIV-1 epitopes presented by HLA-A*2601. Four epitopes endogenously presented by this allele induced peptide-specific CD8 T-cells. HIV-infected individuals predominantly detected 2 of the epitopes, which might be useful for vaccine development. HLA-A*2601 is common in Asia.
- Immunodominant epitope recognized in 4/6 HIV-infected individuals with HLA-A*2601. This epitope is highly conserved in clade E (CRF01), and moderately conserved in clade B.

HXB2 Location RT (449–457)
Author Location Pol

Epitope ETKLGKAGY
Epitope name A26-EY9(pol)
Immunogen HIV-1 infection
Species (MHC) human (A26)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location RT (449–457)
Author Location RT
Epitope ETKLGKAGY
Epitope name EY9(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A26)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A26-restricted epitope ETKLGKAGY elicited an immune response in Chinese HIV-1 positive subjects as part of peptides DGAANRETKLGKAGYV and ETKLGKAGYVTNKGRQKV.
- 2 of the 8 HLA-A26 carriers responded to ETKLGKAGY-containing peptide #225 with average magnitude of CTL response of 380 SFC/million PBMC, and to peptide #226 with average magnitude of CTL response of 575 SFC/million PBMC (author communication and Fig.1).

HXB2 Location RT (451–459)
Author Location Pol (606–)
Epitope KLGKAGYVT
Epitope name Pol606
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* RT
Adjuvant: Incomplete Freund's Adjuvant (IFA)
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was an intermediate A2 binder that did not induce CTL or CD8+ T-cell IFN gamma responses in transgenic mice. Responses were detected in 2/17 HIV+ HLA-A2 subjects.

HXB2 Location RT (451–459)
Author Location
Epitope KLGKAGYVT
Epitope name Pol 606
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords immunodominance, variant cross-recognition or cross-neutralization
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Pol 606 KLGKAGYVT epitope was found in 7 patients but only 2 had CTL immune responses to it. Lack of recall response in 5 patients could be due to lack of processing or immune subdominance.
- Though poorly immunogenic in A2 tg mice, was anchor-optimization of natural Pol 606(9T) to Pol606(9V), KLGKAGYVv, induced cross-reaction and higher immunogenicity.

HXB2 Location RT (451–459)
Author Location Pol (606–)
Epitope KLGKAGYVT
Epitope name Pol606
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay

CTL CD8+

Keywords rate of progression, escape, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Pol epitope KLGKAGYVT, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients. DK1 had sequence variant rLGKAGYVT.

HXB2 Location RT (458–478)
Author Location RT
Epitope `VTDRGRQKIVSLTETTNQKTE`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- A sequence polymorphism at residue S in Pol reacting peptide VTDRGRQKIVsLTETTNQKTE was associated with host HLA-B*0801. No known HLA-B8-restricted epitope was in this sequence.

HXB2 Location RT (467–484)
Author Location (C consensus)
Epitope `VSLTETTNQKTELQAIQL`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*18)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location RT (469–477)
Author Location Pol
Epitope `LTDTTNQKT`
Subtype B, C, AE
Immunogen HIV-1 infection
Species (MHC) human
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, HLA associated polymorphism
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- Epitope LTDTTNQKT was recognized by at least 4 patients with restricting HLA supertype and infected with several HIV subtypes. Predicted HLA restriction for this epitope was to suptertype A1.

HXB2 Location RT (470–484)
Author Location Pol (625–639)
Epitope `TDTTNQKTELQAIHL`
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008

- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.
- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.

- CTL immune response to consensus sequence TDTTNQKTELQAIHL was elicited in subject 00016. Consensus epitope of subjects was the same as Clade B consensus.

HXB2 Location RT (477–486)
Author Location RT
Epitope TELQAIQLAL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1801)
Assay type CD8 T-cell Elispot - IFNγ
Keywords HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- TELQAIQLAL is a previously described HLA-B*1801-restricted epitope (part of Pol(RT) reacting peptide TNQTELQAIqLALDSGSEVN) that contains a B*1801-associated sequence polymorphism at residue Q (TELQAIqLAL).

HXB2 Location RT (481–505)
Author Location RT (648–672 PV22)
Epitope AIYLALQDSGLEVNIVTDSQYALGI
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Kalams *et al.* 1994; Menendez-Arias *et al.* 1998

- A CTL response used to study gene usage in HLA-B14 response.
- This epitope occurs in the p15 (RNAse) domain of Pol p66 RT.

HXB2 Location RT (481–505)
Author Location RT (648–672)
Epitope AIYLALQDSGLEVNIVTDSQYALGI
Immunogen HIV-1 infection
Species (MHC) human
References Menendez-Arias *et al.* 1998; Price *et al.* 1995

- Study of cytokines released by HIV-1 specific activated CTL.
- This epitope occurs in the p15 (RNAse) domain of Pol p66 RT.

HXB2 Location RT (485–493)
Author Location RT (485–493)
Epitope ALQDSGLEV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, ALQDSGLEV, was detected within overlapping peptides QKTELQAIHLALQDSGL and IHLALQDSGLEVNIV.

HXB2 Location RT (485–493)
Author Location RT (640–648 HXB2R)
Epitope ALQDSGLEV
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Brander *et al.* 1995; Brander *et al.* 1996

- This epitope was recognized by PBMC from 3/14 HIV+ asymptomatic patients.
- This epitope was used along with Env CTL epitope TLTSCNTSV and a tetanus toxin T helper epitope for a synthetic vaccine.
- This vaccine failed to induce a CTL response, although a helper response was evident.
- This epitope occurs in the p15 (RNAse) domain of Pol p66 RT.

HXB2 Location RT (485–493)
Author Location RT (640–648 HXB2R)
Epitope ALQDSGLEV
Immunogen vaccine
Strain: B clade HXB2 *HIV component:* RT
Species (MHC) human (A2)
References Brander *et al.* 1995

- Epitope studied in the context of inclusion in a synthetic vaccine.
- This epitope occurs in the p15 (RNAse) domain of Pol p66 RT.

HXB2 Location RT (485–493)
Author Location Pol (649–659 BH10, LAI)
Epitope ALQDSGLEV
Immunogen HIV-1 infection
Species (MHC) human
References Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is IYLALQDSGLE) has similarity with the epidermal growth factor receptor kinase substrate EPS8, fragment ISAAASDSGVE.

HXB2 Location RT (485–494)
Author Location RT (485–495 HXB2)
Epitope ALQDSGSEVN
Epitope name 51H

CTL CD8+

Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* multiple epitope immunogen *HIV component:* p17/p24 Gag, Pol *Adjuvant:* IL-12
Species (MHC) transgenic mouse (A2)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-specific epitope characteristics, vaccine antigen design
References Bolesta *et al.* 2005

- Immunization of transgenic mice with a codon-optimized hGagp17p24-Polp51 DNA plasmid, consisting of clusters of highly conserved CTL epitopes presented by multiple MHC class I alleles, induced 2- to 5-fold higher CD8+ T-cell responses than the corresponding full-length proteins. The modified proteins had the ribosomal frameshift deleted, as well as the potentially immunosuppressive p15, and protease and integrase. This correlated with higher protection against challenge with Gag and Pol expressing recombinant vaccinia virus. Mice immunized with the hGagp17p24-Polp51 also showed an elevated level of type 1 cytokine production as well as an increased titer of p24- and RT-specific IgG2 antibody responses.
- This was 1 of 4 A2 gag/pol epitopes tested. Transgenic mice immunized with the deleted construct induced more potent EliSpot reactions to this epitope than those immunized with full length Gag/Pol.

HXB2 Location RT (485–505)
Author Location RT (648–672)
Epitope `ALQDSGLEVVTDSQYALGI`
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Brander & Walker 1995

- Unpublished, S. Kalams.
- This epitope occurs in the p15 (RNAse) domain of Pol p66 RT.

HXB2 Location RT (487–503)
Author Location RT
Epitope `QDSGSEVNIVTDSQYAL`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*3910)
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- QDSGSEVNIVTDSQYAL is a previously described HLA-B*39(10)-restricted epitope (part of Pol(RT) reacting peptide ALQDSGSEVNiVTDSQYALGI) that contains a B*39(10)-associated reversion at residue I (QDSGSEVNiVTDSQYAL).

HXB2 Location RT (491–501)
Author Location RT
Epitope `SEVNIVTDSQY`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4403)
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- SEVNIVTDSQY is a previously described HLA-B*4403-restricted epitope (part of Pol(RT) reacting peptide AIQLALQDSGsEVNIVTDSQY) that contains a B*4403-associated reversion at residue S (sEVNIVTDSQY).

HXB2 Location RT (492–501)
Author Location Pol (647–656)
Epitope `EVNIVTDSQY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2601)
Country Japan
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay, Other, HLA binding
Keywords immunodominance, optimal epitope
References Satoh *et al.* 2005

- Reverse immunogenetics was used to identify HIV-1 epitopes presented by HLA-A*2601. 110 peptides were predicted to bind to HLA-A*2601. 24 of these were demonstrated to bind through a HLA-A*2601 stabilization assay. Four of these, including this one, were shown to be epitopes endogenously presented by this allele, that can induce peptide-specific CD8 T-cells. HLA-A*2601 is common in Asia.
- This epitope was recognized in only 1/7 HLA-A*2601 HIV infected individuals.

HXB2 Location RT (492–506)
Author Location (C consensus)
Epitope `EVNIVTDSQYALGII`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*3910)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location RT (492–506)
Author Location (C consensus)

Epitope EVNIVTDSQYALGII
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0802)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location RT (493–502)
Author Location Pol (648–657)
Epitope VNIVTDSQYA
Subtype B
Immunogen HIV-1 infection, peptide-HLA interaction
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance
References Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, VNIVTDSQYA, is similar to human protein HERV, sequence VNIyTDSQYA and human protein Thrombospondin 3 precursor, sequence VNtVTDddYA.

HXB2 Location RT (495–503)
Author Location
Epitope IVTDSQYAL
Epitope name IL9
Immunogen
Species (MHC) human (Cw*0802)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a Cw*0802 epitope.

HXB2 Location RT (496–505)
Author Location
Epitope VTDSQYALGI
Epitope name Pol-VI10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Donor MHC A*3002, A*6801, B*0801, B*1503, Cw*0701, Cw*08
Keywords HAART, ART
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Subject 01RCH51 was an African American on HAART, viral load 980, CD4 count 811.
- Among HIV+ individuals who carried HLA B15, 1/17 (6%) recognized this epitope.

HXB2 Location RT (496–505)
Author Location Pol (651–660)
Epitope VTDSQYALGI
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location RT (496–505)
Author Location Pol (651–660)
Epitope VTDSQYALGI
Epitope name VI10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Donor MHC A*02, A*68, B*14, B*52, Cw*08, Cw*12
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords escape, optimal epitope
References Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- The B consensus form of this epitope,VTDSQYALGI, persisted throughout 6 years of chronic infection in 1 individual.

HXB2 Location RT (496–505)
Author Location Pol (subtype B)
Epitope VTDSQYALGI
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B*1402, B14)
Keywords subtype comparisons
References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.

CTL CD8+

- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among A, B and D clade viruses.

HXB2 Location RT (496–505)
Author Location RT
Epitope VTDSQYALGI
Epitope name VI10(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B15)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide sequence contains the exact sequence of a previously described HLA-B15 optimal epitope, VTDSQYALGI, none of the 21 HLA-B15 carriers responded to it (author communication and Fig.1).

HXB2 Location RT (496–505)
Author Location RT (663–672 IIIB)
Epitope VTDSQYALGI
Immunogen HIV-1 infection
Species (MHC) human (Cw8)
References Brander & Walker 1996

- Unpublished, P. Johnson.
- Published in this database in 1995 as B14, but B14 transfected cells did not present the peptide and it is thought to be presented by the genetically linked Cw8 molecule instead Brander & Walker [1996]
- This epitope occurs in the p15 (RNAse) domain of Pol p66 RT.

HXB2 Location RT (496–505)
Author Location RT
Epitope VTDSQYALGI
Immunogen HIV-1 exposed seronegative
Species (MHC) human (Cw8)
Keywords subtype comparisons, HIV exposed persistently seronegative (HEPS)
References Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A and D subtype consensus are identical to the B clade epitope.
- Thought to be HLA-Cw8 restricted, not B14 as originally reported (C. Brander, B. Walker, and S. Rowland-Jones, personal communication)
- This epitope occurs in the p15 (RNAse) domain of Pol p66 RT.

HXB2 Location RT (497–512)
Author Location (C consensus)
Epitope TDSQYALGIIQAQPDK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0205)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location RT (502–517)
Author Location (C consensus)
Epitope ALGIIQAQPDKSESEL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*3901)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location RT (502–517)
Author Location RT
Epitope ALGIIQAQPDKSESEL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*3910)
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- ALGIIQAQPDKSESEL is a previously described HLA-B*3910-restricted epitope (part of Pol(RT) reacting peptide ALGIIQAQPDkSESELVNQII) that contains a B*3910-associated reversion at residue K (ALGIIQAQPDkSESEL).

HXB2 Location RT (509–518)

Author Location Pol
Epitope QPDKSESELV
Immunogen
Species (MHC) human (B7)
References De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conservered regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFNγ production in an ELISPOT assay.
- QPDKSESELV was newly identified as an HLA-B7 epitope in this study.

HXB2 Location RT (509–518)
Author Location Pol
Epitope QPDKSESELV
Epitope name 1302
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A03, A24, B07, B38, Cw07, Cw12/13
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for QPDKSESELV: 36%

HXB2 Location RT (516–525)
Author Location RT (516–525)
Epitope ELVNQIIEQL
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Haas *et al.* 1998

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules.
- This epitope occurs in the p15 (RNAse) domain of Pol p66 RT.

HXB2 Location RT (520–528)
Author Location Pol (520–528 LAI)
Epitope QIIEQLIKK
Subtype B
Immunogen
Species (MHC) human (A*1101)
Keywords optimal epitope
References Fukada *et al.* 1999; Llano *et al.* 2009

- C. Brander notes this is an A*1101 epitope.

HXB2 Location RT (520–528)
Author Location Pol (675–683)
Epitope QIIEQLIKK
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Keywords subtype comparisons, TCR usage
References Fukada *et al.* 2002

- Counterparts for eight known clade B HLA A*1101 epitopes were generated for clade E (CRF01). Three epitopes, identical among clade A-E, were cross-reactive and recognized by clade E infected individuals. The clade E and B analogs to three more HLA A*1101 epitopes was recognized in a clade specific manner. Two other HLA A*1101 clade B defined epitopes were found not to have stimulated a response in clade E infected individuals.
- QIIEQLIKK was found to elicit clade-specific responses in clade B (QIIEQLIKK is most common) and clade E (qiieElikk is most common). QIIEQLIKK was strongly recognized by CTL from 1/5 B clade infected Japanese subjects, and qiieElikk from 3/7 E clade infected Thai subjects. The variant qiieKliEk, common in the A subtype, was also recognized in 2/7 E clade infected Thai subjects.
- The binding of QIIEQLIKK, qiieElikk and qiieKliEk to HLA A*1101 was similar, but CTL clones from individuals did not cross-react with the cross-clade peptides indicating that the substitutions inhibited TCR interaction.

HXB2 Location RT (520–528)
Author Location RT (80–88)
Epitope QIIEQLIKK
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location RT (520–528)
Author Location Pol (676–684)
Epitope QIIEQLIKK
Epitope name QK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords optimal epitope
References Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- This epitope did not vary.

HXB2 Location RT (520–528)

Author Location Pol (676–684)
Epitope QIIEQLIKK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location RT (520–528)
Author Location RT
Epitope QIIEQLIKK
Epitope name QK9(RT)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A11-restricted epitope ELVSQIIEQLIKKEKVYL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide QIIEQLIKK.
- 2 of the 28 HLA-A11 carriers responded to QIIEQLIKK-containing peptide with average magnitude of CTL response of 75 SFC/million PBMC (author communication and Fig.1).

HXB2 Location RT (520–528)
Author Location Pol
Epitope QIIEQLIKK
Epitope name 1336
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, A23, B49, B57
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for QIIEQLIKK: 48%

HXB2 Location RT (530–538)
Author Location
Epitope KVYLAWVPA
Epitope name Pol-KA9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Donor MHC A*0202, A*0301, B*4501, B*5301, Cw*0401, Cw*1502
Keywords HAART, ART
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- This epitope was newly defined in this study.
- Patient 04RCH86 was Hispanic, not on HAART, and had a viral load of 7600 and CD4 count of i774.
- Among HIV+ individuals who carried HLA A*03, 2/21 (10%) recognized this epitope.

HXB2 Location RT (530–538)
Author Location Pol (685–693)
Epitope KVYLAWVPA
Epitope name KA9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A*0201, A*0301, B*3501, B*51, Cw*04, Cw*06
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords escape, acute/early infection
References Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- The response to this epitope was barely detectable until month 41.

HXB2 Location RT (530–538)
Author Location Pol (680–691 BH10, LAI)

Epitope KVYLAWVPA
Immunogen HIV-1 infection
Species (MHC) human
References Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is IKKEKVYLAWV) has similarity with B-cell growth factor precursor, fragment IKKERLWLGPV.

HXB2 Location RT (530–540)
Author Location (C consensus)
Epitope RVYLSWVPAHK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords epitope processing, rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in a residue outside of the optimized epitope of RVYLSWVPAHK are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location RT (530–540)
Author Location Pol (722–)
Epitope KVYLAWVPAHK
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (A*0301)
Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008

- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location RT (530–540)
Author Location Pol
Epitope KVYLAWVPAHK
Epitope name Pol722
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (A3)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- KVYLAWVPAHK is a Pol epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location RT (530–540)
Author Location Pol
Epitope KVYLAWVPAHK
Epitope name Pol722
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human, mouse (A3 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope KVYLAWVPAHK of the HLA-A3 supertype bound most strongly to HLA-A*1101, -A*0301 and -A*3101 and also to -A*3301 and -A*6801. It was conserved 94% in subtype B and 75% in subtype D. 6/23 HLA-B7 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Pol722.

HXB2 Location RT (532–540)
Author Location Pol (687–)
Epitope YLAWVPAHK
Epitope name Pol687
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was an intermediate A2 binder, and induced a CD8+ T-cell IFN gamma response in 1/6 mice. Responses were detected in 1/17 HIV+ HLA-A2 subjects.

HXB2 Location RT (532–540)
Author Location
Epitope YLAWVPAHK
Epitope name Pol 687
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Pol 687 YLAWVPAHK epitope was found in 10 patients but only 1 had a CTL immune response to it.

HXB2 Location RT (532–540)
Author Location Pol (687–)
Epitope YLAWVPAHK
Epitope name Pol687
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Pol epitope YLAWVPAHK, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients. DK1 had sequence variant YLsWVPAHK.

HXB2 Location RT (532–540)
Author Location Pol (714–722)
Epitope YLAWVPAHK
Immunogen HIV-1 infection
Species (MHC) human (A3 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 5/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801).

HXB2 Location RT (532–540)
Author Location RT (532–540)
Epitope YLAWVPAHK
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Haas *et al.* 1998

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules.
- This epitope occurs in the p15 (RNAse) domain of Pol p66 RT.

HXB2 Location RT (532–540)
Author Location RT Pol (687–695)
Epitope YLAWVPAHK
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 3/7 patients recognized this epitope.

II-B-13 RT-Integrase CTL/CD8+ epitopes

HXB2 Location RT-Integrase (553–2)
Author Location Pol
Epitope STGIRRVLFL
Epitope name SL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- An escape mutation at position 6 (stgirKvlfl) was found not to correspond to the most polymorphic residues in the epitope. This is a novel partially mapped epitope.

HXB2 Location RT-Integrase (560–8)
Author Location Pol (715–723)
Epitope LFLDGIDKA
Immunogen
Species (MHC) human (B81)
Keywords optimal epitope
References Llano *et al.* 2009

II-B-14 Integrase CTL/CD8+ epitopes

HXB2 Location Integrase (9–19)
Author Location (C consensus)
Epitope QEEHEKYHSNW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4403)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the E2 and E3 residues of QEEHEKYHSNW are associated with the presence of the HLA presenting molecule in the host.
- QEEHEKYHSNW not optimized.

HXB2 Location Integrase (9–19)
Author Location Integrase
Epitope QEEHEKYHSNW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4403)
Keywords HLA associated polymorphism
References Rousseau *et al.* 2008

- 3 phylogenetic correction methods—MLL (maximum likelihood character state analysis followed by likelihood ratio test), MLF (maximum likelihood character state analysis followed by Fisher test), and parsimony character state analysis were used to identify points in the HIV-1 subtype C proteome that conferred susceptibility or resistance to CTLs. Associations of HLA-epitope combinations that were inferred to be susceptible or resistant were organized into immunological sets that would help identify the best residues and genes as candidates for vaccines. While all proteins were interrogated, Gag, Pol, Env and Nef were focused upon. Amino acid changes were evaluated for association with plasma viral load.
- Proteome maps may be seen at `http://www.hiv.lanl.gov/content/immunology/hlatem/study5/index.html` with information showing single or multiple sites involving escape and reversion.
- HLA- B and -C alleles associated more with aa changes than HLA-A, suggesting that the former two are more important in driving viral evolution.
- The ratio of susceptible to resistant residues in HIV proteins was in descending order, Vpr>Gag>Rev>Pol>Nef>Vif>Tat>Env>Vpu, showing that epitopes from the earlier proteins are more conserved owing to viral fitness cost upon mutation.
- This previously described Pol HLA B*4403-restricted epitope, QEEHEKYHSNW was susceptible at E2. Variants QaEHEKYHSNW, QdEHEKYHSNW, QgEHEKYHSNW, and QvEHEKYHSNW were resistant to CTL response, but associated with lower viral loads. This epitope is 1 of 7 that suggest a fitness cost to immune escape.

HXB2 Location Integrase (9–19)
Author Location Pol
Epitope QEEHEKYHSNW
Epitope name QW11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 2, qAehekyhsnw, was found not to correspond to the most polymorphic residues in the epitope. This is a novel partially mapped epitope.

HXB2 Location Integrase (10–19)
Author Location Integrase

Epitope EEHEKYHSNW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4403)
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- EEHEKYHSNW is a previously described HLA-B*4403-restricted epitope (part of Pol(Integrase) reacting peptides LFLDGIDKAQeEHEKYHSNWR and FLDGIKDAQEE-HEKYHSNWRA) that contain a B*4403-associated reversion at residue E (eEHEKYHSNW).

HXB2 Location Integrase (20–28)
Author Location Integrase (20–28)
Epitope RAMASDFNL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope RAMASDFNL was predicted to be restricted by HLA A*0201, B*2709 and C*0304

HXB2 Location Integrase (20–28)
Author Location Pol (762–770)
Epitope RAMASDFNL
Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind three of the five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802).

HXB2 Location Integrase (22–31)
Author Location Pol (764–773)
Epitope MASDFNLPPV
Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind all five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802)

HXB2 Location Integrase (28–36)
Author Location (C consensus)
Epitope LPPIVAKEI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0705)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- LPPIVAKEI is an optimal epitope for B*4201, B*0705, and B*5101.

HXB2 Location Integrase (28–36)
Author Location (C consensus)
Epitope LPPIVAKEI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa

Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location Integrase (28–36)
Author Location (C consensus)
Epitope LPPIVAKEI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the P3, I4, A6, and K7 residues of LPPIVAKEI are associated with the presence of the HLA presenting molecule in the host.
- LPPIVAKEI is an optimal epitope for B*4201, B*0705, and B*5101.

HXB2 Location Integrase (28–36)
Author Location Integrase (28–36)
Epitope LPPIVAKEI
Epitope name LI9
Immunogen peptide-HLA interaction
Species (MHC) human (B*4201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords optimal epitope
References Honeyborne *et al.* 2006

- Novel epitopes are defined for four HLA-alleles common in South African Zulu/Xhosa populations: B*3910, B*4201, B*8101 and Cw*1801, by motif inference. HLA-A*2902 was found to overlap those of A1 and A24 supertypes.
- LPPIVAKEI (LI9) was the optimal epitope for HLA-B*4201 with variants LPPIVAKE, PPIVAKEI, LPPIVAKEIv, nLPPIVAKEI having been tested.

HXB2 Location Integrase (28–36)
Author Location Integrase
Epitope LPPIVAKEI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- LPPIVAKEI is a previously described HLA-B*4201-restricted epitope (part of Pol(Integrase) reacting peptides AMASEFNLPPiVAKEIVASCD and SEFNLPPIVAkEIVASCDKCQ) that contains B*4201-associated reversions at residues I and K (LPPiVAKEI/LPPIVAkEI).

HXB2 Location Integrase (28–36)
Author Location Integrase
Epitope LPPIVAKEI
Epitope name LI9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*51)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, HLA associated polymorphism
References Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore et al., Science 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- There are two variant forms of this B57/B5801 epitope at the second position, LPPiVAKEI and LPPvVAKEI. Leslie et al., J Exp Med. 201:891 (2005) suggest that the escape form LPPvVAKEI may have come to dominate the B clade lineage over time due to higher HLA B51 frequencies in B clade epidemic regions. Bhattacharya suggests lineage effects are also playing an important role in the observed amino acid frequencies, and note that the ratio of I/V has not change over time, and that the frequency of I/V in different epidemic populations does not correlate with HLA B51 allele frequency.

HXB2 Location Integrase (28–36)
Author Location Pol (743–751 SF2)
Epitope LPPVVAKEI
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Keywords subtype comparisons, rate of progression
References Tomiyama *et al.* 1999

CTL CD8+

- HLA-B27, -B51, and -B57 are associated with slow progression to AIDS, while HLA-B35, -B8, -B24 are associated with a rapid progression to AIDS (Nat. Med. 2:405, 1996;Lancet 22:1187, 1986;Hum Immunol 22:73, 1988;Hum Immunol 44:156, 1995)
- 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%
- Of the 172 HIV-1 peptides with HLA-B*5101 anchor residues, 33 bound to HLA-B*5101, seven of these peptides were reactive with CTL from 3 B*5101 positive individuals, and six were properly processed.
- Four of the six epitopes were highly conserved among B subtype sequences – LPPVVAKEI is highly conserved.

HXB2 Location Integrase (28–36)
Author Location (C consensus)
Epitope LPPIVAKEI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- LPPIVAKEI is an optimal epitope for B*4201, B*0705, and B*5101.

HXB2 Location Integrase (28–36)
Author Location Integrase (28–36 HXB2)
Epitope LPPVVAKEI
Epitope name LI9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.

HXB2 Location Integrase (28–36)
Author Location Pol (743–749 NL-432)
Epitope LPPVVAKEI
Immunogen HIV-1 infection
Species (MHC) (B*5101)
Assay type Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay, CTL suppression of replication
Keywords binding affinity, class I down-regulation by Nef, rate of progression
References Tomiyama *et al.* 2005

- HLA-B*5101 associated with slow progression to the disease state was studied as related to Nef-mediated HLA class I downregulation. It was shown that different CTLs have different ranges of ability to kill HIV-1 infected CD4+ T cells and suppress HIV-1 replication. This was found to be a function of the specific HIV-1 epitope presented by the corresponding HLA allele to the CTL.
- Certain epitope-recognising CTL clones or lines were therefore capable of killing HIV-1 infected cells even in the presence of Nef-mediated MHC 1 downregulation, while other CTL clones recognising different epitopes were not so capable.
- There was no significant difference in cytokine production or cytokine producing cells between CTLs that were capable of killing CD4+ T-cells infected with HIV-1 and those CTLs that could not kill such HIV-1 infected cells.
- On the basis of studies involving binding abilities and cytolytic activities for four different epitopes that correlate with HLA-B*5101-restricted CTLs, it is suggested that the ability of CTLs to kill infected CD4+ T cells is due to the number of epitopes presented by the HLA on the surface of the CD4+ T cells rather than the ability of TCR to recognise the epitope.

HXB2 Location Integrase (28–36)
Author Location
Epitope LPPIVAKEI
Epitope name LI9
Immunogen
Species (MHC) human (B42)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B42 epitope.

HXB2 Location Integrase (28–36)
Author Location Pol (28–36)
Epitope LPPVVAKEI
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 7 epitopes from this individual that varied over time, although the internal mutations did not become fixed. The lppIvakei variant arose at intermediate time points.

HXB2 Location Integrase (28–36)
Author Location Integrase (28–36)
Epitope LPPIVAKEI
Epitope name LI9
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B51)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords subtype comparisons, computational epitope prediction, mother-to-infant transmission, escape, viral fitness and reversion, optimal epitope
References Leslie *et al.* 2005

- An I4V substitution (LPPvVAKEI) is suggested to be driven by CTL escape in B51-positive subjects. The escape form is the consensus form of the epitope in the B clade, and stable in the absence of HLA-B51. In the C clade the B51 is rare, and the Val escape mutation is also rare.

HXB2 Location Integrase (28–36)
Author Location Integrase
Epitope LPPVVAKEI
Epitope name B51-LI9(Int)
Immunogen HIV-1 infection
Species (MHC) human (B51)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Integrase (28–36)
Author Location Integrase
Epitope LPPVVAKEI
Epitope name LI9(Integrase)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B51-restricted epitope LPPVVAKEI elicited an immune response in Chinese HIV-1 positive subjects as part of peptide MASDFNLPPVVAKEIVA.
- 1 of the 15 HLA-B51 carriers responded to LPPVVAKEI-containing peptide with a magnitude of CTL response of 40 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Integrase (28–36)
Author Location Pol
Epitope LPPIVAKEI
Epitope name Pol1130
Subtype C
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Epitope LPPIVAKEI elicits IFN-gamma ELISpot responses in 2/7 subjects; and bound HLA-B7 with low and high affinities in soluble and cell-based assays respectively. Previously published HLA restrictions of this epitope include B*0705, B*4201, B*5101 (LANL database).

HXB2 Location Integrase (28–36)
Author Location Integrase (27–36)
Epitope LPPIVAKEI
Epitope name LI9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Other
Keywords supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism
References Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alelles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.

CTL CD8+

- Statistically significant associations between numbers of HLA-4201 expressing subjects and epitope LPPIVAKEI were found.
- A strong association between B*4201 and variation in this epitope, LI9, was found.

HXB2 Location Integrase (29–46)
Author Location (C consensus)
Epitope PPIVAKEIVASCDKCQLK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location Integrase (35–45)
Author Location Integrase
Epitope EIVASCDKCQL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- EIVASCDKCQL is a previously described HLA-B*4201-restricted epitope (part of Pol(Integrase) reacting peptide EIVASCDKCQlKGEAIHGQVD) that contains B*4201-associated reversions at residue L (EIVASCDKCQl).

HXB2 Location Integrase (37–45)
Author Location Integrase (37–45)
Epitope VASCDKCQL
Epitope name VL9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Other
Keywords supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism
References Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alelles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Statistically significant associations between numbers of HLA-8101 expressing subjects and epitope VASCDKCQL were found.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope VL9 restriction.

HXB2 Location Integrase (53–60)
Author Location Integrase (54–61)
Epitope QVDCSPGI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, QVDCSPGI, of unknown HLA restriction, was detected within overlapping peptides LKGEAMHGQVDCSPGIW and GQVDCSPGIWQLDCTHL.

HXB2 Location Integrase (62–71)
Author Location Pol
Epitope QLDCTHLEGK
Epitope name 1335
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, A23, B49, B57; A03, A11, B05, B14, Cw08
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for QLDCTHLEGK: 61%.

HXB2 Location Integrase (66–74)
Author Location (C consensus)
Epitope THLEGKIIL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the L9 residue of THLEGKIIL are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location Integrase (66–74)
Author Location
Epitope THLEGKIIL
Epitope name TIL9
Immunogen
Species (MHC) human (B*1510)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*1510 epitope.

HXB2 Location Integrase (66–74)
Author Location Integrase
Epitope THLEGKVIL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Assay type CD8 T-cell Elispot - IFNγ
Keywords HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- THLEGKVIL is a previously described HLA-B*1510-restricted epitope (part of Gag reacting peptide QLDCTHLEGKvILVAVHVASG) that contains B*1510-associated sequence polymorphism at residue V (THLEGKvIL).

HXB2 Location Integrase (66–74)
Author Location Integrase
Epitope THLEGKIIL
Epitope name TL9(Integrase)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B15)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B15-restricted epitope THLEGKIIL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide GIWQLDCTHLEGKIILVA.
- 1 of the 21 HLA-B15 carriers responded to THLEGKIIL-containing peptide with average magnitude of CTL response of 50 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Integrase (78–86)
Author Location Pol (792–800)
Epitope HVASGYIEA
Epitope name HA9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5401)
Country Japan
Assay type Intracellular cytokine staining, Chromium-release assay
Keywords optimal epitope
References Kitano *et al.* 2008

- Asian-expressed HLA-B*5401-restricted epitopes were identified using overlapping-peptide methods and characterized. 5 epitopes from Pol and Nef induced CTL responses that killed target cells in more than 25% of B*5401-carrying tested patients.
- 7 peptides from Pol and Nef are listed in Fig. 2 as candidates for B*5401 restriction. No Gag-specific epitopes were identified in this study from the patient whose lymphocytes were screened.
- HVASGYIEA was defined as an optimal epitope for HLA-B*5401 restriction, using truncated peptides.

HXB2 Location Integrase (82–89)
Author Location RT (797–804 SF2)
Epitope GYIEAEVI
Epitope name Pol797-8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Country Japan
References Ikeda-Moore *et al.* 1997

CTL CD8+

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402.
- This peptide induced CTL in 1/4 HIV-1 + people tested.
- GYIEAEVI bound to A*2402 weakly, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

HXB2 Location Integrase (82–89)
Author Location Pol (797–804 NL-432 or NL-M20A)
Epitope GYIEAEVI
Epitope name Pol797-8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Donor MHC A*2402
Country Japan
Assay type Chromium-release assay, CTL suppression of replication, HLA binding
References Fujiwara *et al.* 2008

- To clarify mechanisms of escape mutation accumulation in the population, the Japanese Nef138-10 (RYPLTFGWCF) epitope was studied amongst hemophiliacs and others, to determine replication suppression abilities of both the wild type and 2F (RfPLTFGWCF) mutant virus. This mutant is conserved due to reduced CTL suppression of viral replication, also preventing viral reversion to WT upon transfer to a new host.
- Epitope Pol797-8, GYIEAEVI, was used as a comparison for positive cytolytic activity of epitope-specific HLA-A*2402 clones against target cells prepulsed with corresponding peptide. These clones partially suppressed NL-M20A viral replication.

HXB2 Location Integrase (83–91)
Author Location Pol (798–806)
Epitope YIEAEVIPA
Subtype B
Immunogen HIV-1 infection, peptide-HLA interaction
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance
References Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, YIEAEVIPA, is similar to an unnamed human protein, sequence gYIEAaVIPAG and human protein p53 inducible protein, sequence EIEAEV.

HXB2 Location Integrase (89–98)
Author Location Pol
Epitope IPAETGQETA
Immunogen
Species (MHC) human (B56)
References De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conservered regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFNγ production in an ELISPOT assay.
- IPAETGQETA was newly identified as an HLA-B56 epitope in this study.

HXB2 Location Integrase (89–98)
Author Location Pol
Epitope IPAETGQETA
Epitope name 1294
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A02, A03, B07, B58, Cw07
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for IPAETGQETA: 8%

HXB2 Location Integrase (89–98)
Author Location Pol (805–814 BH10, LAI)
Epitope IPAETGQETA
Immunogen HIV-1 infection
Species (MHC) human
References Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is PAETGQETAY) has similarity with Integrin beta-4 precursor (GP150)(CD104), fragment PAETNGEITAY.

HXB2 Location Integrase (90–107)
Author Location (C consensus)
Epitope PAETGQETAYFILKLAGR
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*6802)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression

References Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location Integrase (91–100)
Author Location Integrase
Epitope AETGQETAYY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4403)
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008
- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- AETGQETAYY is a previously described HLA-B*4403-restricted epitope (part of Pol(Integrase) reacting peptide SGIEAEGVIPaETGQETAYYI) that contains a B*4403-associated reversion at residue L (aETGQETAYY).

HXB2 Location Integrase (92–99)
Author Location (C consensus)
Epitope ETGQETAY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2601)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- ETGQETAY is an optimal epitope.

HXB2 Location Integrase (96–104)
Author Location Integrase (823–831)
Epitope ETAYFILKL
Immunogen
Species (MHC) human (A*6802)
Keywords subtype comparisons
References Dong & Rowland-Jones 1998
- Epitope found in clade A, B, and D – pers. comm. S. Rowland-Jones and T. Dong.

HXB2 Location Integrase (96–104)
Author Location Pol (subtype A)
Epitope ETAYFILKL
Subtype A
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A*6802)
References Kaul *et al.* 2000
- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T cell epitopes: DTVLEDINL (3 individuals), SLYNTVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

HXB2 Location Integrase (96–104)
Author Location Pol
Epitope ETAYFILKL
Immunogen HIV-1 infection
Species (MHC) human (A*6802)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001c
- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 1/22 HEPS sex worker controls (ML1671)

HXB2 Location Integrase (96–104)
Author Location Pol (744–752)
Epitope ETAYFILKL
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A*6802)
Keywords HIV exposed persistently seronegative (HEPS), immunodominance
References Kaul *et al.* 2001a
- ETAYFILKL cross-reacts with clades A, B and D.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-A*6802 women, 3/12 HEPS and 9/11 HIV-1 infected women recognized this epitope likelihood ratio 7.9, p value 0.01, and HEPS women tended to respond to DTVLEDINL, while infected women to ETAYFILKL.

CTL CD8+

- The dominant response to this HLA allele was to this epitope in 2 of the 3/12 HEPS cases and in all 9/11 HIV-1 infected women that responded to the epitope.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.
- Subject ML 1203 started with CTL responses to A*6802 DTVLEDINL and to B7 FPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A*6802 ETAYFILKL which became dominant, B7 TPGPG(V/I)RYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV.
- Subject ML 1707 started with a CTL response to A*6802 DTVLEDINL prior to seroconversion, and switched to A*6802 ETAYFILKL and A24 RDYVDRFFKTL post-seroconversion.
- Subject ML 1830 made no detectable response prior to seroconversion, but responded to A*6802 DTVLEDINL and A*6802 ETAYFILKL post-seroconversion.

HXB2 Location Integrase (96–104)
Author Location Pol (744–752)
Epitope ETAYFILKL
Immunogen HIV-1 infection
Species (MHC) human (A*6802)
References Appay *et al.* 2000

- This epitope is newly defined in this study.
- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α

HXB2 Location Integrase (101–111)
Author Location (C consensus)
Epitope ILKLAGRWPVK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords epitope processing, rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in a residue outside of the optimized epitope of ILKLAGRWPVK are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location Integrase (105–121)
Author Location (C consensus)
Epitope AGRWPVKVIHTDNGSNF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location Integrase (123–131)
Author Location
Epitope STTVKAACW
Epitope name SW9
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B*57-restricted optimal epitope STTVKAACW was tested for immune response.

HXB2 Location Integrase (123–132)
Author Location Integrase
Epitope SAAVKAACWW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5801)
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- SAAVKAACWW is a previously described HLA-B*5801-restricted epitope (part of Pol(Integrase) reacting peptide HTDNGSNFTSaAVKAACWWAG) that contains a B*5801-associated reversion at residue A (SaAVKAACWW).

HXB2 Location Integrase (123–132)
Author Location Integrase (123–132)
Epitope STTVKAACWW
Immunogen

Species (MHC) human (B57)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Integrase (123–132)
Author Location Integrase
Epitope STTVKAACWW
Epitope name SW10
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords epitope processing, supervised treatment interruptions (STI), rate of progression, immunodominance
References Rodriguez *et al.* 2004

- Protease and integrase are shown to be frequently targeted by CD8 T-cell responses (23% and 68% of 56 HIV+ patients, respectively). Responses tend to cluster in conserved regions of Int, although 1 high conserved region had no responses. CTL frequencies per unit protein length for Pro and Int were similar to other HIV non-structural proteins. Three novel HLA class I-restricted optimal epitopes were found and characterized with fine mapping.
- All 5 HLA-B57 patients recognized this epitope and were long-term nonprogressors.

HXB2 Location Integrase (123–132)
Author Location Pol
Epitope STTVKAACWW
Epitope name SW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Two escape mutations, at positions 2 and 3, were found in the most polymorphic residue in the epitope. These were shared between clades B and C. The T840N mutation at residue 2, sNtvkaacww, was significantly more common in persons expressing HLA-B57, often in conjunction with T841A or V sT[A/V]kaacww.

HXB2 Location Integrase (123–132)
Author Location Integrase
Epitope STTVKAACWW
Epitope name B57-SW10(Int)
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Integrase (123–132)
Author Location
Epitope STTVKAACWW
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords responses in children, mother-to-infant transmission, characterizing CD8+ T cells
References Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.

HXB2 Location Integrase (127–135)
Author Location Pol (869–877)
Epitope KAACWWAGI
Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.

CTL CD8+

- This epitope can bind three of the five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802).

HXB2 Location Integrase (135–143)
Author Location (C consensus)
Epitope IQQEFGIPY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the Q2 residue of IQQEFGIPY are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location Integrase (135–143)
Author Location
Epitope IQQEFGIPY
Immunogen
Species (MHC) human (B*1503)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B*1503 epitope.

HXB2 Location Integrase (135–143)
Author Location Integrase (135–143)
Epitope IQQEFGIPY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Assay type Other
Keywords HLA associated polymorphism
References Boutwell & Essex 2007

- Publicly available HIV-1 subtype C sequences from South Africa and Botswana were analyzed, and 94 HLA-associated amino acid polymorphisms were found. Many polymorphisms were associated with multiple HLA allele classes. 12% associations were negative: association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles accounted for 50% of associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes.
- IQQEFGIPY was a previously defined B*1503 presented epitope that encompassed a polymorphism, IqQEFGIPY,in the second position.

HXB2 Location Integrase (135–143)
Author Location Integrase
Epitope IQQEFGIPY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, rate of progression, immunodominance
References Frahm *et al.* 2006

- CTL responses restricted by HLA-B*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects inspite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominanat CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.
- IQQEFGIPY of clade C is a potential HLA-B*1503-restricted epitope.

HXB2 Location Integrase (135–143)
Author Location Integrase
Epitope IQQEFGIPY
Epitope name IY9(Integrase)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B15)
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords enhancing activity, non-susceptible form
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- The tested peptide sequences, KAACWWAGIKQEFGIPY and GIKQEFGIPYNPQSQGVV, contain a variant, IkQEFGIPY that differs by 1 substitution from the previously described HLA-B15 epitope IQQEFGIPY. None of the 21 HLA-B15 carriers responded to the variant IkQEFGIPY.

HXB2 Location Integrase (135–146)
Author Location Integrase
Epitope IQQEFGIPYNPQ
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).

- IQQEFGIPY is a previously described HLA-B*1503-restricted epitope (part of Pol(Integrase) reacting peptide VKAACWWAGIqQEFGIPYNPQ) that contains a B*1503-associated reversion at residue Q (IqQEFGIPY).

HXB2 Location Integrase (136–143)
Author Location Integrase
Epitope KQEFGIPY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, rate of progression, immunodominance
References Frahm *et al.* 2006

- CTL responses restricted by HLA-B*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects inspite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominanat CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.
- KQEFGIPY of clade B is a potential HLA-B*1503-restricted epitope.

HXB2 Location Integrase (141–150)
Author Location Pol
Epitope IPYNPQSQGV
Epitope name Pol1128
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Novel Pol epitope IPYNPQSQGV elicits IFN-gamma ELISpot responses in 2/7 subjects; and bound HLA-B7 with low and high affinities in soluble and cell-based assays respectively.

HXB2 Location Integrase (141–150)
Author Location Pol
Epitope IPYNPQSQGW
Epitope name Pol893
Subtype B
Immunogen vaccine
Vector/Type: polyepitope *HIV component:* Other
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- IPYNPQSQGW is a Pol epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location Integrase (141–151)
Author Location Pol (893–)
Epitope IPYNPQSQGVV
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (B*0702)
Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008

- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location Integrase (141–151)
Author Location Pol
Epitope IPYNPQSQGVV
Epitope name Pol893
Subtype A, B, C, D
Immunogen HIV-1 infection
Species (MHC) human, mouse (B7 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope IPYNPQSQGVV of the HLA-B7 supertype bound most strongly to HLA-B*5401, and -B*5101 and also to -B*0702 but not to -B*5301 and -B*3501. It was conserved 100% in subtype A, 89% in B, 100% in C and 100% in subtype D. 0/16 HLA-B7 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Pol893.

HXB2 Location Integrase (157–166)
Author Location (C consensus)
Epitope ELKKIIGQVR
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*33)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- ELKKIIGQVR is an optimal epitope.

HXB2 Location Integrase (157–166)
Author Location Integrase
Epitope ELKKIIGQVR
Epitope name ER9
Immunogen
Species (MHC) human (A*3301)
References Zimbwa *et al.* 2007

- E169D is a processing mutation for HLA-B*0702 restricted SPAIFQSSM (SM9) as well as an epitope variation for HLA-A*0301 restricted MTKILEPFR (MR9).
- CTL recognition of Int epitope ELKKIIGQVR was not detected post-infection with either wild type (169E) or mutant 169D HIV-1. ER9 was used as a negative control since Jurkat cell line E6-1 is negative for ER9-restricting HLA-A*3301.

HXB2 Location Integrase (164–172)
Author Location (C consensus)
Epitope QVRDQAEHL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0205)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- QVRDQAEHL is an optimal epitope.

HXB2 Location Integrase (165–172)
Author Location Integrase (165–172)
Epitope VRDQAEHL
Epitope name VL8
Immunogen
Species (MHC) human (Cw*18)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a Cw18 epitope.

HXB2 Location Integrase (165–172)
Author Location (C consensus)
Epitope VRDQAEHL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*1801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- VRDQAEHL is an optimal epitope.

HXB2 Location Integrase (165–172)
Author Location Integrase (165–172)
Epitope VRDQAEHL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*1801)
Assay type Other
Keywords HLA associated polymorphism
References Boutwell & Essex 2007

- Publicly available HIV-1 subtype C sequences from South Africa and Botswana were analyzed, and 94 HLA-associated amino acid polymorphisms were found. Many polymorphisms were associated with multiple HLA allele classes. 12% associations were negative: association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles accounted for 50% of associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes.
- VRDQAEHL was a previously defined Cw1801 presented epitope that encompassed a Cw18 associated polymorphism, VRdQAEHL,in the third position.

HXB2 Location Integrase (165–172)
Author Location Integrase (165–172)
Epitope VRDQAEHL
Immunogen peptide-HLA interaction
Species (MHC) human (Cw*1801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords optimal epitope
References Honeyborne *et al.* 2006

- Novel epitopes are defined for four HLA-alleles common in South African Zulu/Xhosa populations: B*3910, B*4201, B*8101 and Cw*1801, by motif inference. HLA-A*2902 was found to overlap those of A1 and A24 supertypes.
- VRDQAEHL was the optimal epitope for HLA-Cw*1801 with variants VRDQAEH, RDQAEHL, VRDQAEHLk, qVRDQAEHL having been tested.

HXB2 Location Integrase (171–180)
Author Location Pol
Epitope HLKTAVQMAV
Epitope name 1247

Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A01, A02, B08, Cw16
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for HLKTAVQMAV: 82%

HXB2 Location Integrase (173–181)
Author Location
Epitope KTAVQMAVF
Epitope name KF9
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B*57-restricted optimal epitope KTAVQMAVF was tested for immune response.

HXB2 Location Integrase (173–181)
Author Location Integrase (173–181)
Epitope KTAVQMAVF
Epitope name intKF9
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country United Kingdom, Kenya
Assay type CD8 T-cell Elispot - IFNγ
Keywords TCR usage, structure, characterizing CD8+ T cells
References Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B*57-peptide complexes were studied.
- In addition, immunodominancy of the previously mapped B*57 epitopes during chronic infection was assessed. KGFNPEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

HXB2 Location Integrase (173–181)
Author Location Pol (888–896)
Epitope KTAVQMAVF
Immunogen
Species (MHC) human (B*5701)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*5701 epitope.
- Epitope is motif based, personal communication from C. Hay.
- Subtype of B57 not determined.

HXB2 Location Integrase (173–181)
Author Location Pol (888–896)
Epitope KTAVQMAVF
Immunogen
Species (MHC) human (B57)
References Hay 1999

- Epitope is motif based, personal communication from C. Hay.

HXB2 Location Integrase (173–181)
Author Location Pol
Epitope KTAVQMAVF
Epitope name KF9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was quite conserved in people carrying B57, but two substitutions were found in 11 B57+ individuals tested: Rtavqmavf and ktavqmavL.

HXB2 Location Integrase (173–181)
Author Location Pol (889–897)
Epitope KTAVQMAVF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location Integrase (173–181)
Author Location
Epitope KTAVQMAVF
Immunogen HIV-1 infection, vaccine

Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location Integrase (173–181)
Author Location
Epitope KTAVQMAVF
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords responses in children, mother-to-infant transmission, escape
References Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.

HXB2 Location Integrase (177–186)
Author Location Pol (929–)
Epitope QMAVFIHNFK
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (A*0301)
Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008

- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location Integrase (177–186)
Author Location Pol
Epitope QMAVFIHNFK
Epitope name Pol929
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (A3)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- QMAVFIHNFK is a Pol epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location Integrase (177–186)
Author Location Pol (919–928)
Epitope QMAVFIHNFK
Immunogen HIV-1 infection
Species (MHC) human (A3 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 5/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801).

HXB2 Location Integrase (177–186)
Author Location Pol
Epitope QMAVFIHNFK
Epitope name Pol929
Subtype A, B, C, D
Immunogen HIV-1 infection
Species (MHC) human, mouse (A3 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA

References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope QMAVFIHNFK of the HLA-A3 supertype bound most strongly to HLA-A*1101, -A*0301 and -A*3101 and also to -A*6801 and -A*3301. It was conserved 100% in subtype A, 100% in B, 88% in C and 100% in subtype D. 4/23 HLA-A3 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Pol929.

HXB2 Location Integrase (178–186)
Author Location Pol (920–928)
Epitope MAVFIHNFK
Immunogen HIV-1 infection
Species (MHC) human (A3 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801).

HXB2 Location Integrase (179–187)
Author Location Integrase (179–187)
Epitope AVFIHNFKR
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to published restriction above, epitope AVFIHNFKR was predicted to be restricted by HLA A*0301, A*1101, A*3101, A*3301, A*6601 and A*6801.

HXB2 Location Integrase (179–187)
Author Location Pol (921–929)
Epitope AVFIHNFKR
Immunogen HIV-1 infection
Species (MHC) human (A3 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 5/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801).

HXB2 Location Integrase (179–188)
Author Location Integrase (179–188)
Epitope AVFIHNFKRK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Integrase (179–188)
Author Location Integrase (179–188)
Epitope AVFIHNFKRK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*11)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA

CTL CD8+

type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This putative epitope, AVFIHNFKRK, was detected and confirmed within overlapping peptides AVFIHNFKRKGGIGGYSA and RKGGIGGYSAGERIVDII.

HXB2 Location Integrase (179–188)
Author Location Integrase (179–188 LAI)
Epitope AVFIHNFKRK
Subtype B
Immunogen
Species (MHC) human (A*1101)
Keywords optimal epitope
References Fukada *et al.* 1999; Llano *et al.* 2009
- C. Brander notes this is an A*1101 epitope.

HXB2 Location Integrase (179–188)
Author Location Pol (894–903)
Epitope AVFIHNFKRK
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Keywords subtype comparisons
References Fukada *et al.* 2002
- Counterparts for eight known clade B HLA A*1101 epitopes were generated for clade E (CRF01). Three epitopes, identical among clade A-E, were cross-reactive and recognized by clade E infected individuals. The clade E and B analogs to three more HLA A*1101 epitopes was recognized in a clade specific manner. Two other HLA A*1101 clade B defined epitopes were found not to have stimulated a response in clade E infected individuals.
- AVFIHNFKRK is commonly found in viruses representing subtypes A-E. It was strongly recognized by CTL from 4/7 E clade infected Thai subjects.

HXB2 Location Integrase (179–188)
Author Location Pol (894–903 93TH253 subtype CRF01)
Epitope AVFIHNFKRK
Epitope name P894-903
Subtype CRF01_AE
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A11)
Keywords HIV exposed persistently seronegative (HEPS)
References Bond *et al.* 2001
- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was weakly reactive in the HEPS study subjects 265 who was HLA A2/A11 and 128 who was HLA A11/A33, and had been predicted to be a possible A11 epitope using Epimer in Bond *et al.* [2001]

HXB2 Location Integrase (179–188)
Author Location Integrase
Epitope AVFIHNFKRK
Epitope name A11-AK10(Int)
Immunogen HIV-1 infection
Species (MHC) human (A11)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006
- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Integrase (179–188)
Author Location Integrase
Epitope AVFIHNFKRK
Epitope name AK10(Integrase)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11, A3)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008
- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide sequence LKTAVQMAVFIHNFKRK contains the exact sequence of a previously described HLA-A3 optimal epitope, AVFIHNFKRK, none of the 3 HLA-A3 carriers responded to it. 4 of the 28 HLA-A11 carriers responded to the AVFIHNFKRK-containing peptide AVFIHNFKRKGGIGGYSA with average magnitude of CTL response of 150 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Integrase (179–188)
Author Location Pol
Epitope AVFIHNFKRK
Epitope name 1264
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A11, A3, A68)

Donor MHC A01, A68, B15, B40, Cw03; A03, A11, B14, B51, Cw08, Cw13; A25, A68, B18, B27
Country United States
Assay type T-cell Elispot
Keywords binding affinity, supertype, computational epitope prediction, immunodominance, cross-presentation by different HLA
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for AVFIHNFKRK:53% Supertype epitope binding to A11, A03 and A68. Immunodominant.

HXB2 Location Integrase (179–188)
Author Location Integrase (894–904)
Epitope `AVFIHNFKRK`
Epitope name A3-AK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 1/7 individuals began to have detectable responses to this epitope after STI.

HXB2 Location Integrase (179–188)
Author Location Integrase (179–188)
Epitope `AVFIHNFKRK`
Epitope name A3-AK10 Pol
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), escape, early treatment, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The second infecting strain had the variant avfVhnfkrk. The CTL response to the second variant was zero at all timepoints. The CTL response to the first variant was low and declined over time.

HXB2 Location Integrase (179–188)
Author Location Pol
Epitope `AVFIHNFKRK`
Epitope name 1264
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, A23, B49, B57; A03, A24, B27, B57, Cw13, Cw18
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for AVFIHNFKRK: 52%

HXB2 Location Integrase (179–196)
Author Location Pol (894–911)
Epitope `AVFIHNFKRKGGIGGYSA`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location Integrase (185–194)
Author Location Integrase (185–194)
Epitope `FKRKGGIGGY`
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Integrase (185–194)
Author Location (C consensus)
Epitope `FKRKGGIGGY`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ

CTL CD8+

Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

CTL CD8+

HXB2 Location Integrase (185–194)
Author Location (C consensus)
Epitope FKRKGGIGGY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the K4 and G9 residues of FKRKGGIGGY are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location Integrase (185–194)
Author Location Integrase (185–194)
Epitope FKRKGGIGGY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Assay type Other
Keywords HLA associated polymorphism
References Boutwell & Essex 2007

- Publicly available HIV-1 subtype C sequences from South Africa and Botswana were analyzed, and 94 HLA-associated amino acid polymorphisms were found. Many polymorphisms were associated with multiple HLA allele classes. 12% associations were negative: association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles accounted for 50% of associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes.
- FKRKGGIGGY was a previously defined B*1503 presented epitope that encompassed a polymorphism, FKRkGGIGGY,in the fourth position.

HXB2 Location Integrase (185–194)
Author Location Integrase
Epitope FKRKGGIGGY
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, rate of progression, immunodominance
References Frahm *et al.* 2006

- CTL responses restricted by HLA-B*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects inspite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominanat CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.
- FKRKGGIGGY of clades B and C is a potential HLA-B*1503-restricted epitope.

HXB2 Location Integrase (185–194)
Author Location Integrase
Epitope FKRKGGIGGY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- FKRKGGIGGY is a previously described HLA-B*1503-restricted epitope (part of Pol(Integrase) reacting peptide MAVFIHNFKRkGGIGGYSAGE) that contains a B*1503-associated reversion at residue K (FKRkGGIGGY).

HXB2 Location Integrase (185–194)
Author Location Integrase
Epitope FKRKGGIGGY
Epitope name FY10(Integrase)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B15)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.

- Although the tested peptide sequence contains the exact sequence of a previously described HLA-B15 optimal epitope, FKRKGGIGGY, none of the 21 HLA-B15 carriers responded to it (author communication and Fig.1).

HXB2 Location Integrase (186–194)
Author Location
Epitope KRKGGIGGY
Immunogen
Species (MHC) (B*2705)
Keywords optimal epitope
References Payne & Goulder 2009
- Noted by R.P. Payne and P.J. Goulder to be an optimal epitope.

HXB2 Location Integrase (186–194)
Author Location
Epitope KRKGGIGGY
Immunogen
Species (MHC) (B*2705)
Keywords optimal epitope
References Llano *et al.* 2009
- Noted by R.P. Payne and P.J. Goulder to be an optimal epitope.

HXB2 Location Integrase (186–194)
Author Location
Epitope KRKGGIGGY
Epitope name KY9
Immunogen
Species (MHC) human (B*2705)
Keywords optimal epitope
References Llano *et al.* 2009
- C. Brander notes this is a B*2705 epitope.

HXB2 Location Integrase (186–194)
Author Location Pol
Epitope KRKGGIGGY
Epitope name KY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008
- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- KY9, KRKGGIGGY, is a novel HLA-B27-restricted epitope that elicits a CTL IFN-gamma response significantly higher than that of Los Alamos database peptides.

HXB2 Location Integrase (197–204)
Author Location Integrase (196–203)
Epitope GERIVDII
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c
- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, GERIVDII, of unknown HLA restriction, was detected within overlapping peptides RKGGIGGYSAGERIVDII, SAGERIVDIIATDIQTK and DIIATDIQTKELQKQITK.

HXB2 Location Integrase (203–211)
Author Location Integrase (202–212)
Epitope IIATDIQTK
Epitope name IK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*11)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c
- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This novel epitope, IIATDIQTK (IK9), was detected and confirmed within overlapping peptides SAGERIVDIIATDIQTK and DIIATDIQTKELQKQITK.

HXB2 Location Integrase (203–211)
Author Location
Epitope IIATDIQTK
Epitope name IK9
Immunogen

CTL CD8+

Species (MHC) human (A*1101)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a A*1101 epitope.

HXB2 Location Integrase (210–227)
Author Location Pol (925–942)
Epitope TKELQKQIIKIQNFRVYY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location Integrase (214–228)
Author Location Pol (929–943)
Epitope QKQITKIQNFRVYYR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the Progressor.

HXB2 Location Integrase (218–227)
Author Location Integrase
Epitope TKIQNFRVYY
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, rate of progression, immunodominance
References Frahm *et al.* 2006

- CTL responses restricted by HLA-B*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects inspite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominanat CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.
- TKIQNFRVYY of clade B is a potential HLA-B*1503-restricted epitope, with epitope iKIQNFRVYY found in clade C.

HXB2 Location Integrase (218–232)
Author Location Integrase (933–947)
Epitope TKIQNFRVYYRDSRD
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008

- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.
- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.
- CTL immune response to consensus sequence TKIQNFRVYYRDSRD was elicited in subject 00016. Consensus epitope of subject 00015 was the same as Clade B consensus and of subject 00016 was TKIQNFRVYYRDhRD.

HXB2 Location Integrase (218–235)
Author Location RT-Integrase (218–235 HXB2)
Epitope TKIQNFRVYYRDSRDPLW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.

- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 21% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location Integrase (219–226)
Author Location (C consensus)
Epitope KIQNFRYY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the K1 residue of KIQNFRYY are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location Integrase (219–227)
Author Location
Epitope KIQNFRVYY
Epitope name Pol-KY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Donor MHC A*0205, A*3002, B*1402, B*5301, Cw*0401, Cw*0802
Keywords HAART, ART
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Patient 00RCH28 was African American, not on HAART, had a viral load of 5900 and CD4 count of 889, and she also recognized RIRQGLERA, gp160(846-854), A*0205.
- Among HIV+ individuals who carried HLA A30, 6/16 (38%) recognized this epitope.

HXB2 Location Integrase (219–227)
Author Location Integrase (219–227)
Epitope KIQNFRVYY
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Integrase (219–227)
Author Location (C consensus)
Epitope KIQNFRVYY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location Integrase (219–227)
Author Location Integrase (219–227)
Epitope KIQNFRVYY
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.

CTL CD8+

- In addition to the published restriction above, epitope KIQNFRVYY was predicted to be restricted by HLA A1 and A*3002.

HXB2 Location Integrase (219–227)
Author Location Integrase
Epitope KIQNFRVYY
Epitope name KLY9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Country South Africa
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization
Keywords rate of progression
References Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naive patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer A*3002 KLY9 was used to test 20 patients and gave a median ex vivo tetramer frequency of 0.45.

HXB2 Location Integrase (219–227)
Author Location Integrase (219–227)
Epitope KIQNFRVYY
Epitope name KIY9
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Country South Africa
Assay type proliferation, Tetramer binding, Intracellular cytokine staining
References Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

HXB2 Location Integrase (219–227)
Author Location Integrase
Epitope KIQNFRVYY
Epitope name KY9
Immunogen HIV-1 infection
Species (MHC) human (A30)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords epitope processing, supervised treatment interruptions (STI), immunodominance
References Rodriguez *et al.* 2004

- Protease and integrase are shown to be frequently targeted by CD8 T-cell responses (23% and 68% of 56 HIV+ patients, respectively). Responses tend to cluster in conserved regions of Int, although 1 high conserved region had no responses. CTL frequencies per unit protein length for Pro and Int were similar to other HIV non-structural proteins. Three novel HLA class I-restricted optimal epitopes were found and characterized with fine mapping.

HXB2 Location Integrase (219–227)
Author Location Integrase
Epitope KIQNFRVYY
Epitope name KY9(Integrase)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A30)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the peptides tested, FKIQNFRVYYRDSRDPLW and TKELQKQITKIQNFRVYY, contained the exact sequence of a previously described HLA-A30 epitope, KIQNFRVYY, none of the 15 HLA-A30 carriers responded to it (author communication and Fig.1).

HXB2 Location Integrase (219–227)
Author Location
Epitope KIQNFRVYY
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A*2501, A*3002; B*0702, B*1801
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location Integrase (219–227)
Author Location
Epitope KIQNFRVYY
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost, polyepitope *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human
Donor MHC A*3001, A*3002; B*4201/02, B*4403/26/30
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location Integrase (219–227)
Author Location Pol
Epitope KIQNFRVYY
Subtype B, D, AE
Immunogen HIV-1 infection
Species (MHC) human
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- Epitope KIQNFRVYY was recognized by at least 4 patients with restricting HLA supertype and infected with several HIV subtypes. Predicted HLA restriction for this epitope was to supertertype A1.

HXB2 Location Integrase (219–228)
Author Location Pol (934–943 SF2)
Epitope KIQNFRVYYR
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (A*3303)
Assay type Chromium-release assay
Keywords binding affinity, computational epitope prediction
References Hossain *et al.* 2003

- HLA-A*3303 is a common HLA allele in east and southeast Asia. Pol, Gag and Nef SF2 proteins were scanned for potential A*3303 epitopes. 99 potential epitopes were synthesized, and 52/99 bound to A*3303. Six of these served as peptide-targets for lysis by PBMC from infected individual, and clones derived from 4 of these 6 could lyse HIV-vaccinia infected target cells, indicating proper processing.
- This epitope is one of the 4 that are properly processed.

HXB2 Location Integrase (219–228)
Author Location Pol
Epitope KIQNFRVYYR
Epitope name Pol971
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (A3)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- KIQNFRVYYR is a Pol epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location Integrase (219–228)
Author Location Pol (919–928)
Epitope KIQNFRVYYR
Immunogen HIV-1 infection
Species (MHC) human (A3 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.

- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 5/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801).

HXB2 Location Integrase (219–228)
Author Location Pol
Epitope `KIQNFRVYYR`
Epitope name Pol971
Subtype A, B, C, D
Immunogen HIV-1 infection
Species (MHC) human, mouse (A3 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope KIQNFRVYYR of the HLA-A3 supertype bound most strongly to HLA-A*3101, -A*1101 but also to -A*6801, -A*3301 and -A*0301. It was conserved 75% in subtype A, 95% in B, 75% in C and 100% in subtype D. 4/23 HLA-A3 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Pol971.

HXB2 Location Integrase (232–241)
Author Location Pol
Epitope `DPIWKGPAKL`
Epitope name Pol1143
Subtype C
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Novel Pol epitope DPIWKGPAKL elicits IFN-gamma ELISpot responses in 2/7 subjects; and bound HLA-B7 with low affinity in cell-based assays.

HXB2 Location Integrase (241–249)
Author Location Pol (576–584)
Epitope `LLWKGEGAV`
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
References van der Burg *et al.* 1996

- Slow dissociation rate, associated with immunogenicity in transgenic HLA-A*0201/K^b mice.
- CTL generated by *in vitro* stimulation of PBMC derived from uninfected individual.

HXB2 Location Integrase (241–249)
Author Location RT (956–964 HXB2R)
Epitope `LLWKGEGAV`
Epitope name LR28
Subtype B
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade LAI *Adjuvant:* Incomplete Freund's Adjuvant (IFA), Montanide (ISA 720), P30, PLG
Species (MHC) mouse (A*0201)
Keywords binding affinity, vaccine-specific epitope characteristics, immunodominance
References Peter *et al.* 2001

- The stability of peptide binding to HLA-A2.1 was determined for six HLA-A2.1 peptides included in this vaccine study – ILKEPVHGV (RT), SLYNTVATL (p17), SLLNATDIAV (gp41) and LLWKGEGAV (RT) all bound with high affinity comparable to a influenza epitope reference (GILGFVFTL), while RGPGRAFVTI and VIYQYMDDL bound with a lower affinity (relative binding activity = 0.01).
- The four high-affinity peptides formed stable complexes with half-lives ranging between 8 and 32 hours, while the low affinity peptides had half lives of less than an hour.
- HLA-A2.1 transgenic mice were immunized with the six HIV-1 peptides and P30, as a universal T-helper epitope, with IFA or Montanide or microspheres as adjuvants.
- All peptides except VIYQYMDDL induced a stong CTL response in Cr-release assays - stronger responses were observed when peptides were delivered alone, indicating immunodominance when the combination was used.

HXB2 Location Integrase (241–249)
Author Location RT (956–964 HXB2R)
Epitope `LLWKGEGAV`
Epitope name LR28
Subtype B
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade LAI *Adjuvant:* Incomplete Freund's Adjuvant (IFA), IL-12, P30
Species (MHC) mouse (A*0201)
Keywords vaccine-specific epitope characteristics, immunodominance
References Peter *et al.* 2002

- When HIV-1 peptides were used to vaccinate HLA-A2.1 transgenic A2-Kb mice, strong responses to five peptides were observed when the peptides were given individually, but immunodominance limited the response to some of the peptides when they were given in combination Peter *et al.* [2001]. IL-12 can counteract immunodominance in BALB/c mice, so it was given with the multiple epitope vaccination, and was instead found to specifically eliminate the HLA-A2.1-epitope

CTL responses, but not Kb CTL responses. This was possibly a consequence of transient depletion of T-cells, B cells and macropahges in the spleen.

HXB2 Location Integrase (241–249)
Author Location Pol
Epitope LLWKGEGAV
Epitope name L9V
Immunogen vaccine
Vector/Type: measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140ΔV3
Species (MHC) transgenic mouse (A*0201)
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells
References Lorin *et al.* 2005a

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

HXB2 Location Integrase (241–249)
Author Location RT (241–249)
Epitope LLWKGEGAV
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope LLWKGEGAV was predicted to be restricted by HLA A*0201, A*0204, A*0205 and A*0209.

HXB2 Location Integrase (241–249)
Author Location Pol (956–964)
Epitope LLWKGEGAV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords dendritic cells
References Kundu *et al.* 1998b

- Allogeneic dendritic cells (DCs) were obtained from HLA-identical siblings, pulsed with rgp160 MN or A2-restricted HIV-1 epitope peptides, and infused monthly into six HIV-infected patients.
- 1/6 showed increased Env-specific CTL and increased lymphoproliferative responses, 2/6 showed increase only in proliferative responses, and 3/6 showed no change – pulsed DCs were well tolerated.
- LLWKGEGAV is a conserved HLA-A2 epitope included in this study – 6/6 patients had this sequence as their HIV direct sequence, but only four of these had a detectable CTL response.

HXB2 Location Integrase (241–249)
Author Location Pol (956–964 HXB2R)
Epitope LLWKGEGAV
Immunogen peptide-HLA interaction
Species (MHC) human (A2)
References Parker *et al.* 1992; Parker *et al.* 1994

- Studied in the context of HLA-A2 peptide binding.

HXB2 Location Integrase (241–249)
Author Location Pol (956–964 HXB2R)
Epitope LLWKGEGAV
Immunogen peptide-HLA interaction
Species (MHC) human (A2)
References Brander *et al.* 1995

- No CTL activity found in HIV-infected subjects, epitope studied in the context of inclusion in a synthetic vaccine.

HXB2 Location Integrase (241–249)
Author Location Pol (956–964)
Epitope LLWKGEGAW
Immunogen HIV-1 infection
Species (MHC) human (A*0201, A2)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location Integrase (258–275)
Author Location RT
Epitope KVVPRRKAKIIRDYGKQM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

CTL CD8+

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, KVVPRRKAKIIRDYGKQM, had an overall frequency of recognition of 15.3% - 20.3% AA, 7.7% C, 9.1% H, 19% WI.

HXB2 Location Integrase (260–268)
Author Location Integrase (260–268)
Epitope VPRRKAKII
Immunogen
Species (MHC) human (B42)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Integrase (260–268)
Author Location Integrase (260–268)
Epitope VPRRKVKII
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B42)
Assay type Other
Keywords epitope processing, HLA associated polymorphism
References Boutwell & Essex 2007

- Publicly available HIV-1 subtype C sequences from South Africa and Botswana were analyzed, and 94 HLA-associated amino acid polymorphisms were found. Many polymorphisms were associated with multiple HLA allele classes. 12% associations were negative: association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles accounted for 50% of associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes.
- VPRRKVKII was a previously defined B42 presented epitope that was associated with a polymorphism, VPRRKVKII|k seen just after the last position in that epitope.

HXB2 Location Integrase (260–268)
Author Location Pol
Epitope VPRRKAKII
Epitope name Pol1132
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Previously published epitope VPRRKAKII elicits IFN-gamma ELISpot responses in 3/7 subjects; and bound HLA-B7 with medium and high affinities in soluble and cell-based assays respectively.

HXB2 Location Integrase (263–271)
Author Location Integrase (263–271)
Epitope RKAKIIRDY
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Integrase (263–271)
Author Location Integrase (263–271)
Epitope RKAKIIRDY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Donor MHC A*2301, B*1503, B*3501, Cw2, Cw7
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.

- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

HXB2 Location Integrase (263–271)
Author Location (C consensus)
Epitope RKAKIIKDY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location Integrase (263–271)
Author Location (C consensus)
Epitope RKAKIIKDY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords epitope processing, rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the A3 residue of RKAKIIKDY are associated with the presence of the HLA presenting molecule in the host. Mutation of a residue outside of the optimized epitope also associated with HLA.

HXB2 Location Integrase (263–271)
Author Location Integrase
Epitope RKAKIIRDY
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, rate of progression, immunodominance
References Frahm *et al.* 2006

- CTL responses restricted by HLA-B*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects inspite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominanat CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.
- RKAKIIRDY of clade B is a potential HLA-B*1503-restricted epitope, with epitope RKAKIIkDY found in clade C.

HXB2 Location Integrase (263–271)
Author Location Integrase
Epitope RKAKIIRDY
Epitope name B15-RY9(Int)
Immunogen HIV-1 infection
Species (MHC) human (B15)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Integrase (263–271)
Author Location Integrase
Epitope RKAKIIRDY
Epitope name RY9(Integrase)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B15)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.

CTL CD8+

- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B15-restricted epitope RKAKIIRDY elicited an immune response in Chinese HIV-1 positive subjects as part of peptide KVVPRRKAKIIRDYGKQM.
- 1 of the 21 HLA-B15 carriers responded to RKAKIIRDY-containing peptide with a magnitude of CTL response of 1,150 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Integrase (266–273)
Author Location Integrase (266–272)
Epitope `KIIRDYGK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, KIIRDYGK, of unknown HLA restriction, was detected within overlapping peptides KVVPRRKAKIIRDYGKQM and KIIRDYGKQMAGDDCVA.

HXB2 Location Integrase (266–275)
Author Location (C consensus)
Epitope `KIIKDYGKQM`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the I3 residue of KIIKDYGKQM are associated with the presence of the HLA presenting molecule in the host.
- KIIKDYGKQM not optimized.

HXB2 Location Integrase (266–275)
Author Location Integrase (266–275)
Epitope `KIIKDYGKQM`
Epitope name KM10
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Other
Keywords supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism
References Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alelles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Statistically significant associations between numbers of HLA-4201 expressing subjects and epitope KIIKDYGKQM were found.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope KM10 restriction.

II-B-15 Pol CTL/CD8+ epitopes

HXB2 Location Pol
Author Location
Epitope
Immunogen computer prediction
Species (MHC) (A*0201, B*3501)
Keywords subtype comparisons, computational epitope prediction
References Schönbach *et al.* 2002

- Computational methods (artificial neural networks, hidden Markov models, binding matrices based on HLA association rates) were used to identify HLA-A*0201 and HLA-B*3501 HIV T-cell epitope candidates from 533 Gag, Env and Pol sequences of which 374 were derived from HIV-1, 97 were derived from HIV-2 and 62 from SIV. Comparisons to known epitopes and between clades were made.

HXB2 Location Pol
Author Location Pol
Epitope
Immunogen HIV-1 infection
Species (MHC) human (A*0201, Cw*08)
References Shacklett *et al.* 2000

- HIV-1 specific, MHC class I-restricted CTL killing was detected in duodenal and rectal gut associated lymphoid tissue (GALT) sites from three infected individuals – the distribution of class I restricted CTL was different in the peripheral blood samples and GALT samples.

HXB2 Location Pol
Author Location RT (IIIB)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords epitope processing, escape
References Moore *et al.* 2002b

- HIV polymorphisms in the RT protein were examined relation to HLA alleles found in a population of 473 participants in the Western Australian HIV Cohort Study. 64 significant associations between polymorphisms at particular positions and HLA alleles were detected, for HLA-B7, -B12, -B35 and -B15. Fifteen of these were in positions with known epitopes, 4 in anchor residues, 11 in other positions. Six additional polymorphic sites associated with particular HLA molecules flanked known epitopes and may relate to processing.
- 25 negative associations were also found between polymorphism and HLA alleles. The authors propose this is due to escape mutations in epitopes presented by common HLA types dominating in the population, and give examples of five amino acids which are in the consensus and tend to be stable in those with the most common HLA allele, HLA-A2.

HXB2 Location Pol
Author Location Pol
Epitope
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement
References Wu *et al.* 2005

- A flow cytometric assay for validation of HIV-1 gag- or pol-specific- CD8/HLA-A2 T-cells was shown to be sensitive and specific, being able to detect HIV-1 CTL at the single T-cell level. An inverse correlation between HIV plasma viremia and gag- and pol-specific-CD8/HLA-A2 T-cells was observed.

HXB2 Location Pol
Author Location Pol
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Keywords rate of progression
References Jin *et al.* 2002

- Patients with HLA-B*35 variants B*3502, B*3503, B*3504, and B*5301 tend to proceed to AIDS more quickly than those with B*3501.
- Of 32 patients with HLA-B*35 alleles CD8+ CTL responses were quantified using an intracellular cytokine staining assay – 75% had responses to Pol, 69% to Gag, 50% to Nef, and 41% to Env.
- The overall magnitude of CTL responses did not differ between those bearing B*3501 and the others. A higher percentage of Gag responses was observed in those that had lower RNA levels that carried B*3501, and there was a negative association with viral load and CTL activity. The data is consistent with higher levels of CTL responses contributing to protection in B*3501 individuals, but not in B*3502, B*3503, B*3504, and B*5301 individuals.

HXB2 Location Pol
Author Location Pol
Epitope
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade HXB2, B clade NL43 *HIV component:* Gag, Pol
Species (MHC) mouse (H-2^d)
References Huang *et al.* 2001

- Different HIV strains were used for different regions: gag HXB2, pol NL43
- Mice were immunized with four humanized DNA constructs: GagPol, that would form a pseudoparticle carrying Gag and Pol, Gag, Pol or a GagPol fusion construct.
- The GagPol pseudoparticle, Gag and GagPol fusion construct all elicited strong anti-Gag CTL, but only the GagPol fusion construct elicited strong anti -Pol CTL.

HXB2 Location Pol
Author Location RT (LAI)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Buseyne *et al.* 1998a

- This study showed a correlation between strong CTL memory and breadth of response in 7-12 month old infants, and remaining AIDS-free for the first year of life, higher absolute CD4 and CD8 cells, and lower viral load.

HXB2 Location Pol
Author Location p66 (LAV)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, dendritic cells
References Zheng *et al.* 1999

- Protein delivery (gp160 LAV, p66 LAV, and p24 NY5) to human dendritic cells (DC) with liposomes provides enhanced memory CTL response relative to delivery of protein alone.
- Chloroquine administration enhanced epitope presentation, and brefeldin A and peptide aldehyde inhibitors inhibited antigen presentation, suggesting epitopes were processed by classical proteasome pathway.

HXB2 Location Pol
Author Location Pol (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression, Th1
References Wasik *et al.* 2000

- HIV+ infants that progressed rapidly to AIDS had lower Th1 responses and decreased production of beta-chemokines and IL-2 relative to other HIV+ infants.

- No HIV+ infants had no demonstrable CTL at birth, but Th1 responses accompanied by CTL responses developed in children with slowly progressive disease, and not in rapid progressors.
- CTLp frequencies were determined by limiting dilution using autologous B cells infected with vaccina/HIV constructs.

HXB2 Location Pol
Author Location Pol (LAI)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp41, Protease, V3
Species (MHC) human
References Salmon-Ceron *et al.* 1999

- The vaccine used was a rec canarypox with HIV-1 gp120 MN, tm/gag/protease LAI (vCP205), alone or with p24E-V3 MN synthetic peptide (CLTB-36))
- Twenty HIV negative subjects were vaccinated in phase I trial with combinations of vCP205 and CLTB-36.
- Immunization with vCP205 induced HIV-1-specific ABs to gp120, V3, and p24 antigens, and CTL immune responses against vCP205 were detected after the fourth immunization in 33% of the subjects against Env, Gag and Pol, but the CLTB-36 peptide did not produce AB or CTL immune responses against p24 or gp160.

HXB2 Location Pol
Author Location Pol (172–219 subtype B)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade SF2 *HIV component:* Env, Gag, Nef, Protease
Species (MHC) human
References Gorse *et al.* 1999b

- The vaccine used was rec canarypox expressing HIV-1 env, gag, pol, nef and protease (vCP300) with or without administration of HIV-1 SF-2 rgp120.
- In vitro inducible CTL activity against HIV-1 Env, Gag, Pol, and Nef antigens was observed in 79% (15 of 19) of vaccine recipients.
- The combination of vCP300 and vP1291 together resulted in an overall increase in CTL induction and detection sensitivity.

HXB2 Location Pol
Author Location Pol (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Betts *et al.* 1999

- This study demonstrated an inverse correlation between HIV Type I plasma viral load and CTL activity directed against HIV-1 Pol, and stronger combined effects of Pol- and Env-specific CTL, in long-term survivors (LTS) of HIV-1 infection.

HXB2 Location Pol
Author Location Pol (BRU)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Aladdin *et al.* 1999

- In vitro measurements of CTL-activity by Cr release assay in bulk culture showed no correlation between CTL-activity (gp120, Gag, Pol and Nef) and disease progression as measured by viral load, CD4 and time to death.

HXB2 Location Pol
Author Location RT (LAI)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Buseyne *et al.* 1998b

- In infants with positive CTL responses, most responses showed cross-clade reactivity with somewhat diminished recognition of epitopes from different subtypes.

HXB2 Location Pol
Author Location RT
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Env, Gag, Pol, Vif *Adjuvant:* B7, IL-12
Species (MHC) mouse
References Kim *et al.* 1997c

- A gag/pol, vif or gp160 DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules B7 and IL-12, gave a dramatic increase in both the cytotoxic and proliferative responses in mice.
- When IL-12 was present, CTL response could be detected even without *in vitro* stimulation.

HXB2 Location Pol
Author Location RT
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Trickett *et al.* 1998

- Twelve HIV-1 infected patients were re-infused with their own lymphocytes, cryopreserved from an earlier time point in the infection.
- Improvement in CD4+ and CD8+ T cells were seen in 7/12, and an increase in the CTL response to Pol was seen in one patient.

HXB2 Location Pol
Author Location RT
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Froebel *et al.* 1997

- Two HIV-1 infected children with contrasting disease courses were followed longitudinally – one died of AIDS, the other is a long-term non-progressor.
- Reactivity against Gag, Pol, Env and Tat proteins was tested by PBMC bulk cultured cells reacting with protein expressed in vaccinia constructs in autologous EBV transformed B cells.
- The child who progressed consistently had CTL against Pol and Tat.
- The long-term non-progressing child had no detectable CTL, but was heterozygous for a mutation in the CCR5 receptor and for HLA-B49, which has been shown to be associated with slower progression.

HXB2 Location Pol
Author Location Pol (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Betts *et al.* 1997

- 6/8 individuals from Zambia infected with C clade virus had CTL that were able to make response to B clade HIV-1 IIIB vaccinia-expressed Gag, Pol and Env proteins.
- A vigorous cross-clade response was not limited to a particular protein, and the level of recognition of different proteins varied among the six patients.

HXB2 Location Pol
Author Location RT
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References De Maria *et al.* 1997

- CD3+ cells that also carry a natural killer cell receptor (NKR+) can exhibit down regulation of T cell function.
- Anti-NKR IgM MAb masked this inhibitory function and increased HIV-1 specific CTL activity in phytohemagglutinin-activated PBMC cultured in the presence of IL-2 from 3/5 patients, and in one other case anti-NKR MAb brought HIV-1 specific CTL activity to detectable levels.

HXB2 Location Pol
Author Location Pol (LAI, MN)
Epitope
Immunogen HIV-1 exposed seronegative
Species (MHC) human
References Goh *et al.* 1999

- 13/37 exposed uninfected individuals with repeated high-risk sexual exposure had HIV-1 specific CTL against Env, Gag, Pol, or a combination of proteins – CTL activity was correlated with a CCR5 wildtype genotype.
- In this group, the highest CTLp frequencies were directed at Gag, but the most common response was to Env and four individuals had responses to multiple HIV-1 proteins.

HXB2 Location Pol
Author Location Pol (LAI)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: canarypox *HIV component:* Gag, gp120, gp41, Nef, Protease, RT
Species (MHC) human
References Evans *et al.* 1999

- A Canarypox vaccine expressing gp120, gp41, Gag, Protease, Nef and Pol CTL epitopes gave rise to CTL that could be detected in 61% of the volunteers – responses to Gag, Env, Nef and Pol were detected 3-6 months after the last vaccination.

HXB2 Location Pol
Author Location Gag/Pol (MN)
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Env, Gag, Pol *Adjuvant:* CD80, CD86
Species (MHC) chimpanzee
References Kim *et al.* 1998

- The study explores the use of co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses.

HXB2 Location Pol
Author Location Pol (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Jin *et al.* 1998a

- CTL precursor frequencies were determined in HIV-1 infected pregnant women, and significantly higher CTLp frequencies to Pol and Nef were found in non-transmitting mothers than in transmitting mothers;

HXB2 Location Pol
Author Location Pol
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Young *et al.* 2001

- Addition of recombinant rec human IL12 (rhIL12) to cultures increased HIV-specific lysis of HIV-Gag, Pol and gp120 vaccinia expressed antigens (11/15 tested increased lysis by > 5%) if the culture was derived from HIV+ individuals who had CD4 cells/ul > 500.
- 2/10 individuals with <200 CD4 cells/ul, and 3/10 individuals with 200-500 CD4cells/ul, had an increase of >5% upon treatment of the culture with rhIL12, so a few individuals in late stage disease had CD8 cells that maintained responsiveness to rhIL12.

HXB2 Location Pol
Author Location RT (subtype A, B, D)
Epitope
Subtype A, B, D
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Cao *et al.* 2000

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in HIV infected Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, Pol, RT or Nef from HIV-1 clades A, B, and D.
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype.

HXB2 Location Pol
Author Location Pol
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References White *et al.* 2001

- HIV-specific CTL activity was detected in the female reproductive tract of only 1/3 HIV-infected women who underwent a hysterectomy, although CTL could be identified in the PBMC of all three women.

HXB2 Location Pol
Author Location Pol (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Jin *et al.* 2000a

- The CTL precursor level (CTLp) was measured in long term non-progressors (LTNP) with low viral load using limiting dilution analysis and measuring CTL against Env Gag and Pol expressed in vaccinia in autologous targets.
- LTNPs have high memory CTL numbers and low viral load.

HXB2 Location Pol
Author Location Pol
Epitope
Immunogen HIV-1 exposed seronegative
Species (MHC) human
Keywords review, HIV exposed persistently seronegative (HEPS)
References Rowland-Jones *et al.* 2001

- This is a review that summarizes observations about HIV-specific CTL found in the HIV-1 exposed persistently seronegative (HEPS) population.
- The CTL responses assayed by ELISPOT and by CTL precursor frequencies by limiting dilution analysis indicate that CTL in HEPS individuals tend to be of a lower magnitude than in chronic HIV-1 infections – the responses in HEPS cases are below the level of detection by tetramer assays.
- CD8+ CTL responses tend to be detectable in HEPS subjects only if they are recently exposed, and the response diminishes if exposure is reduced – it is not clear if there is a stable memory population in HEPS cases.
- CD8+ CTL responses in the HEPS population are associated with HIV-1 specific CD4+ T cell responses, assayed by proliferation assays, IL-2 secretion, and ELISPOT, and the authors consider the possibility that HIV-1-specific T-help responses improve the "quality" of the CD8+ response in HEPS individuals relative to HIV-1 infected individuals, who tend to have a poor HIV-1-specific T-help response.
- HIV-1 specific CD8+ CTL responses in HIV-1 infected individuals show reduced levels of perforin, and the T cells may not mature properly, and although similar studies have not been conducted in HEPS individuals this is considered as a possible difference in the CTL immune response in HEPS and HIV-1 infected people.

HXB2 Location Pol
Author Location
Epitope
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission
References De Maria *et al.* 1994; Kuhn *et al.* 2002

- 6/24 HIV uninfected infants (ages 15-50 months) born to HIV+ mothers had HIV-1 specific CTL responses to vaccinia-expressed Nef, Gag/Pol, Env.
- Reviewed in Kuhn *et al.* [2002].

HXB2 Location Pol
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission, rate of progression
References Kuhn *et al.* 2002; Wasik *et al.* 1999

- In HIV-infected infants HIV-specific, CTL responses were not detectable in icord blood or in PBMC collected shortly after birth and were absent or remained very low in 3 infants with a rapidly progressive disease. For those who progressed more slowly, the HIV-specific CTL activity varied.
- The two infants with high levels of Env peptide-stimulated IL-2 responses had the highest CTLp frequencies.
- Stronger responses were detected after initiation of the antiretroviral therapy.
- Two babies that were not infected though born to HIV+ mothers had detectable though low HIV-specific CTLp responses to Env (1/2), Pol (2/2), Gag (1/2) cord blood and transiently in PBMC after birth.
- Reviewed in Kuhn *et al.* [2002].

HXB2 Location Pol
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection

Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission
References Aldhous *et al.* 1994; Kuhn *et al.* 2002

- Six of nine HIV vertically infected infants had HIV-1 specific CTL responses to vaccinia expressed Tat (4/6), Pol (6/6), Env (1/6), or Gag (1/6), but not all responses were detected at all time points.
- Two of eleven babies that were not infected though born to HIV+ mothers had detectable responses Tat (1/2), Pol (2/2), Gag (1/2).
- Reviewed in Kuhn *et al.* [2002].

HXB2 Location Pol
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed; however, epitopes were not found that span the invariant, most highly conserved regions of RT and Protease. This might be due to the virus evolving conserved features that disallow the CTL responses in these most conserved regions, as functional constraints for enzyme function would not tolerate change, and normal capacity for immune escape by rapid evolution is lost in these domains.

HXB2 Location Pol
Author Location
Epitope
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, subtype comparisons
References Loemba *et al.* 2002

- Therapeutic RT inhibitors were used to select *in vitro* for resistance mutations in subtype C viruses. Many of the resistance mutations were located within analogs to CTL epitopes that had been defined for the B subtype,

HXB2 Location Pol
Author Location (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, acute/early infection
References Ortiz *et al.* 2002

- Subjects treated with HAART early in HIV-infection showed a correlation between the number of viremic episodes and the total as well as the Pol-specific CD8 T-cell activity as measured by Elispot SFC per million PBMC summed across Pol, Env, Nef and Gag. The subjects treated early after infection had higher levels of CD8+ T-cell activity (N = 31) than those treated later (N = 23), and a greater capacity to enhance CD8+ T-cell responses to viremic episodes.

HXB2 Location Pol
Author Location (MN)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Edwards *et al.* 2002

- 96% (26/27) chronically infected HIV-1 infected patients elicited gamma-IFN CD8+ T-cell responses against Gag.
- Nef and/or Pol CTL responses were detected in 86% of the subjects.
- The magnitude and breadth of Gag and p24 T-cell responses correlated with absolute CD4 counts, and inversely correlated with viral load.
- Pol and Int CTL responses correlated positively with absolute CD4+ T-cell count.
- Nef and Env responses did not correlate with either CD4 counts or viral load.

HXB2 Location Pol
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, dendritic cells
References Larsson *et al.* 2002b

- Autologous mature dendritic cells with rec vaccinia expressing Gag, Pol, Nef and Env could amplify CD8+ T-cell Elispot responses 4-38 fold in five HIV+ patients on successful HAART treatment, relative to autologous monocytes. Some weak responses could only be detected using mature dendritic cells as APCs, and this approach could be useful for detection of low frequency memory cells.

HXB2 Location Pol
Author Location (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords immunotherapy
References Trickett *et al.* 2002

- Conditions were optimized for ex-vivo expansion of CD8+ and CD4+ T-cells with the goal of functional T-cell production for autologous immunotherapy. 10,000-fold expansions were obtained in 14 days with optimized concentrations of IL-2, anti-CD3 and anti-CD28 coated microspheres, and decreasing amounts of serum over the first 8 days.

HXB2 Location Pol
Author Location (IIIB)
Epitope

Subtype B
Immunogen HIV-1 and HCV co-infection
Species (MHC) human
Keywords rate of progression
References Lauer *et al.* 2002

- HIV-1 and HCV immune responses were studied in 22 individuals who were co-infected with HIV-1 and hepatitis C virus (HCV). IFNgamma production was measured in an Elispot assay of CD8+ T-cells using targets expressing either Gag, RT, Env and Nef in a vaccinia construct, or one of seven HCV proteins.
- All 22 patients targeted at least one protein. 20/22 patients recognized RT, 17/22 patients recognized Gag, 13/22 subjects recognized Env and 11/22 patients recognized Nef. Robust CTL activity was independent of disease progression or viral load.
- Despite high HCV viral loads, very few HCV CD8+ T-cell Elispot responses were detected. In a control HCV infected person who did not have HIV-1, strong anti-HCV responses were mounted.
- HIV-specific CD4 proliferative responses were detected in 9/17 coinfected patients, but no HCV responses were detected.

HXB2 Location Pol
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, responses in children
References Scott *et al.* 2001

- CTL responses before and after initiation of ART were studied in 13 HIV-1 vertically infected infants <6 months of age, and 4 that were >6 months of age.
- Before ART 2/13 infants <6 months of age showed IFNgamma Elispot CD8+ T-cell responses, one to Nef and one to Env and Nef, and these responses became undetectable after successful therapy– 3 infants were coinfected with CMV and all 3 had CMV-specific CD8+ T-cell responses.
- One older infant, at 23 months, had CTL responses against all for proteins tested, Gag, Pol, Nef and Env, and had the lowest plasma viremia of the study group. 3/4 infants older than 6 months of age responded to either Nef or Pol.
- Administration of ART over 48 weeks broadened the HIV-1-specific CTL response in 2/4 of the older children that were incomplete responders.

HXB2 Location Pol
Author Location (IIIB, MN)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords dendritic cells
References Larsson *et al.* 2002a

- Dendritic cells acquire and present HIV-1 antigens derived from dead, apoptotic cells or from non-infectious, fusion-competent HIV-1 virions, and these DC cells could stimulate CD4+ and CD8+ T-cells resulting in IFNgamma production in an Elispot assay. Both HLA Class I and class II molecules were used for presentation. This may be an important aspect of the initial immune response to HIV-1 infection of CD4+ cells in the mucosal subepithelia.

HXB2 Location Pol
Author Location (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, supervised treatment interruptions (STI)
References Ortiz *et al.* 2001

- Immune responses in eight chronically HIV-1 infected patients undergoing HAART therapy structured treatment interruptions (STI) were studied. STI boosted HIV-1 specific CTL responses and elevated CTL responses were maintained up to 22 weeks after the last treatment interruption, but viral load rebound to pretreatment levels and CD4 T-cell count decline was observed. CD8 responses in PBMC were measured by cytokine flow cytometry with gp160, Gag p55, RT-Pol and Nef expressed in vaccinia.

HXB2 Location Pol
Author Location Protease-RT
Epitope
Immunogen SHIV infection, vaccine
Vector/Type: peptide *HIV component:* Protease, RT
Species (MHC) macaque
Assay type Intracellular cytokine staining
Keywords HAART, ART, vaccine-specific epitope characteristics, vaccine-induced epitopes, escape, immunotherapy
References Stratov *et al.* 2005

- CD8 T-cells targeting epitopes spanning drug resistance induced mutations were detected in 3/25 individuals harboring multidrug-resistant HIV-1. Novel CD8 T-cell responses were detected against epitopes with common protease inhibitor fitness mutations. T-cell immunity to drug-resistant variants was confirmed in SHIV-infected macaques, where CD8 and CD4 immune responses to RT and protease resistance mutations were elicited using peptide-based immunotherapy.
- The SHIV infected macaques that responded best to the peptide vaccine were those that did not yet have progressive disease. Thus peptide immunotherapy for multidrug resistance has the best hope of success if given to those who are not yet fully immunocompromised.

HXB2 Location Pol
Author Location Pol
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type T-cell Elispot
References Wang *et al.* 2006b

- The association between T cell response and CD4+ T cell counts or CD4+ was investigated, using overlapping peptides corresponding to natural B clade and C consensus sequences.

CTL CD8+

- T cell responses and CD4+ count were correlated for Gag p24 and Gag p17 (B and C clades)and for Pol (C clade). CD4+ counts were higher in patients with Tat and /or Rev T cell response than in patients without Tat and Rev response.

II-B-16 Vif CTL/CD8+ epitopes

HXB2 Location Vif (3–11)
Author Location Vif
Epitope NRWQVMIVW
Epitope name NW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- NW9, NRWQVMIVW, is a novel HLA-B27-restricted epitope that elicits a CTL IFN-gamma response in the same range as Los Alamos database peptides.

HXB2 Location Vif (17–26)
Author Location (LAI)
Epitope RIRTWKSLVK
Subtype B
Immunogen
Species (MHC) human (A*0301)
Keywords optimal epitope
References Altfeld 2000; Llano *et al.* 2009

HXB2 Location Vif (17–26)
Author Location Vif (17–26 SF2)
Epitope RIRTWKSLVK
Epitope name RK10
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
References Altfeld *et al.* 2001a

- CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- 10/29 (35%) individuals tested responded to Vif.
- This epitope was recognized by 3/15 individuals expressing A*0301 allele.
- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- Overlapping Vif peptides QVDRMRIRTWKSLVK and RIRTWKSLVKHHMYI both reacted with T-cells from AC-06 and contained epitope RIRTWKSLVK.

HXB2 Location Vif (17–26)
Author Location Vif (17–26)
Epitope RIRTWKSLVK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Vif (17–26)
Author Location
Epitope RIRTWKSLVK
Epitope name Vif-RK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A03, 3/21 (14%) recognized this epitope.

HXB2 Location Vif (17–26)
Author Location Vif (17–26)
Epitope RIRTWKSLVK
Epitope name A3-RK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 1/7 individuals had detectable responses to this epitope after STI.

HXB2 Location Vif (17–26)
Author Location Vif (17–26)

Epitope RIRTWKSLVK
Epitope name A3-RK10 Vif
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), escape, early treatment, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The second infecting strain had the variant riStwkslvk. The initial CTL response to persisted to against both variants after the superinfection was established.

HXB2 Location Vif (17–26)
Author Location Vif (17–26)
Epitope RIRTWKSLVK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these eptiopes, but this increased over time.

HXB2 Location Vif (17–26)
Author Location (B consensus)
Epitope RIRTWKSLVK
Epitope name RK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A02, A03, B08, B62, Cw10, Cw7; A03, B07, Cw7
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 2/9 individuals recognized this epitope, presented by HLA-A3.

HXB2 Location Vif (17–26)
Author Location Vif
Epitope RIRTWKSLVK
Epitope name RK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 6, rirtwNslvk, was found not to correspond to the most polymorphic residue in the epitope.

HXB2 Location Vif (17–26)
Author Location Vif
Epitope RIRTWKSLVK
Epitope name A3-RK10(Vif)
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Vif (17–26)

Author Location Vif
Epitope RIRTWKSLVK
Epitope name RK10(Vif)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptides (IVWQVDRMRIRTWKSLVK and RIRTWKSLVKHHMYISKK) contained the exact sequence of a previously described HLA-A3 optimal epitope, RIRTWKSLVK, none of the 3 HLA-A3 carriers responded to it.

HXB2 Location Vif (17–26)
Author Location
Epitope RIRTWKSLVK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

HXB2 Location Vif (23–31)
Author Location Vif (23–)
Epitope SLVKHHMYV
Epitope name Vif23(9V)
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* Vif
Adjuvant: Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced CTL and CD8+ T-cell IFN gamma responses in mice. Response was detected in 1/17 HIV+ HLA-A2 subjects.
- The variant slvkhhmyI was an intermediate A2 binder, and stimulated immune reponses in fewer A2 transgenic mice. The same person recognized both variants.

HXB2 Location Vif (23–31)
Author Location
Epitope SLVKHHMYI
Epitope name VIf 23(9I)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords variant cross-recognition or cross-neutralization
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Vif 23(9I) epitope, SLVKHHMYI, was found in 3 patients but only 1 patient had a CTL immune response to it.
- Variant Vif 23(9Vvar), SLVKHHMYv, had a substitution in the C-terminal primary anchor-binding position and was detected by the patient who responded to the natural epitope.
- Cross-reaction between the natural Vif 23(9I) and variant (9Vvar) was found in A2tg mice.
- Another variant, Vif 23(2Vvar), SvVKHHMYI, was most immunogenic of the Vif epitopes studied, cross-reacting with Vif 23(9I).

HXB2 Location Vif (23–31)
Author Location Vif (23–)
Epitope SLVKHHMYI

CTL CD8+

Epitope name Vif 23 (9I)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Vif epitope SLVKHHMYI, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients. DK1 had variant sequence SLVKHHMYv.

HXB2 Location Vif (23–31)
Author Location Vif (23–)
Epitope SLVKHHMYV
Epitope name Vif 23 (9V)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Vif epitope SLVKHHMYV, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients.

HXB2 Location Vif (27–41)
Author Location Vif
Epitope HHMYISKKAKGWGWFYR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot – 33% (23/70) targeted one or more Vif peptides, and this peptide was the most frequently recognized epitope in Vif (25%).
- The regulatory proteins Rev and Tat combined contributed to 3%, and the accessory proteins Vif, Vpr and Vpu to 7%, of the total magnitude of HIV-1 specific CTL responses in a subset of 22 HIV-1 infected individuals in whom all HIV-1 proteins were studied.

HXB2 Location Vif (28–36)
Author Location Vif (28–36)
Epitope HMYISKKAK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Vif (28–36)
Author Location Vif (28–36)
Epitope HMYISKKAK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Vif (28–36)
Author Location Vif (28–36)
Epitope HMYISKKAK
Epitope name A3-HK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.

CTL CD8+

- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 2/7 individuals had detectable responses to this epitope after STI.

HXB2 Location Vif (28–36)
Author Location Vif
Epitope HMYISKKAK
Epitope name A3-HK9(Vif)
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Vif (28–36)
Author Location Vif
Epitope HMYISKKAK
Epitope name HK9(Vif)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A3-restricted epitope HMYISKKAK elicited an immune response in Chinese HIV-1 positive subjects as part of peptide VKHHMYISKKAKGW-LYKH.
- 1 of the 3 HLA-A3 carriers responded to HMYISKKAK-containing peptidewith a magnitude of CTL response of 70 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Vif (31–39)
Author Location
Epitope ISKKAKGWF
Epitope name IF9
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B*57-restricted optimal epitope ISKKAKGWF was tested for immune response.

HXB2 Location Vif (31–39)
Author Location Vpr (31–39)
Epitope ISKKAKGWF
Epitope name vifIF9
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country United Kingdom, Kenya
Assay type CD8 T-cell Elispot - IFNγ
Keywords TCR usage, structure, characterizing CD8+ T cells
References Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B*57-peptide complexes were studied.
- In addition, immunodominancye of the previously mapped B*57 epitopes during chronic infection was assessed. KGFN-PEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

HXB2 Location Vif (31–39)
Author Location Vif (31–39 SF2)
Epitope ISKKAKGWF
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
References Altfeld *et al.* 2001a

- CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- 10/29 (35%) individuals tested responded to Vif.
- This epitope was recognized by 2/6 individuals expressing B*5701 allele.

HXB2 Location Vif (31–39)
Author Location Vif (31–39)
Epitope ISKKAKGWF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Vif (31–39)
Author Location Vif (31–39)
Epitope ISKKAKGWF
Immunogen
Species (MHC) human (B*5701)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Vif (31–39)
Author Location Vif
Epitope VSKKAKGWI
Epitope name VI9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 1,Askkakwi, was found in the most polymorphic residue in the epitope.

HXB2 Location Vif (31–39)
Author Location Vif
Epitope ISKKAKGWF
Epitope name B57-IF9(Vif)
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Vif (31–39)
Author Location Vif
Epitope ISKKAKGWF
Epitope name IF9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- IF9, ISKKAKGWF, is a known HLA-B57-restricted epitope used as a positive control for eliciting CTL IFN-gamma response.

HXB2 Location Vif (31–39)
Author Location
Epitope ISKKAKGWF
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords responses in children, mother-to-infant transmission, escape
References Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount

CTL CD8+

functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.

HXB2 Location Vif (31–39)
Author Location
Epitope ISKKAKGWF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

HXB2 Location Vif (32–40)
Author Location Vif
Epitope SQ/KRASGQFY/F
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Keywords HLA associated polymorphism
References Rousseau *et al.* 2008

- 3 phylogenetic correction methods—MLL (maximum likelihood character state analysis followed by likelihood ratio test), MLF (maximum likelihood character state analysis followed by Fisher test), and parsimony character state analysis were used to identify points in the HIV-1 subtype C proteome that conferred susceptibility or resistance to CTLs. Associations of HLA-epitope combinations that were inferred to be susceptible or resistant were organized into immunological sets that would help identify the best residues and genes as candidates for vaccines. While all proteins were interrogated, Gag, Pol, Env and Nef were focused upon. Amino acid changes were evaluated for association with plasma viral load.
- Proteome maps may be seen at `http://www.hiv.lanl.gov/content/immunology/hlatem/study5/index.html` with information showing single or multiple sites involving escape and reversion.
- HLA- B and -C alleles associated more with aa changes than HLA-A, suggesting that the former two are more important in driving viral evolution.
- The ratio of susceptible to resistant residues in HIV proteins was in descending order, Vpr>Gag>Rev>Pol>Nef>Vif>Tat>Env>Vpu, showing that epitopes from the earlier proteins are more conserved owing to viral fitness cost upon mutation.
- This previously described Vif HLA B*1503-restricted epitope, SQ/KRASGQFY/F was susceptible at K2. Variants SgRASGQFY/F, SqRASGQFY/F and SrRASGQFY/F were resistant to CTL response, but associated with lower viral loads. This epitope is 1 of 7 that suggest a fitness cost to immune escape.

HXB2 Location Vif (32–40)
Author Location Vif
Epitope SRKAKGWFY
Epitope name SY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- SY9, SRKAKGWFY, is a novel HLA-B27-restricted epitope that elicits a CTL IFN-gamma response in the same range as Los Alamos database peptides.

HXB2 Location Vif (41–57)
Author Location (C consensus)
Epitope RHHYESRHPKVSSEVHI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location Vif (48–57)
Author Location Vif (48–57 SF2)
Epitope HPRVSSEVHI
Epitope name HI10

CTL CD8+

Immunogen HIV-1 infection
Species (MHC) human (B*0702)
References Altfeld *et al.* 2001a

- CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- 10/29 (35%) individuals tested responded to Vif.
- This epitope was recognized by 3/8 individuals expressing B*0702 allele.
- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- Overlapping Vif peptides HHYESTHPRVSSEVH and THPRVSSEVHIPLG both reacted with T-cells from AC-06 and contained epitope HPRVSSEVHI.

HXB2 Location Vif (48–57)
Author Location Vif (48–57)
Epitope HPRVSSEVHI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Vif (48–57)
Author Location Vif (48–57)
Epitope HPRVSSEVHI
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Vif (48–57)
Author Location (C consensus)
Epitope HPKVSSEVHI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location Vif (48–57)
Author Location (C consensus)
Epitope HPKVSSEVHI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the H1 residue of HPKVSSEVHI are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location Vif (48–57)
Author Location
Epitope HPKVSSEVHI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Donor MHC A*2301, A*2902, B*4101, B*4201, Cw*1701
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- Known epitope HPKVSSEVHI is HLA-B*4201-restricted. Response to a peptide containing this epitope was detected in 2 rapid progressors 12 weeks post-infection.

HXB2 Location Vif (48–57)
Author Location Vif (48–57)
Epitope HPRVSSEVHI
Epitope name B7-HI10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 2/4 individuals had detectable responses to this epitope after STI.

HXB2 Location Vif (48–57)
Author Location Vif (48–57)
Epitope HPRISSEVHI
Epitope name B7-HM0 Vif
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), escape, early treatment, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The second infecting strain had the variant hpKissevhi. The CTL response was equal against both variants, and declined over time.

HXB2 Location Vif (48–57)
Author Location (B consensus)
Epitope HPRISSEVHI
Epitope name HI10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A03, B07, Cw7
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location Vif (48–57)
Author Location (B consensus)
Epitope HPKISSEVHI
Epitope name HKI10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A03, B07, Cw7
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
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Author Location Vif
Epitope HPRISSEVHI
Epitope name HI10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 2, hSrissevhi, was found not to correspond to the most polymorphic residue in the epitope.

HXB2 Location Vif (48–57)
Author Location Vif
Epitope HPRVSSEVHI
Epitope name B7-HI10(Vif)
Immunogen HIV-1 infection
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.

CTL CD8+

- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Vif (48–57)
Author Location Vif
Epitope HPKISSEVHI
Epitope name HI10(Vif)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B7-restricted epitope HPKISSEVHI elicited an immune response in Chinese HIV-1 positive subjects as part of peptides KHHYDSTHPKISSEVHI and HPKISSEVHIPLGDARLV.
- 1 of the 9 HLA-B7 carriers responded to an HPKISSEVHI-containing peptide with a magnitude of CTL response of 140 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Vif (48–57)
Author Location Vif
Epitope HPRISSEVHI
Epitope name Vif1136
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Previously published epitope HPRISSEVHI elicits IFN-gamma ELISpot responses in 5/7 subjects; and bound HLA-B7 with high affinities in soluble and cell-based assays.

HXB2 Location Vif (48–57)
Author Location
Epitope HPRVSSEVHI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

HXB2 Location Vif (48–57)
Author Location Vif (48–57)
Epitope HPKVSSEVHI
Epitope name HI10
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Other
Keywords supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism
References Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alelles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Statistically significant associations between numbers of HLA-4201 expressing subjects and epitope HPKVSSEVHI were found.

- Functional avidity is correlated with selection pressure observed in HLA allele-epitope HI10 restriction

HXB2 Location Vif (54–63)
Author Location (C consensus)
Epitope EVHIPLGEAR
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*6801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the R10 residue of EVHIPLGEAR are associated with the presence of the HLA presenting molecule in the host.
- EVHIPLGEAR not optimized.

HXB2 Location Vif (56–72)
Author Location
Epitope HIPLGEARLVIKTYWGL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0301, A*2301, B*1503, B*5802, Cw*0210, Cw*0602
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression, optimal epitope
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- HIPLGEARLVIKTYWGL is of unknown restriction. Response was detected in a rapid progressor 12 weeks post-infection.

HXB2 Location Vif (57–65)
Author Location Vif
Epitope IPLGEAKLV
Epitope name Vif1154
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Novel Vif epitope IPLGEAKLV elicits IFN-gamma ELISpot responses in 1/7 subjects; and bound HLA-B7 with low and medium affinities in soluble and cell-based assays respectively.

HXB2 Location Vif (57–66)
Author Location Vif (57–66)
Epitope IPLGDAKLII
Immunogen
Species (MHC) human (B51)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Vif (57–66)
Author Location Vif (57–66)
Epitope IPLGDAKLII
Epitope name II10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A*0201, A*0301, B*3501, B*51, Cw*04, Cw*06
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords escape, acute/early infection
References Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- The peptide that carries this epitope was recognized at high levels early in infection, and the response to this epitope diminished over time. The epitope sequence varied between months 3 and 32.

HXB2 Location Vif (57–66)
Author Location Vif
Epitope IPLGDARLVI
Epitope name Vif1135
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.

CTL CD8+

- Novel Vif epitope IPLGDARLVI elicits IFN-gamma ELISpot responses in 2/7 subjects; and bound HLA-B7 with low and high affinities in soluble and cell-based assays respectively.

HXB2 Location Vif (57–66)
Author Location Vif
Epitope IPLGDAKLII
Epitope name II10(Vif)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords non-susceptible form
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- The tested peptide sequence, HIPLGDArLvITTYWGLH, contains a variant, IPLGDArLvI that differs by 2 substitutions from the previously described HLA-B51 epitope IPLGDAKLII. None of the 15 HLA-B51 carriers responded to the variant IPLGDArLvI.

HXB2 Location Vif (61–69)
Author Location Vif
Epitope DAKLIITTY
Epitope name Vif-DY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Donor MHC A*02, A*03, B*35, B*51
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords rate of progression, acute/early infection, memory cells
References Sabbaj *et al.* 2007

- CD127 hi memory CTLs were correlated with different patient groups - subjects with chronic HIV-1 infection or controllers or those treated early with ART. For patients with chronic infection, CD127 hi CTL levels decrease greatly. Early ART treatment alone maintained these long-lived memory T cells.
- In response to epitope DY9, DAKLIITTY, a patient with oscillating ART had IFN-gamma secretion by CD127 lo cells during viremia and CD127hi cell-IFN-gamma production during viremic control. Shortly after ART cessation, CD127 mixed cells secreted IFN-gamma. HLA-restriction is to -B*35.

HXB2 Location Vif (61–69)
Author Location Vif (61–69)
Epitope DAKLIITTY
Epitope name DY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Donor MHC A*0201, A*0301, B*3501, B*51, Cw*04, Cw*06
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords escape, acute/early infection
References Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- The peptide that carries this epitope was recognized early in infection but the response diminished over time. A point mutation of epitope position 7 (T to K, DAKLIIkTY) was detected at high frequency at a chronic infection timepoint, 34 months. The K variant was an escape form, and had low avidity by gamma IFN Elispot.

HXB2 Location Vif (61–69)
Author Location
Epitope DAKLVITTY
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp160 boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A2A2; B35, B62
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location Vif (61–69)
Author Location
Epitope DAKLVITTY
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay

Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location Vif (61–80)
Author Location Vif (61–80)
Epitope `EARLVIKTYWGLQTGERDWH`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location Vif (62–70)
Author Location Vif
Epitope `ARLVITTYW`
Epitope name AW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- AW9(Vif), ARLVITTYW, is a novel HLA-B27-restricted epitope that elicits a CTL IFN-gamma response in the same range as Los Alamos database peptides.

HXB2 Location Vif (64–81)
Author Location Vif
Epitope `LVITTYWGLHTGERDWHL`
Epitope name VIF-09
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, LVItTYWGLhtGERDWHL differs from the consensus C sequence LVIkTYWGLqtGERDWHL at 3 amino acid positions, i.e. by 16.7%.

HXB2 Location Vif (71–90)
Author Location Vif (71–90)
Epitope `GLQTGERDWHLGHGVSIEWR`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location Vif (72–89)
Author Location (C consensus)
Epitope `LQTGERDWHLGHGVSIEW`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5703)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression

CTL CD8+

References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location Vif (73–81)
Author Location Vif (73–81)
Epitope HTGERDWHL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Donor MHC A*03, A*24, B*35, B*40
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, variant cross-recognition or cross-neutralization, superinfection
References Yang *et al.* 2005b

- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
- The response to this epitope, HTGERDWHL, was present before superinfection but waned afterward. The epitope from the first strain had the substitution hPgerdwhl, while the second strain matched the test peptide.

HXB2 Location Vif (79–87)
Author Location Vif (79–87)
Epitope WHLGHGVSI
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Keywords optimal epitope
References Llano *et al.* 2009

- An A-list optimal epitope.

HXB2 Location Vif (79–87)
Author Location Nef (C consensus)
Epitope WHLGHGVSI
Epitope name WI9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Donor MHC A*2601, A*7401, B*0801, B*1510, Cw*0202, Cw*0801
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was one of two used to illustrate how specific epitopes were characterized with regard to defining the optimal epitope and the HLA restricting element. HLA allelic associations in the population with peptide recognition was generally high predictive of the epitope within the 15 mer.

HXB2 Location Vif (79–87)
Author Location (C consensus)
Epitope WHLGHGVSI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location Vif (79–87)
Author Location (C consensus)
Epitope WHLGHGVSI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords epitope processing, rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the V7 residue of WHLGHGVSI are associated with the presence of the HLA presenting molecule in the host. Mutation of a residue outside of the optimized epitope is also associated with the HLA.

HXB2 Location Vif (79–87)
Author Location Vif (79–87)
Epitope WHLGHGVSI

Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Assay type Other
Keywords epitope processing, HLA associated polymorphism
References Boutwell & Essex 2007

- Publicly available HIV-1 subtype C sequences from South Africa and Botswana were analyzed, and 94 HLA-associated amino acid polymorphisms were found. Many polymorphisms were associated with multiple HLA allele classes. 12% associations were negative: association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles accounted for 50% of associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes.
- WHLGHGVSI was a previously defined B*1510 presented epitope that was associated with a polymorphism, d|WHLGHGVSI,in the first position before that epitope. This epitope was embedded in a previoulsy identified CTL immunoreactive region.

HXB2 Location Vif (79–87)
Author Location
Epitope `WHLGHGVSI`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Donor MHC A*2301, A*2902, B*1510, B*4501, Cw*0602, Cw*1601
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression, optimal epitope
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- Known epitope, WHLGHGVSI, is HLA-B*1510-restricted. Response to a peptide containing this epitope was detected in an early controller 12 weeks post-infection.

HXB2 Location Vif (79–87)
Author Location Vif
Epitope `WHLGQGVSI`
Epitope name WI9(Vif)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*38)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B38-restricted epitope WHLGQGVSI elicited an immune response in Chinese HIV-1 positive subjects as part of peptide LHTGERD-WHLGQGVSIEW.

HXB2 Location Vif (79–87)
Author Location Vif (79–87)
Epitope `WHLGQGVSI`
Immunogen HIV-1 infection
Species (MHC) human (B*3801)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Vif (79–87)
Author Location Vif
Epitope `WHLGHVSI`
Epitope name WI8(Vif)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B15)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide sequence, LHTGERD-WHLGQGVSIEW, contains the exact sequence of a previously described HLA-B15 epitope, WHLGHVSI, none of the 21 HLA-B15 carriers responded to it (author communication and Fig.1).

HXB2 Location Vif (85–102)
Author Location (C consensus)
Epitope `VSIEWRLRRYSTQVDPGL`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*18)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location Vif (93–110)

CTL CD8+

Author Location Vif
Epitope RYSTQVDPGLADQLIHLY
Epitope name VIF-13
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, RYSTQVdPGLADQLIHly differs from the consensus C sequence RYSTQVePGLADQLIHmh at 3 amino acid positions, i.e. by 16.7%.

HXB2 Location Vif (101–109)
Author Location Vif (101–)
Epitope GLADQLIHL
Epitope name Vif101(9L)
Immunogen HIV-1 infection, vaccine, computer prediction
Vector/Type: peptide *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder that induced CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 3/17 HIV+ HLA-A2 subjects.
- The variant gladqlihM was an intermediate A2 binder, but still could stimulate a response in HLA-A2 transgenic mice. It was not recognized by the 3 people who recognized with GLADQLIHL.

HXB2 Location Vif (101–109)
Author Location
Epitope GLADQLIHL
Epitope name VIf 101(9L)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords variant cross-recognition or cross-neutralization
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Vif 101 (9L) GLADQLIHL epitope was not found in any patients but 2 patients had immune responses to it.
- 7 CTL cross-reacting variants were tested: they were L9I (GLADQLIHi), L9M (GLADQLIHm), G1S (sLADQLIHL), G1N (nLADQLIHL), G1D (dLADQLIHL), G1E (eLADQLIHL) and G1H.L9Q (hLADQLIHq). 8 of 11 patients cross-reacted with G1N and G1D. A2tg mice immunized with Vif101 also induced cross-reacting CTL to L9I, G1S, L9M and to a lesser extent to G1E, G1H.L9Q.
- Vif101 (9L)-induced CTLs cross-reacted to Vif101 (9M) which though not found in any of the Danish isolates studied, is common worldwide among clade C (70%), clade D (35%) and clade H (33%) HIV-1-isolates.

HXB2 Location Vif (101–109)
Author Location Vif (101–)
Epitope GLADQLIHL
Epitope name Vif 101 (9L)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.

- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Vif epitope GLADQLIHL, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients. DK1 had variant sequence dLADQLIHL.

HXB2 Location Vif (101–110)
Author Location Vif
Epitope DLADQLIHLY
Epitope name 1237
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A02, A30, B39; A01, A02, B08, Cw16
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for DLADQLIHLY: 54%

HXB2 Location Vif (102–111)
Author Location Vif (102–111 SF2)
Epitope LADQLIHLHY
Immunogen HIV-1 infection
Species (MHC) human (B*1801)
References Altfeld *et al.* 2001a

- CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- 10/29 (35%) individuals tested responded to Vif.
- This epitope was recognized by 2/5 individuals expressing B*1801 allele.

HXB2 Location Vif (102–111)
Author Location Vif (102–111)
Epitope LADQLIHLHY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1801)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Vif (102–111)
Author Location Vif (102–111)
Epitope LADQLIHLHY
Immunogen HIV-1 infection
Species (MHC) human (B*1801)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Vif (102–111)
Author Location Vif (102–110)
Epitope LADQLIHLHY
Epitope name LY10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B18)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords optimal epitope
References Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- This epitope did not vary.

HXB2 Location Vif (102–111)
Author Location Vif (102–110)
Epitope LADQLIHLHY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B18)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location Vif (102–111)
Author Location
Epitope LADQLIHLHY
Subtype B

CTL CD8+

Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated, traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

HXB2 Location Vif (106–123)
Author Location (C consensus)
Epitope `LIHMHYFDCFADSAIRKA`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*6801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location Vif (121–135)
Author Location Vif (121–135)
Epitope `RNAILGHIVSPRCEY`
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008

- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.
- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.
- CTL immune response to consensus sequence RNAILGHIVSPRCEY was elicited in subject 00015. Consensus epitope of subject 00015 was RNAILGHvVSPiCdY and of subject 00016 was RNAILGrIVSPRCEY.

HXB2 Location Vif (127–135)
Author Location Vif
Epitope `HIVSPRCEY`
Epitope name HY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A29)
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 3, HIgSPRCEY, was found not to correspond to the most polymorphic residue in the epitope.

HXB2 Location Vif (127–135)
Author Location Vif (125–135)
Epitope `HIVSPRCEY`
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC 1261: A*0201, A29, B58, B62, Cw*0304, Cw*1601
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance

of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

HXB2 Location Vif (149–157)
Author Location Vif (149–)
Epitope `ALAALITPK`
Epitope name Vif149
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* Vif *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003
- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 1/17 HIV+ HLA-A2 subjects.

HXB2 Location Vif (149–157)
Author Location
Epitope `ALAALITPK`
Epitope name VIf 149
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
References Thorn *et al.* 2007
- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Vif 149 epitope, ALAALITPK, was found in 1 patient but only 1 other patient had a CTL immune response to it. Lack of epitope in patients could explain the lack of CTL recall response to the test peptide.

HXB2 Location Vif (149–157)
Author Location Vif (149–)
Epitope `ALAALITPK`
Epitope name Vif 149
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape, acute/early infection
References Fomsgaard *et al.* 2008
- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive noncontroller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Vif epitope ALAALITPK, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients. DK1 had variant sequence ALkALvipt.

HXB2 Location Vif (151–168)
Author Location (C consensus)
Epitope `TALIKPKKIKPPLPSVRK`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*1701)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location Vif (155–163)
Author Location Vif
Epitope `TPKKIKPPL`
Epitope name Vif1138
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

CTL CD8+

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Novel Vif epitope TPKKIKPPL elicits IFN-gamma ELISpot responses in 1/7 subjects; and bound HLA-B7 with medium and high affinities in soluble and cell-based assays respectively.

HXB2 Location Vif (158–166)
Author Location Vif (158–)
Epitope KIKPPLPSV
Epitope name Vif158(2I)
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* Vif *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced CD8+ T-cell IFN gamma responses in mice. Responses were detected in 1/17 HIV+ HLA-A2 subjects.
- The substitution kTkpplpsv was also a good binder, but did not elicit a response in transgenic mice, and no reponse to this variant was detected among the 17 HIV+ people tested.

HXB2 Location Vif (158–166)
Author Location
Epitope KIKPPLPSV
Epitope name VIf 158(2I)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords variant cross-recognition or cross-neutralization
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Vif 158(2I), KIKPPLPSV, was found in 2 patients but another patient who harbored the Vif 58(2T) variant had a CTL immune response to this natural epitope. This epitope was immunogenic in A2tg mice.
- Variant Vif 158(2T), KtKPPLPSV, which was undetected by a patient who recognized the natural epitope and does not elicit a response in A2tg mice, may be a non-immunogenic or non-binding escape mutant. It was however present in 6 of 11 patients tested.

HXB2 Location Vif (158–166)
Author Location Vif (158–)
Epitope KIKPPLPSV
Epitope name Vif 158(2I)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Vif epitope KIKPPLPSV, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients. DK1 had variant sequence rtKPPLPSV.

HXB2 Location Vif (158–168)
Author Location Vif (158–168)
Epitope KTKPPLPSVKK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Vif (158–168)

Author Location Vif (158–168)
Epitope KTKPPLPSVKK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Vif (158–168)
Author Location
Epitope KTKPPLPSVKK
Immunogen HIV-1 infection
Species (MHC) human (A03)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope KTKPPLPSVKK elicited a magnitude of response of 580 SFC with a functional avidity of 0.05nM and binding affinity of 1.4nM.

HXB2 Location Vif (158–168)
Author Location (B consensus)
Epitope KTKPPLPSVKK
Epitope name KK11
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A02, A11, B18, B44, Cw12, Cw5
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location Vif (158–168)
Author Location Vif (158–168)
Epitope KTKPPLPSVKK
Epitope name A3-KK11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 2/7 individuals had detectable responses to this epitope after STI.

HXB2 Location Vif (158–168)
Author Location Vif (158–168)
Epitope RRKPPLPSIAK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), escape, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response to 25 distinct epitopes, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The second infecting strain had the variant rTkpplpsVTk. The patient maintained persistent reactive CTL against both variants after the superinfection was established.

HXB2 Location Vif (158–168)
Author Location Vif
Epitope RIKPPLPSVTK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.

CTL CD8+

- RIKPPLPSVTK had to mutations overtime, in positions 1 and 10: KikpplpsvKk

HXB2 Location Vif (158–168)
Author Location Vif
Epitope KIKPPLPSVTK
Epitope name KK11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 10, KIKPPLPSVkK, was found in the most polymorphic residue in the epitope.

HXB2 Location Vif (158–168)
Author Location Vif
Epitope KTKPPLPSVKK
Epitope name A3-KK11(Vif)
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Vif (158–168)
Author Location Vif
Epitope KTKPPLPSVKK
Epitope name KK11(Vif)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords non-susceptible form
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- The tested peptide sequence, TALTTPKkIKPPLPSVrK, contains a variant, KiKPPLPSVrK that differs by 2 substitutions from the previously described HLA-A3 epitope KTKPPLPSVKK. None of the 3 HLA-A3 carriers responded to the variant KiKPPLPSVrK.

HXB2 Location Vif (160–169)
Author Location Vif
Epitope KPPLPSVKKL
Immunogen
Species (MHC) human (B7)
References De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conservered regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFNγ production in an ELISPOT assay.
- KPPLPSVKKL was newly identified as an HLA-B7 epitope in this study.

HXB2 Location Vif (160–169)
Author Location Vif
Epitope KPPLPSVKKL
Epitope name 1296
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A03, A24, B07, B38, Cw07, Cw12/13
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for KPPLPSVKKL: 23%

HXB2 Location Vif (161–169)
Author Location Vif
Epitope PPLPSVRKL
Epitope name Vif1155
Subtype B

Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Novel Vif epitope PPLPSVRKL elicits IFN-gamma ELISpot responses in 1/7 subjects; and bound HLA-B7 with low and medium affinities in soluble and cell-based assays respectively.

HXB2 Location Vif (166–174)
Author Location Vif
Epitope VTKLTEDRW
Epitope name VW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- VW9, VTKLTEDRW, is a novel HLA-B57-restricted epitope that elicits a CTL IFN-gamma response in the same range as Los Alamos database peptides.

HXB2 Location Vif (168–176)
Author Location Vif
Epitope KLTEDRWNK
Epitope name 1344
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, A24, B27, B57, Cw13, Cw18
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for KLTEDRWNK: 54%

HXB2 Location Vif
Author Location Vif
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Nef, Vif, Vpu
Species (MHC) mouse (H-2^d)
Keywords subtype comparisons, Th1
References Ayyavoo *et al.* 2000

- Splenocytes from BALB/c mice immunized with pVVN-P DNA were incubated with Vif, Vpu or Nef antigens for 3 days and assayed for IL-4 and IFN-gamma levels.
- Antigen stimulation increased IFN-gamma production in pVVN-P immunized mice, indicating a Th1 response.
- IL-4 production was not significantly changed after antigen stimulation compared to control levels.
- Cross-clade CTL activity was also observed: A, B clade, CRF01(AE) clade antigens could serve as targets for the B clade immunization-stimulated CTL – an HIV-1 AC recombinant, however, did not stimulate a CTL response, but was expressed at lower levels on the target cell.

HXB2 Location Vif
Author Location Vif
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Nef, Vif, Vpu
Species (MHC) mouse (H-2^d)
Keywords subtype comparisons, Th1
References Ayyavoo *et al.* 2000

- Splenocytes from BALB/c mice immunized with pVVN-P DNA were incubated with Vif, Vpu or Nef antigens for 3 days and assayed for IL-4 and IFN-gamma levels.
- Antigen stimulation increased IFN-gamma production in pVVN-P immunized mice, indicating a Th1 response.
- IL-4 production was not significantly changed after antigen stimulation compared to control levels.
- Cross-clade CTL activity was also observed: A, B clade, CRF01(AE) clade antigens could serve as targets for the B clade immunization-stimulated CTL – an HIV-1 AC recombinant, however, did not stimulate a CTL response, but was expressed at lower levels on the target cell.

HXB2 Location Vif
Author Location Vif
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Env, Gag, Pol, Vif *Adjuvant:* B7, IL-12
Species (MHC) mouse
References Kim *et al.* 1997c

- A gag/pol, vif or env DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules B7 and IL-12, gave a dramatic increase in both the cytotoxic and proliferative responses in mice.

- When IL-12 was present, CTL response could be detected even without *in vitro* stimulation.

II-B-17 Vpr CTL/CD8+ epitopes

HXB2 Location Vpr (1–18)
Author Location Vpr
Epitope MEQAPENQGLQREPYNEW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Novel unmapped epitope. A mutation occurred over time in an individual that reacted to this peptide: MEQAPENQGpQREPYNEW.

HXB2 Location Vpr (1–18)
Author Location Vpr (1–18)
Epitope MEQAPENQGLQREPYNEW
Immunogen HIV-1 infection
Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008

- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 87 possible amino acid polymorphisms were defined in this previously published CTL epitope, MEQAPENQGLQREPYNEW.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr (7–15)
Author Location Vpr (7–15)
Epitope DQGPQREPY
Subtype B
Immunogen HIV-1 infection, peptide-HLA interaction
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance
References Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, DQGPQREPY, is similar to human protein Carcinoma associated protein, sequence qRPDQGPQRPP, and human proline-rich protein, sequence DQGPQRpP.

HXB2 Location Vpr (9–26)
Author Location (C consensus)
Epitope GPQREPYNEWTLELLEEL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0704)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location Vpr (9–26)
Author Location Vpr
Epitope GPQREPYNEWTLELLEEL
Epitope name VPR-02
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.

- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, GPQREPYNEWTLELLEEL differs from the consensus C sequence GPQREPYNEWTLELLEEL at 0 amino acid positions, i.e. the two clades' peptides are identical.

HXB2 Location Vpr (9–26)
Author Location Vpr (9–26)
Epitope GPQREPYNEWTLELLEEL
Immunogen HIV-1 infection
Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008

- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 87 possible amino acid polymorphisms were defined in this previously published CTL epitope, GPQREPYNEWTLELLEEL.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr (12–20)
Author Location Vpr (12–20 SF2)
Epitope REPHNEWTL
Immunogen HIV-1 infection
Species (MHC) human (B*4002)
Keywords acute/early infection
References Altfeld *et al.* 2001a

- CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- Individuals with long-term nonprogressive and treated chronic HIV-1 infection targeted Vpr more frequently than individuals with treated acute infection.
- Only one B*4002+ individual was tested, and had a CTL response against REPHNEWTL.
- Vpr is a frequent target of HIV-1 specific CD8+ T-cells – a response was detected in 45% of individuals tested and Vpr and p17 were the most preferentially targeted proteins per unit length by CD8+ T-cells.

HXB2 Location Vpr (12–20)
Author Location Vpr (12–20)
Epitope REPHNEWTL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*4002)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Vpr (12–20)
Author Location Vpr
Epitope REPHNEWTL
Epitope name B40-RL9(Vpr)
Immunogen HIV-1 infection
Species (MHC) human (B40)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Vpr (12–20)
Author Location
Epitope REPHNEWTL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated, traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.

- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

HXB2 Location Vpr (12–20)
Author Location Vpr (12–20)
Epitope REPHNEWTL
Immunogen HIV-1 infection
Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008

- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 53 possible amino acid polymorphisms were defined in this previously published CTL epitope, REPHNEWTL.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr (12–20)
Author Location Vpr
Epitope REPYNEWTL
Epitope name RL9(Vpr)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope REPYNEWTL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide GPQREPYNEWTLELLEEL. This epitope differs from the previously described HLA-B40-restricted epitope sequence, REPHNEWTL, at 1 residue, REPyNEWTL.
- 4 of the 20 HLA-B40 carriers responded to REPyNEWTL-containing peptide with average magnitude of CTL response of 705 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Vpr (19–28)
Author Location Vpr
Epitope TLEILEELKN
Epitope name TN10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3?)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One mutation, at position 1, Aleileelkn,occurred over time. This is a novel unmapped epitope.

HXB2 Location Vpr (19–28)
Author Location Vpr (19–28)
Epitope TLEILEELKN
Immunogen HIV-1 infection
Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008

- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 51 possible amino acid polymorphisms were defined in this previously published CTL epitope, TLEILEELKN.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr (25–40)
Author Location Vpr (25–40 HXB2)
Epitope ELKNEAVRHFPRIWLH
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.

- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- Responses to this peptide were detected in 17% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location Vpr (25–40)
Author Location Vpr (25–40)
Epitope ELKNEAVRHFPRIWLH
Immunogen HIV-1 infection
Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008

- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 87 possible amino acid polymorphisms were defined in this previously published CTL epitope, ELKNEAVRHFPRIWLH.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr (25–42)
Author Location Vpr
Epitope ELKNEAVRHFPRIWLHSL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, ELKNEAVRHFPRIWLHSL, had an overall frequency of recognition of 25.3% - 32.2% AA, 19.2% C, 20.5% H, 23.8% WI. This peptide is included in a 27 aa Vpr highly reactive region to be used for vaccine design.

HXB2 Location Vpr (29–37)
Author Location Vpr
Epitope EAVRHFPRI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*51)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords binding affinity
References Cao *et al.* 2008

- For the first time, viral immune evasion is reported via an insertion mutation, in an ART-naive patient. A 3 aa repeat, SPT inserted within p6<sup>Pol<sup> epitope NL8 is reported. This insertion is associated often with ART drug resistance to NRTI drugs. Thus immune pressure and drug resistance may cause HIV-1 to select the same variation.
- A concomitant insertion mutation APP, is seen in p6<sup>Gag<sup>, permitting viral budding.
- Epitope EAVRHFPRI which showed early, rapid escape in subject PIC1362 bound its MHC I less strongly than NL8, NSPTRREL.

HXB2 Location Vpr (29–37)
Author Location Vpr (29–37 2001 HIV-1 subtype B cons)
Epitope EAVRHFPRI
Epitope name EI9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- Last position (9)in the epitope had potentially experienced positive selection. EAVRHFPRt and EAVRHFPRl escape variants were found.

HXB2 Location Vpr (29–37)
Author Location Vpr (29–37)
Epitope EAVRHFPRI
Immunogen
Species (MHC) human (B51)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Vpr (29–37)
Author Location Vpr (29–37 B)
Epitope EAVRHFPRI
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A*0201, A*2501, B18, B51, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

HXB2 Location Vpr (29–37)
Author Location Vpr
Epitope EAVRHFPRI
Epitope name EL9
Immunogen
Species (MHC) (B51)
Keywords review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion
References Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

HXB2 Location Vpr (29–37)
Author Location Vpr
Epitope EAVRHFPRI
Epitope name B51-EI9(Vpr)
Immunogen
Species (MHC) human (B51)
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Vpr (29–37)
Author Location Vpr (29–37)
Epitope EAVRHFPRI
Immunogen HIV-1 infection
Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008

- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 52 possible amino acid polymorphisms were defined in this previously published CTL epitope, EAVRHFPRI.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr (29–37)
Author Location Vpr
Epitope EAVRHFPRI
Epitope name EI9(Vpr)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords non-susceptible form
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.

- The tested peptide sequence, ELKREAVRHFPRpWLHGL, contains a variant, EAVRHFPRp that differs by 2 substitutions from the previously described HLA-B51 epitope EAVRHFPRI. None of the 15 HLA-B51 carriers responded to the variant EAVRHFPRp.

HXB2 Location Vpr (29–43)
Author Location
Epitope EAVRHFPRIWLHGLG
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A*2501, A*3002; B*0702, B*1801
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location Vpr (29–43)
Author Location
Epitope EAVRHFPRIWLHGLG
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade MN *HIV component:* gp160
Species (MHC) human
Donor MHC A1, A33; B44, B8
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location Vpr (30–38)
Author Location
Epitope AVRHFPRIW
Epitope name AW9
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B*57-restricted optimal epitope AVRHFPRIW was tested for immune response.

HXB2 Location Vpr (30–38)
Author Location Vpr (30–38)
Epitope AVRHFPRIW
Epitope name vprAV9
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country United Kingdom, Kenya
Assay type CD8 T-cell Elispot - IFNγ
Keywords TCR usage, structure, characterizing CD8+ T cells
References Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B*57-peptide complexes were studied.
- In addition, immunodominance of the previously mapped B*57 epitopes during chronic infection was assessed. KGFNPEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

HXB2 Location Vpr (30–38)
Author Location Vpr (29–38 SF2)
Epitope AVRHFPRIW
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords acute/early infection
References Altfeld *et al.* 2001a

- CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- This epitope was recognized by 4/6 individuals expressing B*5701 allele.
- Individuals with long-term nonprogressive and treated chronic HIV-1 infection targeted Vpr more frequently than individuals with treated acute infection.
- Vpr is a frequent target of HIV-1 specific CD8+ T-cells – a response was detected in 45% of individuals tested and Vpr and p17 were the most preferentially targeted proteins per unit length by CD8+ T-cells.

HXB2 Location Vpr (30–38)

CTL CD8+

Author Location Vpr (29–38)
Epitope AVRHFPRIW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Vpr (30–38)
Author Location Vpr (30–38)
Epitope AVRHFPRIW
Immunogen
Species (MHC) human (B*5701)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Vpr (30–38)
Author Location Vpr
Epitope AVRHFPRIW
Epitope name AW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- AW9, AVRHFPRIW, is a known HLA-B27-restricted epitope used as a positive control for eliciting CTL IFN-gamma response.

HXB2 Location Vpr (30–38)
Author Location
Epitope AVRHFPRIW
Epitope name Vpr-AW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B57, 1/7 (14%) recognized this epitope.

HXB2 Location Vpr (30–38)
Author Location Vpr (30–38)
Epitope AVRHFPRIW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location Vpr (30–38)
Author Location Vpr
Epitope AVRHFPRIW
Epitope name AW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- AW9(Vpr), AVRHFPRIW, is a known HLA-B57-restricted epitope used as a positive control for eliciting CTL IFN-gamma response.

HXB2 Location Vpr (30–38)
Author Location
Epitope AVRHFPRIW
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords responses in children, mother-to-infant transmission, escape
References Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.

HXB2 Location Vpr (30–38)
Author Location Vpr
Epitope AVRHFPRIW
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B57, B63)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, cross-presentation by different HLA, optimal epitope
References Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This epitope was recognized by 30% of B63-positive subjects and 14% of B57/58-positive subjects.

HXB2 Location Vpr (30–38)
Author Location
Epitope AVRHFRPIW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated, traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

HXB2 Location Vpr (30–38)
Author Location Vpr (30–38)
Epitope AVRHRPRIW
Immunogen HIV-1 infection
Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008

- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 52 possible amino acid polymorphisms were defined in this previously published CTL epitope, AVRHRPRIW.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr (31–39)
Author Location Vpr (31–39)
Epitope VRHFPRIWL
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Vpr (31–39)
Author Location Vpr
Epitope VRHFPRIWL
Epitope name VL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords superinfection
References Streeck *et al.* 2008b

- Loss of viral replication control by an elite controller after superinfection was found to coincide with rapid recombination events in 2, ∼50 residue regions of Gag and Env that include immunodominant epitopes KK10 (KRWIILGLNK) and CL9 (CAPAGFAIL). Viral escape was seen at both epitopes and consequent CTL responses against the epitope-variants.
- CTL responses to previously described HLA-B27-restricted VRHFPRIWL, were seen post-superinfection and -recombination.

HXB2 Location Vpr (31–39)
Author Location Vpr (31–39)
Epitope VRHFPRIWL
Immunogen HIV-1 infection

CTL CD8+

Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008

- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 48 possible amino acid polymorphisms were defined in this previously published CTL epitope, VRHFPRIWL.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr (31–50)
Author Location Vpr (31–50)
Epitope VRHFPRPWLHSLGQYIYETY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 8 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location Vpr (31–50)
Author Location Vpr (31–50)
Epitope VRHFPRWLHSLGQYIYETY
Immunogen HIV-1 infection
Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008

- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 107 possible amino acid polymorphisms were defined in this previously published CTL epitope, VRHFPRWLHSLGQYIYETY.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr (34–42)
Author Location Vpr (34–)
Epitope FPRPWLHGL
Epitope name Vpr34
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* Vpr *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced a CD8+ T-cell IFN gamma response in 1/6 mice. Responses were detected in 3/17 HIV+ HLA-A2 subjects.

HXB2 Location Vpr (34–42)
Author Location
Epitope FPRPWLHGL
Epitope name Vpr 34
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords variant cross-recognition or cross-neutralization
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Vpr 34 epitope FPRPWLHGL was not present in any patients and only 2 had a CTL immune response to it.

HXB2 Location Vpr (34–42)
Author Location Vpr (158–)
Epitope FPRPWLHGL
Epitope name Vpr34
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.

- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Vpr epitope FPRPWLHGL, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients. DK1 had variant sequence FPRPWLHsL.

HXB2 Location Vpr (34–42)
Author Location Vpr (34–42 SF2)
Epitope FPRIWLHGL
Epitope name FL9
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Keywords acute/early infection
References Altfeld *et al.* 2001a

- CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- This epitope was recognized by 2/2 individuals expressing B*8101 allele and 4/8 individuals expressing B*0702 allele.
- Individuals with long-term nonprogressive and treated chronic HIV-1 infection targeted Vpr more frequently than individuals with treated acute infection.
- Vpr is a frequent target of HIV-1 specific CD8+ T-cells – a response was detected in 45% of individuals tested and Vpr and p17 were the most preferentially targeted proteins per unit length by CD8+ T-cells.
- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- FPRIWLHGL was the only epitope identified in Vpr for AC-06.

HXB2 Location Vpr (34–42)
Author Location Vpr (34–42)
Epitope FPRIWLHGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Vpr (34–42)
Author Location Vpr (34–42)
Epitope FPRIWLHGL
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Vpr (34–42)
Author Location Vpr
Epitope FPRIWLHGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Donor MHC A*0301, A*2301, B*0702, B*1503
Country United States
Keywords escape, acute/early infection
References Bernardin *et al.* 2005

- Full HIV genomes from nine individuals were analyzed for mutations prior to seroconversion and 7 to 28 days later. It was found that the influence of the host's HLA type was reflected within weeks of infection; a statistically significant number of early nonsynonymous mutations were observed within previously reported CTL epitopes.
- H to Y mutation was observed in position 7.

HXB2 Location Vpr (34–42)
Author Location (C consensus)
Epitope FPRWLHGL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- FPRWLHGL is an optimal epitope for B*4201, B*8101, and B*0702.

HXB2 Location Vpr (34–42)
Author Location
Epitope FPRPWLHGL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0702, B*4201, B*8101)
Donor MHC A*2301, A*2902, B*4101, B*4201, Cw*1701
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

CTL CD8+

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- Known epitope FPRPWLHGL is HLA-B*0702, -B*4201 and -B*8101-restricted. Response to a peptide containing this epitope was detected in 2 rapid progressors 12 weeks post-infection.

HXB2 Location Vpr (34–42)
Author Location (C consensus)
Epitope FPRWLHGL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- FPRWLHGL is an optimal epitope for B*4201, B*8101, and B*0702.

HXB2 Location Vpr (34–42)
Author Location Vpr (34–42 SF2)
Epitope FPRIWLHGL
Epitope name FL9
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Keywords acute/early infection
References Altfeld *et al.* 2001a

- CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- This epitope was recognized by 2/2 individuals expressing B*8101 allele and 4/8 individuals expressing B*0702 allele.
- Individuals with long-term nonprogressive and treated chronic HIV-1 infection targeted Vpr more frequently than individuals with treated acute infection.
- Vpr is a frequent target of HIV-1 specific CD8+ T-cells – a response was detected in 45% of individuals tested and Vpr and p17 were the most preferentially targeted proteins per unit length by CD8+ T-cells.

HXB2 Location Vpr (34–42)
Author Location Vpr (34–42)
Epitope FPRIWLHGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Vpr (34–42)
Author Location Vpr (34–42)
Epitope FPRIWLHGL
Immunogen
Species (MHC) human (B*8101)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Vpr (34–42)
Author Location (C consensus)
Epitope FPRWLHGL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- FPRWLHGL is an optimal epitope for B*4201, B*8101, and B*0702.

HXB2 Location Vpr (34–42)
Author Location (C consensus)
Epitope FPRPWLHGL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0702, B*4201, B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords cross-presentation by different HLA, characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location Vpr (34–42)

Author Location
Epitope FPRIWLHGL
Immunogen HIV-1 infection
Species (MHC) human (B07, B81)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA associations (B07, B81), an additional HLA (B42) was statistically predicted to be associated with this epitope.

HXB2 Location Vpr (34–42)
Author Location Vpr (34–42)
Epitope FPRIWLHGL
Epitope name B7-FL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 1/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 2/4 individuals had detectable responses to this epitope after STI.

HXB2 Location Vpr (34–42)
Author Location Vpr (34–42)
Epitope FPRTWLHGL
Epitope name B7-FL9 Vpr
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), escape, early treatment, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The second infecting strain had the variant fpWtwlhgl. The CTL response declined over time and the response to the second variant was lower than to the first one all the time points.

HXB2 Location Vpr (34–42)
Author Location Vpr
Epitope FPRIWLHGL
Epitope name FL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A2, B44, B7, Cw5, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 8, FPRIWLHdL was found not to correspond to the most polymorphic residue in the epitope.

HXB2 Location Vpr (34–42)
Author Location Vpr (34–42)
Epitope FPRIWLHGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location Vpr (34–42)
Author Location Vpr
Epitope FPRIWLHGL
Epitope name B7-FL9(Vpr)
Immunogen HIV-1 infection
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins

References Altfeld *et al.* 2006
- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Vpr (34–42)
Author Location Vpr
Epitope FPRPWLHGL
Epitope name FL9(Vpr)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008
- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope FPRPWLHGL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide HFPRPWLHGLGQHIYETY. This epitope differs from the previously described HLA-B7-restricted epitope, FPRIWLHGL, at 1 residue, FPRpWLHGL.
- 1 of the 9 HLA-B7 carriers responded to an FPRpWLHGL-containing peptide with a magnitude of CTL response of 100 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Vpr (34–42)
Author Location Vpr
Epitope FPRPWLHGL
Epitope name Vpr1125
Subtype C
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008
- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Epitope FPRPWLHGL elicits IFN-gamma ELISpot responses in 3/7 subjects; and bound HLA-B7 with high affinities in soluble and cell-based assays. Previously published HLA restrictions of this epitope include A*0204, A*0201 (LANL database).

HXB2 Location Vpr (34–42)
Author Location
Epitope FPRIWLHGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002
- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated, traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

HXB2 Location Vpr (34–42)
Author Location Vpr (34–42)
Epitope FPRPWLHSL
Epitope name FL9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Other
Keywords supertype, cross-presentation by different HLA, TCR usage
References Leslie *et al.* 2006
- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related

but different HLA alelles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope restriction
- Statistically significant associations between numbers of HLA-B8101, -0702 and -B4201 expressing subjects and epitope FPRPWLHSL were found.
- Only B*0702 was associated with variation within this epitope, FL9.

HXB2 Location Vpr (34–42)
Author Location Vpr (34–42)
Epitope FPRIWLHGL
Immunogen HIV-1 infection
Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008
- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 58 possible amino acid polymorphisms were defined in this previously published CTL epitope, FPRIWLHGL.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr (41–49)
Author Location Vpr
Epitope SLGQHIYET
Epitope name Vpr41
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* anchored gp120, Vpr *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type T-cell Elispot, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003
- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced CTL and CD8+ T-cell IFN gamma responses in mice. Responses to the peptide were not detected in 17 HIV+ HLA-A2 subjects.

HXB2 Location Vpr (41–49)
Author Location
Epitope SLGQHIYET
Epitope name Vpr 41
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords computational epitope prediction, immunodominance, escape, variant cross-recognition or cross-neutralization
References Thorn *et al.* 2007
- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Previously defined Vpr 41 SLGQHIYET, a rare HLA-A2 epitope, was found in only 1 HLA-A2+ patient and no immune response was detected to it. It was, however, recognized by 1 HLA-A2- patient.

HXB2 Location Vpr (41–49)
Author Location Vpr (41–49)
Epitope SLGQHIYET
Immunogen HIV-1 infection
Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008
- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 49 possible amino acid polymorphisms were defined in this previously published CTL epitope, SLGQHIYET.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr (41–55)
Author Location
Epitope GLGQHIYETYGDTWA
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A3, A32; B38, B64
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b
- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.

- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was recognized by a placebo patient after infection.

HXB2 Location Vpr (41–57)
Author Location (C consensus)
Epitope `GLGQYIYETYGDTWTGV`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*66)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location Vpr (41–57)
Author Location Vpr (41–57)
Epitope `GLGQYIYETYGDTWTGV`
Immunogen HIV-1 infection
Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008

- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 82 possible amino acid polymorphisms were defined in this previously published CTL epitope, GLGQYIYETYGDTWTGV.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr (46–54)
Author Location Vpr (46–54 2001 HIV-1 subtype B cons)
Epitope `IYETYGDTW`
Epitope name IW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2501)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.

HXB2 Location Vpr (46–54)
Author Location Vpr (46–54)
Epitope `IYETYGDTW`
Immunogen HIV-1 infection
Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008

- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 36 possible amino acid polymorphisms were defined in this previously published CTL epitope, IYETYGDTW.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr (48–57)
Author Location (C consensus)
Epitope `ETYGDTWTGV`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*6802)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the W7 residue of ETYGDTWTGV are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location Vpr (48–57)
Author Location Vpr (48–57)
Epitope `ETYGDTWTGV`
Immunogen
Species (MHC) human (A*6802)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an A*6802 epitope.

HXB2 Location Vpr (48–57)
Author Location Vpr (48–57)
Epitope `ETYGDTWTGV`

Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*6802)
Assay type Other
Keywords HLA associated polymorphism
References Boutwell & Essex 2007

- Publicly available HIV-1 subtype C sequences from South Africa and Botswana were analyzed, and 94 HLA-associated amino acid polymorphisms were found. Many polymorphisms were associated with multiple HLA allele classes. 12% associations were negative: association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles accounted for 50% of associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes.
- ETYGDTWTGV was a previously defined A*6802 presented epitope that encompassed a supertype A2 associated polymorphism, eTYGDTWTGV,in the first position of that epitope.
- The epitope eTYGDTWTGV is partially embedded in a CTL immunodominant region.

HXB2 Location Vpr (48–57)
Author Location
Epitope `ETYGDTWTGV`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*6802)
Donor MHC A*6802, B*1510, Cw*0304
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- Known epitope ETYGDTWTGV is HLA-A*6802-restricted. Response to a peptide containing this epitope was detected in a rapid progressor 12 weeks post-infection.

HXB2 Location Vpr (48–57)
Author Location Vpr (48–57)
Epitope `ETYGDTWTGV`
Immunogen HIV-1 infection
Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008

- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 50 possible amino acid polymorphisms were defined in this previously published CTL epitope, ETYGDTWTGV.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr (48–57)
Author Location Vpr
Epitope `ETYGDTWAGV`
Epitope name EV10(Vpr)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope ETYGDTWAGV elicited an immune response in Chinese HIV-1 positive subjects as part of peptide GLGQHIYETYGDTWAGV. This epitope differs from the previously described HLA-A68-restricted epitope, ETYGDTWTGV, at 1 residue, ETYGDTWaGV.

HXB2 Location Vpr (52–62)
Author Location Vpr (52–62)
Epitope `DTWAGVEAIIR`
Immunogen HIV-1 infection
Species (MHC) human (A*6801)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Vpr (52–62)
Author Location Vpr
Epitope `DTWAGVEAIIR`
Epitope name DR11(Vpr)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A68)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.

- Previously described HLA-A68-restricted epitope DTWAGVEAIIR elicited an immune response in Chinese HIV-1 positive subjects as part of peptide ETYGDTWAGVEAIIRIL.

HXB2 Location Vpr (52–62)
Author Location Vpr (52–62)
Epitope DTWAGVEAIIR
Immunogen HIV-1 infection
Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008

- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 66 possible amino acid polymorphisms were defined in this previously published CTL epitope, DTWAGVEAIIR.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr (53–63)
Author Location Vpr (53–63)
Epitope TWAGVEAIIRI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*11)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, TWAGVEAIIRI, was detected within overlapping peptides ETYGDTWAGVEAIIRIL and AGVEAIIRILQQLFIHF.

HXB2 Location Vpr (53–63)
Author Location Vpr (53–63)
Epitope TWAVEAIIRI
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A1, A3, B14, B7, Cw*0702, Cw*0802
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

HXB2 Location Vpr (53–63)
Author Location Vpr (53–63)
Epitope TWAVEAIIRI
Immunogen HIV-1 infection
Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008

- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 69 possible amino acid polymorphisms were defined in this previously published CTL epitope, TWAVEAIIRI.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr (55–70)
Author Location Vpr
Epitope AGVEAIIRILQQLLFI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot – 40% (28/70) targeted one or more Vpr peptides, and this peptide was the most frequently recognized epitope in Vpr (41%).
- The regulatory proteins Rev and Tat combined contributed to 3%, and the accessory proteins Vif, Vpr and Vpu to 7%, of the total magnitude of HIV-1 specific CTL responses in a subset of 22 HIV-1 infected individuals in whom all HIV-1 proteins were studied.

HXB2 Location Vpr (55–70)
Author Location Vpr (55–70)
Epitope AGVEAIIRILQQLLFI
Immunogen HIV-1 infection
Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008

- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 86 possible amino acid polymorphisms were defined in this previously published CTL epitope, AGVEAIIRILQQLLFI.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr (59–67)
Author Location Vpr (59–67)
Epitope AIIRILQQL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, AIIRILQQL, was detected within overlapping peptides ETYGDTWAGVEAIIRIL and AGVEAIIRILQQLFIHF.

HXB2 Location Vpr (59–67)
Author Location Vpr (58–66 LAI)
Epitope AIIRILQQL
Subtype B
Immunogen
Species (MHC) human (A*0201)
Keywords optimal epitope
References Altfeld *et al.* 2001c; Llano *et al.* 2009

- C. Brander notes this is an A*0201 epitope.

HXB2 Location Vpr (59–67)
Author Location Vpr (58–66 SF2)
Epitope AIIRILQQL
Epitope name AL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords acute/early infection
References Altfeld *et al.* 2001a

- CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- This epitope was recognized by 8/24 individuals expressing A*0201 allele.
- Epitope is located within a highly conserved alpha helix in Vpr.
- Individuals with long-term nonprogressive and treated chronic HIV-1 infection targeted Vpr more frequently than individuals with treated acute infection.
- Vpr is a frequent target of HIV-1 specific CD8+ T-cells – a response was detected in 45% of individuals tested and Vpr and p17 were the most preferentially targeted proteins per unit length by CD8+ T-cells.
- The A2 epitopes Vpr AIIRLLQQL and p17 SLYNTVATL do not account for the dominance of Vpr and p17, the result holds even when HLA-A2+ individuals are excluded.

HXB2 Location Vpr (59–67)
Author Location Vpr (59–)
Epitope AIIRILQQL
Epitope name Vpr-59
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords binding affinity, subtype comparisons, supertype, computational epitope prediction, immunodominance
References Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- AIIRILQQL binds to four HLA-A2 supertype alleles: A*0203, A*0201, A*0206 and A*6802 (highest affinity), but not A*0202.
- 5/22 individuals with chronic HIV-1 infection recognized this epitope, but with low magnitude responses in ELISPOT.
- 2/12 HLA-A2 patients with acute HIV-1 infection responded strongly to this peptide, but during chronic infection SL9 and Gag-386 tended to be immunodominant while Vpr-59 was weak and sub-dominant.
- One of the the acutely infected individuals, AC13, was HLA A*0201/68 B44/14 and also had a strong acute response to gp41 epitope SV10 SLLNATDIAV.
- This peptide was shown to be properly processed and presented in TAP-competent B-cell lines *in vitro*.

HXB2 Location Vpr (59–67)
Author Location Vpr (58–66)
Epitope AIIRILQQL

Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Vpr (59–67)
Author Location Vpr (59–67)
Epitope AIIRILQQL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Donor MHC A*0201, A32, B49, B51, Cw1, Cw7
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

HXB2 Location Vpr (59–67)
Author Location Vpr
Epitope AIIRILQQL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Donor MHC A1, A19, B*3501, B44, Cw16, Cw7; A*0201, A19, B14, B44, Cw16, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
References Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-A*0201 restricted eptiope, AIIRILQQL, was mutated to AI(L)RILQQL in the daughter D2 isolate.

HXB2 Location Vpr (59–67)
Author Location Vpr (59–)
Epitope AIIRILQQL
Epitope name AL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords acute/early infection
References Goulder *et al.* 2001a

- Data from patient AC13 suggest a role for this epitope in initial control of viremia in acute infection, as it is one of several subdominant CTL epitopes recognized during the initial decline in viremia.
- A CTL response to SL9, SLYNTVATL, was not evident until 18 months post-presentation.

HXB2 Location Vpr (59–67)
Author Location Vpr (59–67 SF2)
Epitope AIIRILQQL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A2+ individuals that had a CTL response to this epitope broken down by group: 1/10 group 1, 0/6 group 2, and 0/4 group 3.

HXB2 Location Vpr (59–67)
Author Location
Epitope AIIRILQQL
Epitope name Vpr-AL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A02, 4/35 (11%) recognized this epitope.

HXB2 Location Vpr (59–67)
Author Location Vpr (59–67)
Epitope ALIRILQQL
Epitope name AL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords escape, optimal epitope
References Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For one of the escape variants, a novel CD8 T-cell response equal in magnitude to the wild type, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wild type.
- An escape mutation occurred at position 5 of this epitope, alirSlqql.

HXB2 Location Vpr (59–67)
Author Location Vpr
Epitope ALIRILQQL
Epitope name AL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 5, ALIRsLQQL, was found in the most polymorphic residue in the epitope. One escape mutation, at position 3,ALtRILQQL was found not to correspond to the most polymorphic residue in the epitope.

HXB2 Location Vpr (59–67)
Author Location Vpr (59–67)
Epitope ALIRILQQL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords escape, acute/early infection, variant cross-recognition or cross-neutralization, optimal epitope
References Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was recognized both in acute and chronic infection, but slightly more frequently in chronic infection.
- A less common form of this epitope, with the I to L change in the second position, ALIRILQQL binds to HLA-A2 at lower concentrations and can serve as an HLA-A2 epitope during acute infection. It binds well to A*0201, A*0202, A*0203, and A*0206. This is an example of a less immunogenic form of the epitope, AiIRILQQL becoming the most common circulating form.

HXB2 Location Vpr (59–67)
Author Location Vpr
Epitope AIIRILQQL
Epitope name A2-AL9(Vpr)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Vpr (59–67)
Author Location Vpr
Epitope AIIRILQQL
Epitope name AL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States

Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords superinfection
References Streeck *et al.* 2008b

- Loss of viral replication control by an elite controller after superinfection was found to coincide with rapid recombination events in 2, ∼50 residue regions of Gag and Env that include immunodominant epitopes KK10 (KRWIILGLNK) and CL9 (CAPAGFAIL). Viral escape was seen at both epitopes and consequent CTL responses against the epitope-variants.
- CTL responses to previously described HLA-A2-restricted AIIRILQQL were seen post-superinfection and -recombination.

HXB2 Location Vpr (59–67)
Author Location Vpr
Epitope AIIRILQQL
Epitope name AL9(Vpr)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A2-restricted epitope AIIRILQQL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide AGVEAIIRILQQLFIHF.
- 1 of the 55 HLA-A2 carriers responded to AIIRILQQL-containing peptide with a magnitude of CTL response of 130 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Vpr (59–67)
Author Location Vpr (59–67)
Epitope AIIRILQQL
Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind four of the five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802).

HXB2 Location Vpr (59–67)
Author Location
Epitope AIIRILQQL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated, traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

HXB2 Location Vpr (59–67)
Author Location Vpr (59–67)
Epitope AIIRILQQL
Immunogen HIV-1 infection
Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008

- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 49 possible amino acid polymorphisms were defined in this previously published CTL epitope, AIIRILQQL.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr (62–70)
Author Location Vpr (62–)
Epitope RILQQLLFI
Epitope name Vpr-62
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords binding affinity, subtype comparisons, supertype, computational epitope prediction
References Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- This epitope binds to three HLA-A2 supertype alleles: A*0202, A*6802 (strongest affinity) and A*0203.
- 3/22 chronically infected patients had a weak ELISPOT response to this epitope.
- 0/12 HLA-A2 patients with acute HIV-1 infection responded to this peptide.

HXB2 Location Vpr (62–70)
Author Location Vpr (62–70)
Epitope RILQQLLFI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Vpr (62–70)
Author Location Vpr
Epitope RILQQLLFI
Epitope name Vpr 62
Subtype M
Immunogen vaccine, in vitro stimulation or selection
Vector/Type: DNA, peptide *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, mouse, humanized mouse (A*0201)
Assay type Cytokine production, T-cell Elispot
Keywords subtype comparisons, computational epitope prediction, escape, TCR usage, variant cross-recognition or cross-neutralization
References McKinney *et al.* 2004

- This study examined variant recognition of epitopes presented by A*0201 and A*1101. Numerous amino acid substitutions can be introduced into epitopes without disrupting their recognition by CTLs, although epitopes with multiple substitutions were less recognized. An algorithm was constructed for prediction of epitopes capable of inducing responses to a great number of variant epitopes.
- A total of 23 variant forms of Vpr 62 were identified. More than 95% of the variant epitopes were recognized by CTLs from mice immunized with the parental form.
- Vpr 62 epitope (parent or variant form) was present in 96% of HIV sequences of many M group subtypes.

HXB2 Location Vpr (62–70)
Author Location Vpr (162–)
Epitope RILQQLLFI
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (A*0201)
Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008

- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location Vpr (62–70)
Author Location Vpr (62–70)
Epitope RILQQLLFI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords acute/early infection, optimal epitope
References Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized during chronic infection.

HXB2 Location Vpr (62–70)
Author Location Vpr
Epitope RILQQLLFI
Epitope name A2-RI9(Vpr)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.

CTL CD8+

- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Vpr (62–70)
Author Location Vpr
Epitope RILQQLLFI
Epitope name Vpr62
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords antibody binding site definition and exposure
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- RILQQLLFI is a Vpr epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location Vpr (62–70)
Author Location Vpr (62–70)
Epitope RILQQLLFI
Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind three of the five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802).

HXB2 Location Vpr (62–70)
Author Location Vpr
Epitope RILQQLLFI
Epitope name Vpr62
Subtype A, B, C, D
Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope RILQQLLFI of the HLA-A2 supertype bound most strongly to HLA-A*0201, -A*0206 and -A*0603 and also to -A*6802 and -A*0202. It was conserved 25% in subtype A, 74% in B, 50% in C and 100% in subtype D. 2/22 HLA-A2 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Vpr62.

HXB2 Location Vpr (62–70)
Author Location Vpr (62–70)
Epitope RILQQLFI
Immunogen HIV-1 infection
Species (MHC) human
Keywords computational epitope prediction, HLA associated polymorphism
References Srinivasan *et al.* 2008

- 976 Vpr sequences were studied from global HIV-1 isolates to comprehensively analyze amino acid polymorphisms. Since several polymorphic residues were part of CTL epitopes, HIV-1 immune evasion in Vpr is noted.
- 38 possible amino acid polymorphisms were defined in this previously published CTL epitope, RILQQLFI.
- Using half-time estimates of disassociation of the molecule containing the epitope from specific HLA Class I molecules, 12 additional CTL epitopes were predicted across Vpr (Table 17).

HXB2 Location Vpr
Author Location
Epitope
Immunogen vaccine
Vector/Type: adenovirus *HIV component:* Gag-Pol, Nef, Vpr
Species (MHC) mouse
References Muthumani *et al.* 2002

- Vpr can cause cells to go into G2 arrest, and it surpresses immune cell activation and inflammatory cytokine production, so co-immunization of BALB/c mice with recombinant adenovirus expressing Vpr and HIV-1 antigens Nef or Gag/Pol was tested to see if Vpr reduced the immune response to the other HIV antigens.
- Vpr compromised CD8+ T-cell lytic responses and T-helper proliferative responses in mice co-immunized with Vpr and Nef or Gag/Pol.
- In vitro, Vpr reduced T-cell cytokine production of IL-12 and TNFalpha, indicative of Vpr-mediated immune suppression.

II-B-18 Tat CTL/CD8+ epitopes

HXB2 Location Tat (2–11)
Author Location (LAI)
Epitope EPVDPRLEPW
Subtype B
Immunogen
Species (MHC) (B*5301)
Keywords optimal epitope
References Addo *et al.* 2001; Llano *et al.* 2009

HXB2 Location Tat (2–11)
Author Location
Epitope EPVDPRLEPW
Epitope name Tat-EW10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5301)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B*5301, 3/15 (20%) recognized this epitope.

HXB2 Location Tat (2–11)
Author Location (C consensus)
Epitope EPVDPNLEPW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location Tat (2–11)
Author Location (C consensus)
Epitope EPVDPNLEPW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- EPVDPNLEPW is an optimal epitope.

HXB2 Location Tat (2–11)
Author Location Tat (2–11 BRU)
Epitope EPVDPRLEPW
Epitope name Tat 1
Immunogen HIV-1 infection
Species (MHC) human (B53)
References Addo *et al.* 2001

- Rev and Tat are expressed early in the virus life cycle and thus may be important targets for CTL against HIV early in infection and for vaccines – therefore CTL responses against Tat and Rev were screened using overlapping peptides.
- 11/57 (19.3%) HIV-1 + individuals recognized at least 1 Tat peptide, and 21/57 (37%) responded to at least 1 Rev peptide.
- EPVDPRLEPW was recognized by four individuals, but only two were B53, thus this epitope can probably be presented by other HLA alleles.

HXB2 Location Tat (2–11)
Author Location Tat (2–11)
Epitope EPVDPRLEPW
Immunogen HIV-1 infection
Species (MHC) human (B53)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Tat (2–11)
Author Location Tat
Epitope EPVDPRLEPW
Epitope name EW10
Immunogen HIV-1 infection
Species (MHC) human (B53)
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords class I down-regulation by Nef
References Bobbitt *et al.* 2003

- Nef, through Nef-mediated MHC-1 down-regulation, is not the only viral protein to influence levels of HIV-specific CTL recognition. The Rev L60F mutation, a common natural variant, can decrease CTL recognition of late gene products. The Rev mutation impacts the early to late gene switch, reducing late gene product production (Gag, Pol, Env, Vpu, Vpr and Vif), while increasing Nef production, both of which reduce the impact CTL recognition of late gene products. As expected, Rev L60F rendered HIV infected cells more resistant to CTL that recognized epitopes from the late proteins Env and Gag. Gag expression is reduced more than Env, and Gag-specific CTL were more profoundly affected. Conversely CTL against an epitope in an early gene product, Tat, were more effeciently recognized when infected with viruses carrying the Rev L60F mutation.

CTL CD8+

- Patients in the asymptomic phase with active immune responses had more CTL resistant viruses, with lower Rev activity, lower Gag expression and greater resistance to Gag-specific CTL killing, while viruses isolated from people with AIDS were more sensitive to CTL killing.

HXB2 Location Tat (2–11)
Author Location
Epitope EPVDPRLEPW
Immunogen HIV-1 infection
Species (MHC) human (B53)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope EPVDPRLEPW elicited a magnitude of response of 405 SFC with a functional avidity of 0.075nM and binding affinity of 54.

HXB2 Location Tat (2–11)
Author Location
Epitope EPVDPRLEPW
Immunogen
Species (MHC) human (B58)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B58 epitope.

HXB2 Location Tat (2–11)
Author Location Tat
Epitope EPVDPNLEPW
Epitope name EW10(Tat)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B58)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide sequence contains the exact sequence of a previously described HLA-B58 optimal epitope, EPVDPNLEPW, as part of peptide MEPVDPNLEPWKHPGSQPK, none of the 14 HLA-B58 carriers responded to it (author communication and Fig.1).

HXB2 Location Tat (2–11)
Author Location Tat
Epitope EPVDPNLEPW
Epitope name Tat1140
Subtype C
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Previously published Tat epitope EPVDPNLEPW elicits IFN-gamma ELISpot responses in 2/7 subjects; and bound HLA-B7 with low affinities in soluble and cell-based assays respectively.

HXB2 Location Tat (2–11)
Author Location
Epitope WPVDPRLEPW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

HXB2 Location Tat (3–11)

Author Location Tat (3–11 HXB2)
Epitope PVDPRLEPW
Epitope name PW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2501)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Positions 5 and 7 in the epitope had potentially experienced positive selection. PVDPRLdPW, PVDPsLEPW and PVDPkLEPW escape variants were found.

HXB2 Location Tat (3–11)
Author Location Tat
Epitope PVDPRLEPW
Epitope name PW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- PW9(Tat), PVDPRLEPW, is a novel HLA-B57-restricted epitope that elicits a CTL IFN-gamma response in the same range as Los Alamos database peptides.

HXB2 Location Tat (12–21)
Author Location Tat (12–21 SUMA)
Epitope KHPGSQPKTA
Epitope name Tat KA10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*1103, A*2402, B*1402, B*1501, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, acute/early infection, characterizing CD8+ T cells
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape muations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

HXB2 Location Tat (16–30)
Author Location Tat (16–30)
Epitope SQPKTACNKCYCKRC
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location Tat (17–25)
Author Location
Epitope QPKTACTNC
Immunogen vaccine
Vector/Type: DNA *HIV component:* Tat *Adjuvant:* E. coli heat labile enterotoxin
Species (MHC) mouse (H-2^d)
Assay type Chromium-release assay
Keywords vaccine antigen design
References Morris *et al.* 2001a

- To identify a peptide capable of inducing a Tat-specific CTL response, overlapping 9mers were used to immunize mice intranasally. This Tat epitope maps within a region previously identified as the site of T- and B-cell epitopes identified in HIV patients.

HXB2 Location Tat (17–25)

CTL CD8+

Author Location
Epitope QPKTACTNC
Immunogen vaccine
Vector/Type: ISCOM *Strain:* multiple epitope immunogen *HIV component:* Env, Gag, Tat
Species (MHC) mouse (H-2^d)
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Pahar *et al.* 2006

- Rhesus macaques were immunized intrarectally with an ISCOM vaccine containing a single SIV-Gag CTL epitope, a single human HIV-Env Th epitope, plus a negative control mouse H-2d Tat epitope. Following challenge with SHIV-SF162p4, immunized macaques became infected, but had significantly lower viral loads than non-immunized animals.
- This epitope was used as a negative control; it is a known mouse epitope, but is non-reactive in primates.

HXB2 Location Tat (17–26)
Author Location Tat (17–26)
Epitope QPKTACTTCY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Tat (17–26)
Author Location Tat
Epitope QPKTACTNCY
Epitope name Tat1160
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Novel Tat epitope QPKTACTNCY elicits IFN-gamma ELISpot responses in 1/7 subjects; and bound HLA-B7 with low affinity in cell-based assays.

HXB2 Location Tat (17–26)
Author Location
Epitope QPKTACTTCY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

HXB2 Location Tat (17–26)
Author Location Tat
Epitope QPKTPCNKCY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords HLA associated polymorphism
References Rousseau *et al.* 2008

- 3 phylogenetic correction methods—MLL (maximum likelihood character state analysis followed by likelihood ratio test), MLF (maximum likelihood character state analysis followed by Fisher test), and parsimony character state analysis were used to identify points in the HIV-1 subtype C proteome that conferred susceptibility or resistance to CTLs. Associations of HLA-epitope combinations that were inferred to be susceptible or resistant were organized into immunological sets that would help identify the best residues and genes as candidates for vaccines. While all proteins were interrogated, Gag, Pol, Env and Nef were focused upon. Amino acid changes were evaluated for association with plasma viral load.
- Proteome maps may be seen at http://www.hiv.lanl.gov/content/immunology/hlatem/study5/index.html with information showing single or multiple sites involving escape and reversion.
- HLA- B and -C alleles associated more with aa changes than HLA-A, suggesting that the former two are more important in driving viral evolution.
- The ratio of susceptible to resistant residues in HIV proteins was in descending order, Vpr>Gag>Rev>Pol>Nef>Vif>Tat>Env>Vpu, showing that epitopes from the earlier proteins are more conserved owing to viral fitness cost upon mutation.

CTL CD8+

- This Tat HLA-B*42-restricted epitope, QPKTPCNKCY, lies within a set of 6 immunological associations, experiencing conflicting selective pressures.

HXB2 Location Tat (18–26)
Author Location Tat (18–26)
Epitope PKTACTNCY
Subtype B
Immunogen HIV-1 infection, peptide-HLA interaction
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance
References Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, PKTACTNCY, is similar to human protein Zinc finger protein, sequence SQPKsACgNCY.

HXB2 Location Tat (20–28)
Author Location Tat
Epitope TACNNCYCK
Epitope name 1342
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, A23, B49, B57
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for TACNNCYCK: 46%

HXB2 Location Tat (20–29)
Author Location Tat
Epitope TACNNCYCKK
Epitope name 1279
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A68)
Donor MHC A01, A68, B15, B40, Cw03
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for TACNNCYCKK:74%. This peptide bound A68, not A11.

HXB2 Location Tat (24–32)
Author Location Tat (24–32 BORI)
Epitope NCYCKKCCY
Epitope name Tat NY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2902)
Donor MHC A*2902, B*1402, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, immunodominance, escape, acute/early infection, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient BORI had high viral loads and rapid CD4 decline. BORI mounted 8 detected responses. BORI did not control viral replication well, and escape mutations occurred early and in most epitopes, 6/7 that were precisely identified.
- There were five variants of the NCYCKKCCY epitope in BORI, and new changes kept accruing. kCYCKKCCY was apparent by day 31, kCYCKrCCY by day 218, and kCYCK-qCCY by day 556; all conferred escape, the double mutants abrogating the response. NCYCKKyCY and NCYCKKCCc were also transiently present at day 55, but were not tested for CTL escape.

HXB2 Location Tat (24–32)
Author Location Tat (24–32 WEAU)
Epitope NCYCKRCCF
Epitope name Tat NF9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2902)
Donor MHC A*2902, B*0801, B*4403

Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, immunodominance, escape, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.
- There was a weak response to this epitope during acute infection that was lost by early infection. The epitope variant kCYCKRCCF was evident by day 72, and other variants were evident in samples taking at 391 and 772 days, including NCYCKkCCF,tCYCKRCCF, kCYCKsCCF and kCYCKkCCF. It was not determined if these were specifically escape mutations, but the CTL response diminished in vivo as kCYCKRCCF variant came up.

HXB2 Location Tat (24–32)
Author Location Tat (24–32)
Epitope `NCYCKKCCF`
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*2902, B*1402; A*2902, B*0801, B*4403
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rates for this epitope, NCYCKKCCF, were found to be 0.047 and 0.006/day (optimistic escape rates = 0.051 and 0.013), with SE of 0.054 and 0.004 respectively.
- In the first subject, 3 mutations in this Tat epitope (N24K, N24K+K29R, N24K+K29Q) were all shown to confer escape. In the second subject, peptide recognition was not tested, but by analogy with another patient it was suggested that a N to K mutation at position 1 of the epitope Tat 24-32 conferred escape. An additional N to T mutation at position 1 was also considered likely to be an escape mutation.

HXB2 Location Tat (29–43)
Author Location Tat (29–43)
Epitope `KCCFHCQVCFTTKGL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*03, A*24, B*35, B*40
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, variant cross-recognition or cross-neutralization, superinfection, characterizing CD8+ T cells
References Yang *et al.* 2005b

- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
- A early response to this peptide KCCFHCQVCFTTKGL was detected that waned prior to superinfection. The embedded epitope and HLA presenting molecule were not resolved. The initial and superinfecting strains had different versions of the peptide, oCCFHCQVCFiTKGL and KCClHCQVCFTrKGL respectively.

HXB2 Location Tat (30–37)
Author Location Tat (30–37)
Epitope `CCFHCQVC`
Immunogen
Species (MHC) human (Cw*12)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Tat (30–37)
Author Location Tat (30–37)
Epitope `CCFHCQVC`
Epitope name CC8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*12)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States

CTL CD8+

Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords escape, optimal epitope
References Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- A mutation occurred at position 3 of this epitope, ccMhcqvc, but significant cross-recognition was observed between the escape variant and the wildtype epitope.

HXB2 Location Tat (30–37)
Author Location Tat
Epitope CCFHCQVC
Epitope name CC8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*12)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 3, CClHCQVC, was found in the most polymorphic residue in the epitope.

HXB2 Location Tat (30–37)
Author Location Tat
Epitope CCFHCQVC
Epitope name CC8
Immunogen
Species (MHC) (Cw*12)
Keywords review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion
References Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

HXB2 Location Tat (30–37)
Author Location Tat (30–37)
Epitope CCFHCQVC
Immunogen HIV-1 infection
Species (MHC) human (Cw*1203)
Donor MHC A26, A3, B*3801, B7, Cw*0702, Cw*1203; A*0201, A*2501, B18, B51, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, early treatment
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- Two individuals recognized this epitope both presented by Cw*1203.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.

HXB2 Location Tat (30–37)
Author Location Tat (30–37)
Epitope CCFHCQVC
Immunogen HIV-1 infection
Species (MHC) human (Cw*1203)
Donor MHC A26, A3, B*3801, B7, Cw*0702, Cw*1203; A*0201, A*2501, B18, B51, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, early treatment
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- Two individuals recognized this epitope both presented by Cw*1203.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.

HXB2 Location Tat (30–37)
Author Location Tat (30–37 HXB2)
Epitope CCFHCQVC
Epitope name CC8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*1203)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- Position 3 in the epitope had potentially experienced positive selection. CClHCQVC and CCFHCQsC escape variants were found.

HXB2 Location Tat (30–37)
Author Location
Epitope CCFHCQVC
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A*2501, A*3002; B*0702, B*1801
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location Tat (31–39)
Author Location Tat (31–39)
Epitope CLHCQVCFI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, B13, B41
Country France
Assay type Other
Keywords computational epitope prediction, escape, acute/early infection, immune evasion
References Guillon *et al.* 2006

- A longitudinal study from primary infection to 5 years postinfection was conducted to determine Tat and Rev gene evolution. 2/4 patients showed Tat gene evolution. It was found that though Tat evolved by mostly nonsynonymous, non-random sequence changes, there was no increase in transactivating capacity or size of Tat protein. Sequence evolution occurred mostly in predicted epitopes that are MHC I restricted.
- Tat and Rev seem to evolve due to CTL pressure later in infection, after seroconversion, and possibly during viral replication.
- The predicted epitope C(l)HCQVCFI, had a variant CfHCQVCFI in the second position.

HXB2 Location Tat (32–41)
Author Location Tat (32–41 SUMA)
Epitope FHCQVCFMTK
Epitope name Tat FK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*1103, A*2402, B*1402, B*1501, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, epitope processing, immunodominance, escape, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape muations in SUMA over time. Early in infection, three overlapping epitopes in Tat carried mutations: FHCQVCFMTK, VCFMTKGLGI, and MTKGLGISY. An M->T substitution

was evident during acute infection in the first sample, at four days of the onset of symptoms, and a rare second variant was seen at day 20 that added a K->E substitution. The M->T substitution abrogated responses to FHCQVCFtTK, VCFtTKGLGI, but not in the third epitope tTKGLGISY. By day 69 a double mutation was evident that persisted through day 435, F->L and T->K. Variants lHCQVCFMkK, VCFMkKGLGI were not recognized,and impact processing of the MkKGLGISY epitope.

HXB2 Location Tat (32–41)
Author Location Tat (32–41)
Epitope FHCQVCFITK
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*1103, A*2402, B*1402, B*1501
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, FHCQVCFITK, was found to be 0.066 (optimistic escape rate = 0.189) per day, with SE of 0.032.
- In this region of Tat there were 3 overlapping CTL epitopes. A T to K mutation at Tat 32 completely abolished in vitro CTL lysis against all three epitopes. In addition, an M to T mutation at Tat 31 completely abolished recognition of two of the epitopes (third not tested). Quantifying the outgrowth of both of the mutations will overestimate the efficiency of a single CTL response.

HXB2 Location Tat (32–49)
Author Location Tat
Epitope FHCQVCFTTKGLGISYGR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, FHCQVCFTTKGLGISYGR, had an overall frequency of recognition of 16.7% - 16.9% AA, 15.4% C, 20.5% H, 9.5% WI.

HXB2 Location Tat (36–45)
Author Location Tat (36–45)
Epitope VCFTTKGLGI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*15)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, VCFTTKGLGI, was detected within overlapping peptides FHCQVCFTTKGLGISYGR and TKGLGISYGRKKRRQRRR.

HXB2 Location Tat (36–45)

CTL CD8+

Author Location Tat (36–45 SUMA)
Epitope VCFMTKGLGI
Epitope name Tat VI10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1501)
Donor MHC A*1103, A*2402, B*1402, B*1501, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, epitope processing, immunodominance, escape, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape muations in SUMA over time. Early in infection, three overlapping epitopes in Tat carried mutations: FHCQVCFMTK, VCFMTKGLGI, and MTKGLGISY. An M->T substitution was evident during acute infection in the first sample, at four days of the onset of symptoms, and a rare second variant was seen at day 20 that added a K->E substitution. The M->T substitution abrogated responses to FHCQVCFtTK, VCFtTKGLGI, but not in the third epitope tTKGLGISY. By day 69 a double mutation was evident that persisted through day 435, F->L and T->K. Variants lHCQVCFMkK, VCFMkKGLGI were not recognized,and impact processing of the MkKGLGISY epitope.

HXB2 Location Tat (36–45)
Author Location Tat (36–45)
Epitope VCFITKALGI
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*1103, A*2402, B*1402, B*1501
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, VCFITKALGI, was found to be 0.066 (optimistic escape rate = 0.189) per day, with SE of 0.032.
- In this region of Tat there were 3 overlapping CTL epitopes. A T to K mutation at Tat 32 completely abolished in vitro CTL lysis against all three epitopes. In addition, an M to T mutation at Tat 31 completely abolished recognition of two of the epitopes (third not tested). Quantifying the outgrowth of both of the mutations will overestimate the efficiency of a single CTL response.

HXB2 Location Tat (36–50)
Author Location (subtype C)
Epitope VCFQTKGLGISYGRK
Subtype C
Immunogen
Species (MHC) human
Keywords immunodominance, escape
References Novitsky *et al.* 2001

- This study is provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort.
- 17 of 46 patient reacted with Tat immunodominant peptide VCFQTKGLGISYGRK.
- Most of the CTL responses occurred despite a mismatch between the autologous viral sequence and peptide – complete matches were seen only in 4 of 19 cases (21%) and the mismatched CTL tended not to respond to the autologous viral peptide indicative of immune escape.

HXB2 Location Tat (36–50)
Author Location Tat (36–50)
Epitope VCFQTKGLGISYGRK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 8 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location Tat (36–52)

Author Location Tat
Epitope VCFTTKALGISYGRKKR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot – 28% (19/70) targeted one or more Tat peptides, and this peptide was the most frequently recognized epitope in Tat (27%).
- The regulatory proteins Rev and Tat combined contributed to 3%, and the accessory proteins Vif, Vpr and Vpu to 7%, of the total magnitude of HIV-1 specific CTL responses in a subset of 22 HIV-1 infected individuals in whom all HIV-1 proteins were studied.

HXB2 Location Tat (38–47)
Author Location (subtype C)
Epitope FQTKGLGISY
Epitope name T38-FY10
Subtype C
Immunogen
Species (MHC) human (B*1503)
Keywords immunodominance
References Novitsky *et al.* 2001

- This study is provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort.
- 17 of 46 patient reacted with Tat immunodominant peptide VCFQTKGLGISYGRK.
- FQTKGLGISY was the optimal epitope in the peptide VCFQTKGLGISYGRK among B*1503+ individuals.

HXB2 Location Tat (38–47)
Author Location Tat (38–47)
Epitope FQTKGLGISY
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Tat (38–47)
Author Location (C consensus)
Epitope FQTKGLGISY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location Tat (38–47)
Author Location (C consensus)
Epitope FQTKGLGISY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- FQTKGLGISY is an optimal epitope.

HXB2 Location Tat (38–47)
Author Location Tat
Epitope FQTKGLGISY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, rate of progression, immunodominance
References Frahm *et al.* 2006

- CTL responses restricted by HLA-B*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects inspite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominanat CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.
- FQTKGLGISY of clade C is a potential HLA-B*1503 restricted epitope.

HXB2 Location Tat (38–47)
Author Location Tat
Epitope FQTKGLGISY
Epitope name B15-FY10(Tat)
Immunogen HIV-1 infection
Species (MHC) human (B15)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.

CTL CD8+

- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Tat (38–47)
Author Location Tat
Epitope FMKKGLGISY
Epitope name FY10(Tat)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope FMKKGLGISY elicited an immune response in Chinese HIV-1 positive subjects as part of peptide as part of peptide LHCQVCFMKKGLGISYGR. This epitope differs from the previously described HLA-B15-restricted epitope , FQTKGLGISY, at 2 residues, FmkKGLGISY.
- 1 of the 21 HLA-B15 carriers responded to FmkKGLGISY-containing peptide with a magnitude of CTL response of 100 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Tat (39–47)
Author Location Tat (39–47 SUMA)
Epitope MTKGLGISY
Epitope name Tat MY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1501)
Donor MHC A*1103, A*2402, B*1402, B*1501, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, epitope processing, immunodominance, escape, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape muations in SUMA over time. Early in infection, three overlapping epitopes in Tat carried mutations: FHCQVCFMTK, VCFMTKGLGI, and MTKGLGISY. An M->T substitution was evident during acute infection in the first sample, at four days of the onset of symptoms, and a rare second variant was seen at day 20 that added a K->E substitution. The M->T substitution abrogated responses to FHCQVCFtTK, VCFtTKGLGI, but not in the third epitope tTKGLGISY. By day 69 a double mutation was evident that persisted through day 435, F->L and T->K. Variants lHCQVCFMkK, VCFMkKGLGI were not recognized, but the CTL response was strong to MkKGLGISY. The authors provide evidence that the F->L and T->K substitutions impact processing of the MTKGLGISY epitope, as the mutations don't abrogate a CTL response to the peptide, but Tat expressed in target cells doesn't allow recognition of the Tat variant.
- MTKGLGISY was the highest level response in acute and early infection.

HXB2 Location Tat (39–47)
Author Location Tat (39–47)
Epitope ITKALGISY
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*1103, A*2402, B*1402, B*1501
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences

in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, VCFITKALGI, was found to be 0.066 (optimistic escape rate = 0.189) per day, with SE of 0.032.
- In this region of Tat there were 3 overlapping CTL epitopes. A T to K mutation at Tat 32 completely abolished in vitro CTL lysis against all three epitopes. In addition, an M to T mutation at Tat 31 completely abolished recognition of two of the epitopes (third not tested). Quantifying the outgrowth of both of the mutations will overestimate the efficiency of a single CTL response.

HXB2 Location Tat (39–49)
Author Location Tat (38–48)
Epitope `ITKGLGISYGR`
Epitope name Tat-4.8
Immunogen HIV-1 infection
Species (MHC) human (A*6801)
Keywords assay standardization/improvement
References Oxenius *et al.* 2002a

- This epitope and HLA-A*6801 presenting molecule were rapidly defined using a modified Elispot assay.
- The 11-mer is the optimal epitope but A*6801 epitopes tolerate length variation.

HXB2 Location Tat (39–49)
Author Location Tat (39–49)
Epitope `ITKGLGISYGR`
Immunogen HIV-1 infection
Species (MHC) human (A*6801)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Tat (39–49)
Author Location Tat (38–48)
Epitope `ITKGLGISYGR`
Epitope name ITK
Immunogen HIV-1 infection
Species (MHC) human (A*6801)
Donor MHC A2, A68.1, B*07, B*3503, Cw*0401, Cw*0702, DQ2, DQ6, DR15, DR17, DR51, DR52
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ
Keywords rate of progression, escape
References Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses,and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relatively efficiency of the variant eptiopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- This was one of 8 reactive epitopes found not to vary over time.

HXB2 Location Tat (39–49)
Author Location Tat (38–49)
Epitope `ITKGLGISYGR`
Immunogen HIV-1 infection
Species (MHC) human (A*6801)
Assay type CD8 T-cell Elispot - IFNγ, Degranulation, CD107a and b cell surface mobilization, Other
Keywords binding affinity, epitope processing, kinetics, characterizing CD8+ T cells
References Gostick *et al.* 2007

- HLA-A*6801 was studied because of its unusual property of weak binding to CD8. Several peptide variants were followed in a CTL clone grown from an A*68 expressing patient who responded to his autologous "index" peptide iTKgLGISYGR. His founder epitope was suggested to be TTKALGISYGR, the "reference" sequence, with variants ITKaLGISYGR and tTKGLGISYGR. The reference sequence TTKALGISYGR is a better agonist in cytokine and degranulation assays than the index peptide iTKgLGISYGR. Surface plasmon resonance shows that both index and reference peptides bind soluble TCR within normal ranges. A mutant HLA-A68 that increases CD8 interaction was found to recognize CTL at lower peptide concentrations and increase cytokine production (IFN-g, MIP-1b, RANTES). However its pattern of variant recognition was not changed. Thus "normalization" of HLA-A*6801 interaction with CD8 does not induce non-specific activation, but does enhance agonist peptide recognition and immune response.

HXB2 Location Tat (39–49)
Author Location Tat (39–49)
Epitope `ITKGLGISYGR`
Subtype B
Immunogen peptide-HLA interaction
Species (MHC) human (A*6801)
Assay type Cytokine production, Flow cytometric T-cell cytokine assay
Keywords binding affinity, co-receptor, characterizing CD8+ T cells
References Laugel *et al.* 2007a

- It was found that CD8 co-receptor differentially fine tunes CTL function via cytokine/chemokine production (MCP-1, MIP1-beta, MIP1-alpha, TNF-alpha, RANTES, IFN-gamma, IL-2 and IL-4). Differential CD8 action was controlled by abrogating its engagement using point-mutated HLA Class I molecules in 4 CTL clones specific for 3 different epitopes from HIV-1 and hTERT.
- An HLA-A*6801 restricted CTL clone, c23, specific for HIV-1 Tat eptiope ITKGLGISYGR found to require a much higher peptide concentration to activate effector functions. This clone did not secrete IL-4.

HXB2 Location Tat (39–49)
Author Location Tat (38–48)
Epitope `ITKGLGISYGR`
Subtype B

Immunogen HIV-1 infection
Species (MHC) human (A68)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Tat (39–49)
Author Location Tat
Epitope ITKGLGISYGR
Epitope name A68-IR11(Tat)
Immunogen HIV-1 infection
Species (MHC) human (A68)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Tat (39–49)
Author Location Tat
Epitope MKKGLGISYGR
Epitope name IR11(Tat)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope MKKGLGISYGR elicited an immune response in Chinese HIV-1 positive subjects as part of peptide LHCQVCFMKKGLGISYGR. This epitope differs from the previously described HLA-A68-restricted epitope, ITKGLGISYGR, at 2 residues, mkKGLGISYGR.

HXB2 Location Tat (40–47)
Author Location Tat
Epitope TKGLGISY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, rate of progression, immunodominance, characterizing CD8+ T cells
References Frahm *et al.* 2006

- CTL responses restricted by HLA-B*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects inspite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominanat CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.
- TKGLGISY of clade B is a potential HLA-B*1503-restricted epitope, with epitope qTKGLGISY found in clade C.

HXB2 Location Tat (40–49)
Author Location
Epitope TKALGISYGR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

HXB2 Location Tat (49–57)
Author Location Tat (49–57)
Epitope RKKRRQRRR
Immunogen vaccine
Vector/Type: DNA, DNA with protein boost *Strain:* B clade LAI *HIV component:* Gag, Nef, Tat *Adjuvant:* IL-18
Species (MHC) mouse (H-2^d)
Keywords Th1
References Billaut-Mulot *et al.* 2001

- DNA vaccinated BALB/c mice primed and boosted with the multiepitopic vaccine with IL18 showed lymphoproliferative responses 7 weeks post immunization.
- Strong but non-lasting HIV-specific CTL responses were detected by a Cr-release assay and DNA prime/DNA boost was more effective than DNA prime protein boost.
- Immunization with either the multiepitopic DNA or with the mixed DNA vaccine induced HIV-1 specific Th1 cytokines (IL-2 and IFN-gamma)
- Co-administration of IL18 increased T-cell responses but decreased anti-HIV antibody levels.

HXB2 Location Tat (49–57)
Author Location Tat (49–57)
Epitope RKKRRQRRR
Immunogen
Species (MHC) mouse
References Kim *et al.* 1997a

- The Tat peptide RKKRRQRRR when conjugated to a protein can cause that protein to be taken up by APCs and presented to CTL.
- The system was demonstrated by vaccinating mice with an OVA-Tat peptide conjugate and immunizing H-2 K^b mice.
- The CTL response to the H-2 K^b specific OVA peptide SIINFEKL was stimulated.

HXB2 Location Tat (58–69)
Author Location Tat
Epitope APQGHPNNQVSI
Epitope name AI12
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A2, B44, B7, Cw5, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 4, APQdHPNNQVSI, was found not to correspond to the most polymorphic residue in the epitope. This is a novel unmapped epitope.

HXB2 Location Tat (83–92)
Author Location Tat
Epitope GPKESKKKVE
Immunogen
Species (MHC) human (B58)
References De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify consevered regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFNγ production in an ELISPOT assay.
- GPKESKKKVE was newly identified as an HLA-B58 epitope in this study.

HXB2 Location Tat
Author Location Tat
Epitope
Immunogen vaccine
Vector/Type: adeno-associated virus (AAV) *HIV component:* Env, Rev, Tat *Adjuvant:* IL-2
Species (MHC) mouse (H-2^d)
References Xin *et al.* 2001

- An AAV vector expressing HIV-1 env, tat, and rev genes (AAV-HIV vector) was used to vaccinate BALB/c mice.
- A single injection stimulated and long lasting serum IgG, fecal IgA, and HIV-specific CTL.
- Boosting enhanced the humoral response, and IL2 enhanced T-cell immunity.

HXB2 Location Tat
Author Location Tat (IIIB)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA), macrophage activating lipopeptide (MALP)
Species (MHC) mouse (H-2^d)
Assay type T-cell Elispot
References Borsutzky *et al.* 2003

- BALB/c mice that were vaccinated intranasally with Tat protein plus mucosal adjuvant macrophage-activating lipopeptide-2 (MALP-2) had increased proliferative, antibody, and IFN-gamma producing T-cell responses than did mice with Tat+IFA delivered by the i.p. route.
- IFA as adjuvant stimulated a Th2-dominant response pattern, and MALP-2 as adjuvant shifted to a Th1 response. In animals vaccinated with Tat+MALP-2, IFN-gamma and IL-2 were the most prominent cytokines, with some IL-6. In contrast, in mice vaccinated with Tat+IFA, IL-6 was the dominant cytokine. Secreted IL-4, IL-5 and IL-10 were below the detection limit in both cases.

HXB2 Location Tat
Author Location Tat
Epitope
Immunogen vaccine

CTL CD8+

Vector/Type: protein *HIV component:* Tat *Adjuvant:* Complete Freund's Adjuvant (CFA), red blood cells
Species (MHC) mouse (H-2^d)
Assay type Chromium-release assay
Keywords dendritic cells, Th1, Th2, immunotherapy
References Dominici *et al.* 2003

- BALB/c mice were immunized with Tat protein bound to red blood cells via biotin-avidin conjugation. This antigen delivery system was successfully internalized by dendritic cells, and induced more consistent anti-Tat Abs responses and sightly increased Tat-specific CTL responses relative to Tat with CFA.

HXB2 Location Tat
Author Location Tat
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Nef, Rev, Tat
Species (MHC) human
Keywords HAART, ART
References Calarota *et al.* 1999

- 9/9 HIV-1 + subjects were given one of three DNA vaccinations for nef, rev or tat, and novel proliferative and CTL responses were generated.
- The nef DNA immunization induced the highest and most consistent CTLp activity, IFN-gamma production, and IL-6 and IgG responses.
- Highly active antiretroviral treatment (HAART) did not induce new HIV-specific CTL responses but reduced viral load, while DNA vaccination induced new immune responses but did not reduce viral load – thus this is a potentially complementary and promising combination.

HXB2 Location Tat
Author Location Tat
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Froebel *et al.* 1997

- Two HIV-1 infected children with contrasting disease courses were followed longitudinally – one died of AIDS, the other is a long-term non-progressor.
- Reactivity against Gag, Pol, Env and Tat proteins was tested by PBMC bulk cultured cells reacting with protein expressed in vaccinia constructs in autologous EBV transformed B cells.
- The child who progressed consistently had CTL against Pol and Tat.
- The long-term non-progressing child had no detectable CTL, but was heterozygous for a mutation in the CCR5 receptor and for HLA-B49, which has been shown to be associated with slower progression.

HXB2 Location Tat
Author Location Tat
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *HIV component:* Nef, Rev, Tat *Adjuvant:* CpG immunostimulatory sequence (ISS)
Species (MHC) human
Keywords review
References Calarota & Wahren 2001

- This review discusses the cellular immune response, and comments on the stimulatory role of CpG motifs and how HIV-1 DNA vaccines can boost the CTL and Th proliferative responses in asymptomatic HIV+ individuals.

HXB2 Location Tat
Author Location Tat
Epitope
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade BH10 *HIV component:* Tat *Adjuvant:* Immune stimulating complexes (ISCOM), CpG immunostimulatory sequence (ISS)
Species (MHC) macaque
References Cafaro *et al.* 2001

- Macaques (macaca fascicularis) were immunized with HIV-1 Tat on an adenovirus major late promotor in a plasmid with 23 CpG sequences, 12 unmethylated.
- The vaccinated animals contained a primary infection challenge with SHIV89.6P, preventing CD4+ T-cell decline in the animals, suggesting Tat may be useful at blocking viral replication at its early stage.

HXB2 Location Tat
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission
References Aldhous *et al.* 1994; Kuhn *et al.* 2002

- Six of nine HIV vertically infected infants had HIV-1 specific CTL responses to vaccinia expressed Tat (4/6), Pol (6/6), Env (1/6), or Gag (1/6), but not all responses were detected at all time points.
- Two of eleven babies that were not infected though born to HIV+ mothers had detectable responses to Tat (1/2), Pol (2/2), Gag (1/2).
- Reviewed in Kuhn *et al.* [2002].

HXB2 Location Tat
Author Location Tat
Epitope
Immunogen HIV-1 infection, vaccine
Species (MHC) human
Keywords review, escape, early-expressed proteins
References Gruters *et al.* 2002

- This paper is a review that makes a case for using Tat and Rev as part of a vaccine strategy.
- CTL against Tat and Rev were found preferentially in long term non-progressors.

- Tat/Rev vaccinations of macaques provided protection or reduction in viremia, with high levels of CTL providing protection from challenge, lower levels of CTL having lower viremia, while Gag/Pol vaccinations with did not result in decreased viremia.
- Early expression of Tat/Rev may in part explain the enhanced benefit of a CTL response directed at these proteins, and CTL escape is more prominent in these proteins.

HXB2 Location Tat
Author Location Tat (BH10)
Epitope
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade BH10 *HIV component:* Tat *Adjuvant:* cationic block copolymer K2
Species (MHC) mouse
Donor MHC H-2d
Assay type proliferation, Chromium-release assay
References Caputo *et al.* 2003

- Mice were immunized intramuscularly with a plasmid DNA vaccine (HIV-1 pCV-tat DNA) alone or complexed with a cationic block polymer K1, K2, or K5, which block digestion by DNAase I and enhance DNA delivery to APC.
- CTL responses to low dose Tat DNA vaccination with K2 were greatly enhanced relative to responses to DNA alone.

HXB2 Location Tat
Author Location Tat
Epitope
Immunogen vaccine
Vector/Type: DNA, protein *HIV component:* Tat *Adjuvant:* aluminum hydroxide, Ribi adjuvant (MPL+TDM) (RIBI)
Species (MHC) macaque
Keywords review, early-expressed proteins
References Fanales-Belasio *et al.* 2002a

- HIV-1 Tat protein is efficiently taken up by monocyte-derived dendritic cells (MDDCs) and promotes Th1 immune responses. A Tat based vaccine can elicit an immune response that can control primary infection in monkeys that are in early stage of in infection with SHIV89.6P.
- Tat-specific CTL activity was detected in four monkeys inoculated with i.m. with pCV-tat.

HXB2 Location Tat
Author Location
Epitope
Immunogen in vitro stimulation or selection
Species (MHC)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords epitope processing, immunodominance, early-expressed proteins, Th1, adjuvant comparison
References Gavioli *et al.* 2004

- HIV-1 Tat protein modulates proteasome composition and activity in B and T cells that either express Tat or are treated with exogenous biologically active Tat protein. This results in modification of Ag processing where presentation of immunodominant EBV epitopes is decreased and presentation of subdominant epitopes is increased. The authors suggest that the immunomodulatory effects of endogenous and exogenous Tat may be beneficial in terms of expanding stimulation of responses to subdominant epitopes, and may be useful as an adjuvant.

HXB2 Location Tat
Author Location Tat
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type T-cell Elispot
References Wang *et al.* 2006b

- The association between T cell response and CD4+ T cell counts or CD4+ was investigated, using overlapping peptides corresponding to natural B clade and C consensus sequences.
- T cell responses and CD4+ count were correlated for Gag p24 and Gag p17 (B and C clades)and for Pol (C clade). CD4+ counts were higher in patients with Tat and /or Rev T cell response than in patients without Tat and Rev response.

II-B-19 Rev CTL/CD8+ epitopes

HXB2 Location Rev (9–23)
Author Location Rev (9–23 HXB2)
Epitope DEELIRTVRLIKLLY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Blazevic *et al.* 1995

- Induces both Th and CTL activities, no HLA restriction analysis performed.

HXB2 Location Rev (9–23)
Author Location
Epitope DEELIRTVRLIKLLY
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A1, A10 (26); B17 (57), B8
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.

CTL CD8+

- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location Rev (10–18)
Author Location Rev (10–18)
Epitope EELLKTVRL
Subtype B
Immunogen HIV-1 infection, peptide-HLA interaction
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance
References Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, EELLKTVRL, is similar to human protein nucleolar RNA associated protein, sequence EELLKeVRL, and a human protein, sequence LLKTVRLlRLL.

HXB2 Location Rev (11–23)
Author Location Rev
Epitope KAVRRLIKFLY
Epitope name KY11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- KY11, KAVRRLIKFLY, is a known HLA-B57-restricted epitope used as a positive control for eliciting CTL IFN-gamma response.

HXB2 Location Rev (12–31)
Author Location Rev (11–30 SF2)
Epitope LLKAVRLIKFLYQSNPPPNF
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Only one subject had CTL that could recognize vaccinia-expressed LAI Rev.
- This subject had a CTL response to this peptide, and was HLA-A2, A24, B13, B35.

HXB2 Location Rev (13–21)
Author Location Rev (13–21)
Epitope LRAVRIIKI
Epitope name LI9
Immunogen HIV-1 infection
Species (MHC) human (B*5701, B*5703)
Country United Kingdom, Kenya
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords escape, optimal epitope
References Makadzange *et al.* 2006

- The study describes the identification of a novel HLA-B*5701, B*5703 optimal epitope LRAVRIIKI, which accounted for 25% and 40% of the total CTL responses in two patients.
- R2K replacement (LkAVRIIKI) resulted in more efficient lysis. I9F (LRAVRIIKf) variant had reduced CTL recognition.

HXB2 Location Rev (14–23)
Author Location
Epitope KAVRLIKFLY
Epitope name KY10
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B*57-restricted optimal epitope KAVRLIKFLY was tested for immune response.

HXB2 Location Rev (14–23)
Author Location Rev (14–23)
Epitope KAVRLIKFLY
Epitope name revKY10

Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country United Kingdom, Kenya
Assay type CD8 T-cell Elispot - IFNγ
Keywords TCR usage, structure, characterizing CD8+ T cells
References Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B*57-peptide complexes were studied.
- In addition, immunodominancy of the previously mapped B*57 epitopes during chronic infection was assessed. KGFNPEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

HXB2 Location Rev (14–23)
Author Location Rev (14–23 subtype B)
Epitope KAVRLIKFLY
Subtype B
Immunogen
Species (MHC) human (B*5701)
Keywords optimal epitope
References Addo *et al.* 2001; Llano *et al.* 2009

- C. Brander notes this is a B*5701 epitope.

HXB2 Location Rev (14–23)
Author Location Rev (14–23 BRU)
Epitope KAVRIKLFLY
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords cross-presentation by different HLA
References Addo *et al.* 2001

- Rev and Tat are expressed early in the virus life cycle and thus may be important targets for CTL against HIV early in infection and for vaccines – therefore CTL responses against Tat and Rev were screened using overlapping peptides.
- 11/57 (19.3%) HIV-1 + individuals recognized at least 1 Tat peptide, and 21/57 (37%) responded to at least 1 Rev peptide.
- This epitope was also recognized by another individual in whom it was restricted by HLA*B5801, an allele closely related to HLA*B5701, suggesting cross-presentation by the two HLA alleles.

HXB2 Location Rev (14–23)
Author Location Rev (14–23)
Epitope KAVRRLIKFLY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Rev (14–23)
Author Location Rev (14–23 subtype B)
Epitope KAVRLIKFLY
Subtype B
Immunogen
Species (MHC) human (B*5801)
Keywords optimal epitope
References Addo *et al.* 2001; Llano *et al.* 2009

- C. Brander notes this is a B*5801 epitope.

HXB2 Location Rev (14–23)
Author Location Rev (14–23 BRU)
Epitope KAVRIKLFLY
Immunogen HIV-1 infection
Species (MHC) human (B*5801)
Keywords cross-presentation by different HLA
References Addo *et al.* 2001

- Rev and Tat are expressed early in the virus life cycle and thus may be important targets for CTL against HIV early in infection and for vaccines – therefore CTL responses against Tat and Rev were screened using overlapping peptides.
- 11/57 (19.3%) HIV-1 + individuals recognized at least 1 Tat peptide, and 21/57 (37%) responded to at least 1 Rev peptide.
- This epitope was also recognized by another individual in whom it was restricted by HLA*B5701, an allele closely related to HLA*B5801, suggesting cross-presentation by the two HLA alleles.

HXB2 Location Rev (14–23)
Author Location Rev (14–23)
Epitope KAVRRLIKFLY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5801)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Rev (14–23)
Author Location Rev
Epitope KTGRLIKLLY
Epitope name KY10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

CTL CD8+

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 8, ktgrlikLly, was found in the most polymorphic residue in the epitope. One escape mutation, at position 5, ktgrFiklly was found not to correspond to the most polymorphic residue in the epitope.

HXB2 Location Rev (14–23)
Author Location
Epitope KAVRLIKFLY
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords responses in children, mother-to-infant transmission
References Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.
- This epitope was recognized less frequently in children than in adults.

HXB2 Location Rev (14–23)
Author Location Rev
Epitope KTVRLIKFLY
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B57, B58, B63)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, cross-presentation by different HLA, optimal epitope
References Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This epitope was recognized by 20% of B63-positive subjects and 12% of B57/58-positive subjects.

HXB2 Location Rev (14–23)
Author Location
Epitope KAVRLIKFLY
Immunogen
Species (MHC) human (B63)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B63 epitope.

HXB2 Location Rev (14–23)
Author Location
Epitope KAVRLIKFLY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated, traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

HXB2 Location Rev (14–23)
Author Location Rev
Epitope RTVRLIKLLY
Epitope name KY10(Rev)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.

- Author defined epitope RTVRLIKLLY elicited an immune response in Chinese HIV-1 positive subjects as a part of peptide DEELLRTVRLIKLLY. This epitope differs from the previously described HLA-B58-restricted epitope, KAVRLIKFLY, at 3 residues, rtVRLIKlLY.
- 6 of the 14 HLA-B58 carriers responded to rtVRLIKlLY-containing peptide with average magnitude of CTL response of 290 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Rev (14–28)
Author Location (C consensus)
Epitope QAVRIIKILYQSNPY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0205)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location Rev (15–22)
Author Location Rev
Epitope AVRIIKIL/M
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords HLA associated polymorphism
References Rousseau *et al.* 2008

- 3 phylogenetic correction methods—MLL (maximum likelihood character state analysis followed by likelihood ratio test), MLF (maximum likelihood character state analysis followed by Fisher test), and parsimony character state analysis were used to identify points in the HIV-1 subtype C proteome that conferred susceptibility or resistance to CTLs. Associations of HLA-epitope combinations that were inferred to be susceptible or resistant were organized into immunological sets that would help identify the best residues and genes as candidates for vaccines. While all proteins were interrogated, Gag, Pol, Env and Nef were focused upon. Amino acid changes were evaluated for association with plasma viral load.
- Proteome maps may be seen at `http://www.hiv.lanl.gov/content/immunology/hlatem/study5/index.html` with information showing single or multiple sites involving escape and reversion.
- HLA- B and -C alleles associated more with aa changes than HLA-A, suggesting that the former two are more important in driving viral evolution.
- The ratio of susceptible to resistant residues in HIV proteins was in descending order, Vpr>Gag>Rev>Pol>Nef>Vif>Tat>Env>Vpu, showing that epitopes from the earlier proteins are more conserved owing to viral fitness cost upon mutation.
- This Rev HLA A*3001-restricted epitope, AVRIIKIL/M was susceptible at R3. Variants AVkIIKIL/M and AVqIIKIL/M were resistant to CTL response, but associated with lower viral loads. This epitope is 1 of 7 that suggest a fitness cost to immune escape.

HXB2 Location Rev (15–23)
Author Location Rev (15–23)
Epitope TVRLIKFLY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*03)
Donor MHC A*03, A*24, B*35, B*40
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords superinfection, characterizing CD8+ T cells
References Yang *et al.* 2005b

- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
- The response to this epitope, TVRLIKFLY, was present only after superinfection. The epitope from the first infecting strain had the substitutions tvKIikfly relative to the test peptide, while the second strain shared the sequence TVRLIKFLY.

HXB2 Location Rev (20–28)
Author Location Rev
Epitope KILYQSNPY
Epitope name 1341
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A02, A03, B08, B51, Cw01, Cw07
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for KILYQSNPY: 36%

HXB2 Location Rev (25–39)
Author Location Rev (25–39 HXB2)
Epitope SNPPPNPEGTRQARR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human

CTL CD8+

References Blazevic *et al.* 1995
- Induces both Th and CTL activities, no HLA restriction analysis performed.

HXB2 Location Rev (33–48)
Author Location Rev (33–48 HXB2)
Epitope GTRQARRNRRRRWRER
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Blazevic *et al.* 1995
- Induces both Th and CTL activities, no HLA restriction analysis performed.

HXB2 Location Rev (37–45)
Author Location Rev
Epitope ARRNRRRRW
Epitope name AW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008
- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- AW9(Rev), ARRNRRRRW, is a novel HLA-B27-restricted epitope that elicits a CTL IFN-gamma response in the same range as Los Alamos database peptides.

HXB2 Location Rev (41–56)
Author Location Rev (41–56 HXB2)
Epitope RRRRWRERQRQIHSIS
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Blazevic *et al.* 1995
- Induces both Th and CTL activities.

HXB2 Location Rev (51–59)
Author Location Rev (51–59)
Epitope QIRTYSGWI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, B13, B41
Country France
Assay type Other
Keywords computational epitope prediction, escape, acute/early infection, immune evasion
References Guillon *et al.* 2006
- A longitudinal study from primary infection to 5 years postinfection was conducted to determine Tat and Rev gene evolution. 2/4 patients showed Tat gene evolution. It was found that though Tat evolved by mostly nonsynonymous, non-random sequence changes, there was no increase in transactivating capacity or size of Tat protein. Sequence evolution occurred mostly in predicted epitopes that are MHC I restricted.
- Tat and Rev seem to evolve due to CTL pressure later in infection, after seroconversion, and possibly during viral replication.
- Epitope QIRTYSGWI did not change in the subjects studied.

HXB2 Location Rev (51–60)
Author Location Rev
Epitope QIRSLSGWIL
Epitope name QL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A2, B44, B7, Cw5, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a
- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 7, QIRSLSeWIL was found not to correspond to the most polymorphic residue in the epitope. This is a novel unmapped epitope.

HXB2 Location Rev (52–60)
Author Location (C consensus)
Epitope IHSISERIL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the H2 residue of IHSISERIL are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location Rev (52–60)
Author Location
Epitope IHSISERIL
Subtype C
Immunogen HIV-1 infection

Species (MHC) human (B*1510)
Donor MHC A*2301, A*2902, B*1510, B*4501, Cw*0602, Cw*1601; A*2301, B*0801, B*1510, Cw*0701, Cw*1601
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- Known epitope IHSISERIL, is HLA-B*1510-restricted. Response to a peptide containing this epitope was detected in an early controller and a rapid progressor 12 weeks post-infection.

HXB2 Location Rev (55–63)
Author Location Rev
Epitope `ISERILSTY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0101)
Donor MHC A*0101, A*0301, B*0801, B*5101; A*0101, B*0801
Country United Kingdom
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords escape, acute/early infection, characterizing CD8+ T cells
References Milicic *et al.* 2005

- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient. In an early acute infection of the donor, the precise timing of transmission determines the viral variants transmitted.
- The second donor in the study shares A*0101 and B*0801 with his partner. The escape variant iserilstF was transmitted, and it abrogates binding to A*0101.

HXB2 Location Rev (55–63)
Author Location Rev (55–63 LAI)
Epitope `ISERILSTY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A1)
Keywords rate of progression
References van Baalen *et al.* 1997

- Predicted to be an HLA-A1 epitope based on anchor residues 2S and 9Y.
- Both forms LSGWL(L or I)STY, with intact anchors, were found in an HLA-A1+ individual with Rev-responsive CTL.
- An HLA-A1 individual who did not make a Rev response had lost the C-term anchor, ISGWILS(T or N)S.
- 3/7 long-term non-progressors and 0/5 progressors were positive for HLA-B57 (associated with prolonged survival)
- CTLp frequencies to Rev and Tat were inversely correlated with rapid progression to AIDS, but not Gag, RT or Nef.

HXB2 Location Rev (55–63)
Author Location Rev (55–63)
Epitope `ISERILSTY`
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A1)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location Rev (55–63)
Author Location RT Pol (55–63)
Epitope `ISERILSTY`
Immunogen HIV-1 infection
Species (MHC) human (A1)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 8/13 patients recognized this epitope, itw was the most commonly recognized of three A*01 epitopes tested.

HXB2 Location Rev (55–63)
Author Location Rev
Epitope `ISERILSTY`
Epitope name A1-IY9(Rev)
Immunogen HIV-1 infection
Species (MHC) human (A1)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.

- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Rev (55–64)
Author Location Rev
Epitope ISERILSTYL
Epitope name IY9(Rev)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A1)
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords non-susceptible form
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- The tested peptide sequence, QRQIRAISgRILSTYLGR, contains a variant, ISgRILSTY that differs by 1 substitution from the previously described HLA-A1 epitope ISERILSTY. None of the 4 HLA-A1 carriers responded to the variant ISgRILSTY.

HXB2 Location Rev (56–64)
Author Location Rev
Epitope SEWILSTHL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 2,SkWILSTHL was found in the most polymorphic residue in the epitope. This is a novel unmapped epitope.

HXB2 Location Rev (57–66)
Author Location Rev (57–66)
Epitope ERILSTYLGR
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Rev (57–66)
Author Location Rev (57–66)
Epitope ERILSTYLGR
Epitope name A3-ER10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 1/7 individuals had detectable responses to this epitope after STI.

HXB2 Location Rev (57–66)
Author Location Rev
Epitope ERILSTYLGR
Epitope name A3-ER10(Rev)
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Rev (57–66)
Author Location
Epitope ERILSTYLGR

CTL CD8+

Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

HXB2 Location Rev (58–66)
Author Location Rev (58–66)
Epitope `RILSTYLGR`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Rev (59–75)
Author Location (C consensus)
Epitope `ILSTCLGRPAEPVPLQL`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1510)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location Rev (63–71)
Author Location Rev (63–71)
Epitope `YLGGSEEPV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, B13, B41
Country France
Assay type Other
Keywords computational epitope prediction, escape, acute/early infection, immune evasion
References Guillon *et al.* 2006

- A longitudinal study from primary infection to 5 years postinfection was conducted to determine Tat and Rev gene evolution. 2/4 patients showed Tat gene evolution. It was found that though Tat evolved by mostly nonsynonymous, non-random sequence changes, there was no increase in transactivating capacity or size of Tat protein. Sequence evolution occurred mostly in predicted epitopes that are MHC I restricted.
- Tat and Rev seem to evolve due to CTL pressure later in infection, after seroconversion, and possibly during viral replication.
- No variants of epitope YLGGSEEPV were found in the subjects studied.

HXB2 Location Rev (66–73)
Author Location Rev (66–)
Epitope `RSAEPVPL`
Epitope name Rev66
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* Rev
Adjuvant: Incomplete Freund's Adjuvant (IFA)
Species (MHC) transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a low A2-binder, and induced a CTL responses in 1/6 A2 transgenic mice. Responses to the peptide were not detected in 17 HIV+ HLA-A2 subjects.

HXB2 Location Rev (66–75)
Author Location Rev (66–75)
Epitope `RPAEPVPLQL`
Epitope name RL10

CTL CD8+

Immunogen HIV-1 infection
Species (MHC) human (B*07)
Assay type CTL suppression of replication
Keywords class I down-regulation by Nef
References Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Late protein Rev epitope RPAEPVPLQL-recognizing CTLs were affected by Nef.

HXB2 Location Rev (66–75)
Author Location Rev
Epitope `RPAEPVPLQL`
Epitope name RL10
Subtype A, B, C, D, F, G
Immunogen HIV-1 infection
Species (MHC) human (B*07)
Country United States
Assay type Chromium-release assay, Other
Keywords subtype comparisons
References Bennett *et al.* 2008

- Cross-clade CTL epitope recognition was tested for functional responses by CTL suppression using endogenously derived cell-surface epitopes rather than supraphysiologic exogenously added peptide epitopes. Functional avidity was actually diminished in non-autologous clade epitopes, calling into question current methods for assessing cross-clade or standard CTL activity and therefore vaccine design.
- RL10 epitope variants used were RPAEPVPLQL for clades B/C/G, RSAEPVPLQL for clade A1, RPTEPVPLQL for clades A2/F2, RSEEPVPLQL for clade D, and RPEEPVPLQL for clade F1. Clade B-elicited CTLs recognized epitopes from all other clades when tested by Cr-release. Suppression of HIV replication however, as well as functional avidity were reduced for different clade consensus epitope sequences.

HXB2 Location Rev (66–75)
Author Location Rev (66–75)
Epitope `RPAEPVPLQL`
Epitope name RL10
Immunogen HIV-1 infection
Species (MHC) human (B07)
Assay type Chromium-release assay, Other
Keywords binding affinity
References Bennett *et al.* 2007

- Standard assays like ELISpot, ICS and tetramer staining do not measure antiviral activity of HIV-infected CTLs, but use exogenous synthetic peptides on uninfected cells, or HLA tetramers. Similarly, functional avidity assesses CTL activity against uninfected target cells. Here functional avidity is compared to the efficiency of actual infected cells' recognition and killing, revealing a sharp threshold between CTL immune antiviral activity and lack of infected cell recognition.
- As previously shown, epitopes and their variants spanned orders of magnitude of SD50. Likewise, CTL clearance of infected cells varied from 0 to 100% with epitope sequence variation. Moreover, direct suppression of HIV-1 replication by CTLs also varied with epitope variant.
- When killing efficiency (KE) using virus-infected cells was compared to functional avidity using synthetic peptides, there was a narrow threshold separating maximal killing from almost none. Since different SL9-specific clones had similar KEs, which were vastly different from RL10-specific CTL KEs, it was obvious that KEs varied with epitope sequence too. Finally, a strong correlation between KE and inhibition of viral replication was also seen.
- This epitope, RPAEPVPLQL, showed marked differences in its functional avidity, killing efficiency, as well as inhibition of viral replication when compared to its variants RsAEPVPLQL, RPtEPVPLQL, RPeEPVPLQL, RPAqPVPLQL, RPAEPVPLhL, RPAEPVPfQL, RPvEPVPLQL, RPeEPVPfQL, RPeEPVPLpL, RPAEPVPfhL, RPtEPVPfQL, RPtEPVPLeL, RPqEPVPLlL and RPtEPVPfhL.

HXB2 Location Rev (66–75)
Author Location
Epitope `RPAEPVPLQL`
Epitope name RL10
Immunogen
Species (MHC) human (B7)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B07 epitope.

HXB2 Location Rev (66–75)
Author Location Rev
Epitope `RSAEPVPLQL`
Epitope name RL10(Rev)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope RSAEPVPLQ elicited an immune response in Chinese HIV-1 positive subjects as part of peptide LGRsAEPVPLQLPPLERL. This epitope differs from the previously described HLA-B7-restricted epitope sequence, RPAEPVPLQ, at 1 residue, RsAEPVPLQL.
- 1 of the 9 HLA-B7 carriers responded to RsAEPVPLQL-containing peptide with a magnitude of CTL response of 750 SFC/million PBMC.

HXB2 Location Rev (66–81)
Author Location Rev (66–78)
Epitope RPAEPVPLQLPPIERL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*13)
Donor MHC A*0301, A*3001, B*1301, B*1402, Cw*0602, Cw*0802
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords epitope processing, immune evasion, viral fitness and reversion, HLA associated polymorphism
References Honeyborne *et al.* 2007

- To determine whether HLA-B*13-restricted CTL responses could partially explain low viremic loads in patients, a cohort of chronic C-clade infected subjects was studied. 6 novel B*13-restricted CTL epitopes were defined from both C- and B-clade viruses, 3 of which were within Gag. B*13-restricted CTL responses correlated with lower viremia, with most immunity targeted against Gag epitopes (p15, p17, p24). Gag epitope escape variants may exact a high viral fitness cost, mutations being seen within and around the optimal epitope.
- An HLA-B*13-restricted epitope was found within the above overlapping peptide sequences, but the optimal epitope was not confirmed.

HXB2 Location Rev (66–81)
Author Location Rev
Epitope RSAEPVPLQLPPLERL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot – 36% (25/70) targeted one or more Rev peptides, and this peptide was the most frequently recognized epitope in Rev (32%).
- The regulatory proteins Rev and Tat combined contributed to 3%, and the accessory proteins Vif, Vpr and Vpu to 7%, of the total magnitude of HIV-1 specific CTL responses in a subset of 22 HIV-1 infected individuals in whom all HIV-1 proteins were studied.

HXB2 Location Rev (66–81)
Author Location Rev
Epitope RSAEPAPLQLPPLERL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Novel unmapped epitope.
- RSAEPAPLQLPPLERL shows a mutation over time in position 6, RSAEPvPLQLPPLERL.

HXB2 Location Rev (67–75)
Author Location (LAI)
Epitope SAEPVPLQL
Subtype B
Immunogen
Species (MHC) (B14)
References van Baalen & Gruters 2000

HXB2 Location Rev (67–75)
Author Location Rev
Epitope SAEPVPLQL
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords escape
References Schutten *et al.* 2001

- Molecularly cloned primary NSI macrophage tropic strain 2.1 and SI non-macrophage tropic strain 1.2 were isolated from study participant ACH320 and use to infect irradiated XID mice that had been reconstituted with human PBMC from B14+ seronegative donors – results indicate CTL may favor selective outgrowth of macrophage tropic strains.
- The CTL clone TCC108 specific for SAEPVPLQL, previously described by van Baalen 1997, and van Baalen 1998, was stimulated *in vitro* and given to the mice to apply specific CTL pressure.
- The macrophage-tropic HIV-1 strain #2.1 escaped CTL pressure more efficiently (7/14 animals) than its non-macrophage-tropic counterpart #1.2(SI) – the latter isolate was suppressed in 13/14 animals – macrophage may serve as a CTL sanctuary and reduced pressure on macrophage tropic HIV strains may allow additional replication to assist with acquisition of escape.
- Specific HIV-1 variants selectively induced by TCC108 were for strain 1.2: SEEPVPLQL, and for strain 2.1: SAEHVPLQL, SAESVPLQL, SVEPVPLQL, SLEPVPLQL, SAEPVPFQL, and SAEPVPFQL.

HXB2 Location Rev (67–75)
Author Location Rev (67–75)
Epitope SAEPVPLQL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords acute/early infection, early-expressed proteins, kinetics
References van Baalen *et al.* 2002

CTL CD8+

- Tat, Rev and Nef are the first HIV proteins expressed upon acute infection of T-cells (< 6 hours), and RT is not expressed until after 24 hours. The B14-restricted Rev-SAEPVPLQL specific CD8 T-cell clone TCC108, and the B57-restricted RT-IVLPEKDSW specific CD8 T-cell clone TCL1C11 were co-incubated with CD4+ cultures innoculated with HIV-1 at low MOI. Co-incubation with the Rev-specific CTL resulted in two logs less HIV-1 production in ten days of culture. When the RT epitope was cloned into the Nef gene of the infecting strain, another early expressed protein, it proved as effective as the Rev epitope at inhibiting viral production. A mathematical model of CTL-target interactions suggest early proteins are important for vaccine design.

HXB2 Location Rev (67–75)
Author Location Rev (67–75)
Epitope SAEPVPLQL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Rev (67–75)
Author Location Rev
Epitope SAEPVPLQL
Epitope name B14-SL9(Rev)
Immunogen HIV-1 infection
Species (MHC) human (B14)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Rev (67–75)
Author Location Rev (67–75 IIIB)
Epitope SAEPVPLQL
Immunogen HIV-1 infection
Species (MHC) human (B14, Cw8)
References van Baalen *et al.* 1998

- The Rev-specific CTL response studied here was from an individual infected with HIV-1 for more than 12 years without developing symptoms – Rev and Tat are expressed early and CTL activity against these proteins has been correlated with long-term survival.
- The CTL clone TCC108 specific for this epitope was studied *in vitro*.
- CTLs added immediately after infection suppressed viral production, indicative of CTL interference with viral production prior to lysis – CTL-mediated lysis occurred after the onset of progeny viral release, but prior to peak viral production.
- Rapid selection of a E69K mutation, which abolished CTL, recognition was observed.
- The epitope was originally listed as B14, but Cw8 and B14 are in linkage disequilibrium, and in this case were not distinguished (pers. comm., Christian Brander, 1999)

HXB2 Location Rev (67–75)
Author Location (LAI)
Epitope SAEPVPLQL
Subtype B
Immunogen
Species (MHC) human (Cw*0501)
Keywords optimal epitope
References Addo *et al.* 2001; Llano *et al.* 2009

HXB2 Location Rev (67–75)
Author Location Rev (SF2)
Epitope SAEPVPLQL
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (Cw5)
Keywords acute/early infection
References Goulder *et al.* 2001a

- Data from patient AC13 suggest a role for this epitope in initial control of viremia in acute infection, as it is one of several subdominant CTL epitopes recognized during the initial decline in viremia.
- A CTL response to SL9, SLYNTVATL, was not evident until 18 months post-presentation.

HXB2 Location Rev (67–75)
Author Location Rev (67–75 SF2)
Epitope SAEPVPLQL
Immunogen HIV-1 infection
Species (MHC) human (Cw5)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with preseroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic

infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-Cw5+ individuals that had a CTL response to this epitope broken down by group: 2/6 group 1, 0/1 group 2, and 0/2 group 3.

HXB2 Location Rev (67–75)
Author Location Rev (67–75)
Epitope SAEPVPLQL
Immunogen HIV-1 infection
Species (MHC) human (Cw5)
Donor MHC A*0201, A1, B44, B57, Cw5, Cw6
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

HXB2 Location Rev (67–75)
Author Location Rev (67–75)
Epitope SAEPVPLQL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw5)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords escape, optimal epitope
References Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- Escape occurred at position 5 of this epitope, saepGplql.

HXB2 Location Rev (67–75)
Author Location Rev
Epitope SAEPVPLQL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw5)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 5, SAEPgPLQL, was found not to correspond to the most polymorphic residue in the epitope.

HXB2 Location Rev (67–75)
Author Location Rev
Epitope SAEPVPLQL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw5)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- 203 days after first testing, epitope SAEPVPLQL showed no variation in a treated patient. Previously published HLA-restriction for SL9 wis HLA-Cw5.

HXB2 Location Rev (67–75)
Author Location Rev (67–75)
Epitope SAEPVPLQL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw5, Cw8)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Rev (67–75)
Author Location Rev (69–77 BRU)
Epitope SAEPVPLQL
Epitope name Rev SL9
Immunogen HIV-1 infection
Species (MHC) human (Cw8)
Keywords HAART, ART, supervised treatment interruptions (STI), acute/early infection
References Addo *et al.* 2001

- Rev and Tat are expressed early in the virus life cycle and thus may be important targets for CTL against HIV early in infection and for vaccines – therefore CTL responses against Tat and Rev were screened using overlapping peptides.
- 11/57 (19.3%) HIV-1 + individuals recognized at least 1 Tat peptide, and 21/57 (37%) responded to at least 1 Rev peptide.
- This epitope is the first HIV-specific CTL epitope resticted by HLA-Cw5.
- This epitope was recognized by 2/5 individuals expressing HLA-Cw8 and by 5/11 individuals expressing Cw5 allele, which differs from Cw8 by 4 amino acids, suggesting promiscuous presentation of the epitope between those HLA molecules.
- Longitudinal data was available for 6 Rev-SL9 responders, who were treated during acute infection, and the response was stable 2 and 12 months after initiaion of HAART, measurements by ELISPOT and flow-based intracellular cytokine staining (ICS) were concordant – in two subjects the response was heightened by transient reexposure to antigen with treatment interruption at 12 to 14 months.

HXB2 Location Rev (67–75)
Author Location Rev
Epitope SAEPVPLQL
Epitope name Cw8-SL9(Rev)
Immunogen HIV-1 infection
Species (MHC) human (Cw8)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Rev (67–75)
Author Location
Epitope SAEPVPLQL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

HXB2 Location Rev (67–75)
Author Location Rev (65–77 BH10, LAI)
Epitope SAEPVPLQL
Immunogen HIV-1 infection
Species (MHC) human
References Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is GRSAEPVPLQLPP) has similarity with transforming growth factor beta binding protein protein I, fragment ARSAEPEVATAPP.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is EPVPLQLPPL) also has similarity with the epidermal growth factor receptor substrate 15, fragment EPVPMSLPPA.

HXB2 Location Rev (67–75)
Author Location Rev (67–75)
Epitope SAEPVPLQL

Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human
Assay type HLA binding
Keywords assay standardization/improvement, characterizing CD8+ T cells
References van Baalen *et al.* 2005

- A new senstitive, non-readioactive assay, called fluorescent antigen-transfected target cell-CTL (FATT-CTL) assay, was developed to measure antigen-specific cytotoxicity ex vivo. Target cells were generated by nucleofection with DNA vectors encoding antigen-GFP fusion proteins. Flow cytometry was used to quantify viable and dead GFP-positive cells after coculture with different effector:target cell ratios. Cytotoxicity was detected at lower effector:target cell ratios than in standard Cr-release assay. Antigen-specific cytotoxicity was detected ex vivo in PBMCs from HIV-1 infected individuals.

HXB2 Location Rev (70–78)
Author Location Rev (70–78)
Epitope `PVPFQLPPL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, B13, B41
Country France
Assay type Other
Keywords computational epitope prediction, escape, acute/early infection, immune evasion
References Guillon *et al.* 2006

- A longitudinal study from primary infection to 5 years postinfection was conducted to determine Tat and Rev gene evolution. 2/4 patients showed Tat gene evolution. It was found that though Tat evolved by mostly nonsynonymous, non-random sequence changes, there was no increase in transactivating capacity or size of Tat protein. Sequence evolution occurred mostly in predicted epitopes that are MHC I restricted.
- Tat and Rev seem to evolve due to CTL pressure later in infection, after seroconversion, and possibly during viral replication.
- The previously described epitope PVPFQLPPL, had a variant PVPlQLPPL in the fourth position.

HXB2 Location Rev (71–78)
Author Location Rev (75–)
Epitope `VPLQLPPL`
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (B*0702)
Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008

- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location Rev (71–78)
Author Location Env
Epitope `VPLQLPPL`
Epitope name Env259
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- VPLQLPPL is an Env epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location Rev (71–78)
Author Location Rev
Epitope `VPLQLPPL`
Epitope name Rev75
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- VPLQLPPL is a Rev epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location Rev (71–78)
Author Location Rev
Epitope `VPLQLPPL`
Epitope name Rev75
Subtype A, B, C, D
Immunogen HIV-1 infection
Species (MHC) human, mouse (B7 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA

CTL CD8+

References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope VPLQLPPL of the HLA-B7 supertype bound most strongly to HLA-B*5101, -B*0702 and -B*5401 and also to -B*3501 but not to -B*5301. It was conserved 25% in subtype A, 68% in B, 38% in C and 100% in subtype D. 1/16 HLA-B7 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Rev75.

HXB2 Location Rev (72–88)
Author Location (C consensus)
Epitope PLQLPPIERLHIDCSES
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*13)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location Rev (73–81)
Author Location Rev (73–81)
Epitope LQLPPLERL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, LQLPPLERL, was detected within overlapping peptide PLQLPPLERLTLDCNED.

HXB2 Location Rev (73–81)
Author Location Rev (73–)
Epitope LQLPPIERL
Epitope name Rev73
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* Rev
Adjuvant: Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced CTL responses in mice. Responses to the peptide were not detected in 17 HIV+ HLA-A2 subjects.

HXB2 Location Rev (73–81)
Author Location
Epitope LQLPPIERL
Epitope name Rev 73
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Previously defined Rev 73 epitope, LQLPPIERL, was not found in any patients and there was no CTL immune response to it.
- No Rev epitope studied was sufficiently conserved to act as a vaccine target.

HXB2 Location Rev (74–82)
Author Location Rev (74–82)
Epitope QLPPLERLT
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, B13, B41
Country France
Assay type Other
Keywords computational epitope prediction, escape, acute/early infection, immune evasion
References Guillon *et al.* 2006

- A longitudinal study from primary infection to 5 years postinfection was conducted to determine Tat and Rev gene evolution. 2/4 patients showed Tat gene evolution. It was found that though Tat evolved by mostly nonsynonymous, non-random sequence changes, there was no increase in transactivating capacity or size of Tat protein. Sequence evolution occurred mostly in predicted epitopes that are MHC I restricted.
- Tat and Rev seem to evolve due to CTL pressure later in infection, after seroconversion, and possibly during viral replication.
- No variants of epitope QLPPLERLT were found in the subjects under study.

HXB2 Location Rev (75–83)
Author Location
Epitope LPPLERLTL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

HXB2 Location Rev (96–104)
Author Location Rev (96–)
Epitope GMGSPQILV
Epitope name Rev96(2M)
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* Rev *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was an intermediate A2 binder, and induced a CD8+ T-cell IFN gamma response in 1/6 mice. Responses were detected in 1/17 HIV+ HLA-A2 subjects.
- The variant gVgspqilv did not elicit a CD8+ T-cell IFN gamma response in transgenic mice, and bound to A2 with low affinity.

HXB2 Location Rev (96–104)
Author Location
Epitope GMGSPQILV
Epitope name Rev 96
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords variant cross-recognition or cross-neutralization
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Rev 96 epitope, GMGSPQILV, was not found in any patients but 1 had a CTL immune response to it.
- No Rev epitope studied was sufficiently conserved to act as a vaccine target.

HXB2 Location Rev (98–116)
Author Location Rev
Epitope GSTQVSVESPTVLEPGTKE
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.

- Novel unmapped epitope. A P->L change occurred in a patient that recognized this peptide, over time: GSTQVSVESlTVLEPGTKE

HXB2 Location Rev (101–109)
Author Location Rev (101–109)
Epitope QILGEPPTV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, B13, B41
Country France
Assay type Other
Keywords computational epitope prediction, escape, acute/early infection, immune evasion
References Guillon *et al.* 2006

- A longitudinal study from primary infection to 5 years postinfection was conducted to determine Tat and Rev gene evolution. 2/4 patients showed Tat gene evolution. It was found that though Tat evolved by mostly nonsynonymous, non-random sequence changes, there was no increase in transactivating capacity or size of Tat protein. Sequence evolution occurred mostly in predicted epitopes that are MHC I restricted.
- Tat and Rev seem to evolve due to CTL pressure later in infection, after seroconversion, and possibly during viral replication.
- The previously described epitope QILGEPPTV, contained variants QILGEhPpV in the sixth and eighth positions and QILGghPpV in the fifth, sixth and eighth positions.

HXB2 Location Rev (101–110)
Author Location Rev
Epitope QVLGESPTVL
Epitope name QL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Two escape mutations, at positions 5 and 7, QVLGkSPTVL and QVLGEStTVL, were found not to correspond to the most polymorphic residues in the epitope. This is a novel unmapped epitope.

HXB2 Location Rev (102–110)
Author Location Rev (102–110)
Epitope ILVESPAVL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, ILVESPAVL, was detected within overlapping peptide TQGVGSPQILVESPAVL.

HXB2 Location Rev (102–110)
Author Location Rev (102–)
Epitope ILVESPAVL
Epitope name Rev102
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* Rev *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder that did not induce CTL or CD8+ T-cell IFN gamma responses in mice, but responses were detected in 2/17 HIV+ HLA-A2 subjects.

HXB2 Location Rev (102–110)
Author Location Rev (102–110)
Epitope ILGEPPTVL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, B13, B41
Country France
Assay type Other
Keywords computational epitope prediction, escape, acute/early infection, immune evasion
References Guillon *et al.* 2006

- A longitudinal study from primary infection to 5 years postinfection was conducted to determine Tat and Rev gene evolution. 2/4 patients showed Tat gene evolution. It was found that though Tat evolved by mostly nonsynonymous, non-random sequence changes, there was no increase in transactivating capacity or size of Tat protein. Sequence evolution occurred mostly in predicted epitopes that are MHC I restricted.
- Tat and Rev seem to evolve due to CTL pressure later in infection, after seroconversion, and possibly during viral replication.
- The previously described epitope ILGEPPTVL varied to ILGEhPhVL in the fifth and seventh positions and ILGghPhVL in the fourth, fifth and seventh positions.

HXB2 Location Rev (102–110)
Author Location
Epitope ILVESPAVL
Epitope name Rev 102
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords variant cross-recognition or cross-neutralization
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Rev 102 epitope ILVESPAVL was found in 1 patient but 2 had CTL immune responses to it. It was not immunogenic in A2tg mice.
- No Rev epitope studied was sufficiently conserved to act as a vaccine target.

HXB2 Location Rev (102–110)
Author Location Rev (102–)
Epitope ILVESPAVL
Epitope name Rev102
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Rev epitope ILVESPAVL, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients. DK1 had variant sequence IpVESPtVL.

HXB2 Location Rev (107–116)
Author Location Rev
Epitope PTVLESGTKE
Epitope name 1277
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A68)
Donor MHC A11, A68, B42, B45, Cw16, Cw17
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for PTVLESGTKE:16%. This epitope can be presented by A68, but did not bind to A11.

HXB2 Location Rev
Author Location Rev
Epitope
Immunogen vaccine
Vector/Type: DNA with CMV promotor with cationic liposome *HIV component:* gp160, Rev
Species (MHC) mouse (H-2^d)
References Ishii *et al.* 1997

- pCMV160/Rev is a DNA vaccine candidate carrying gp160 and Rev linked to a cytomegalovirus (CMV promotor)
- pCMV160/Rev given in conjunction with a cationic liposome gave enhanced DTH, Ab and CTL responses.

HXB2 Location Rev
Author Location Rev
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Rev
Adjuvant: CD40
Species (MHC) mouse (H-2^d)

CTL CD8+

Keywords Th1, Th2
References Ihata *et al.* 1999

- pcRev DNA i.m. vaccination in BALB/c mice induced Th1, Th2 and IgG responses, and enhanced the CTL response to Rev, but did not induce mucosal IgA.

HXB2 Location Rev
Author Location Rev
Epitope
Immunogen vaccine
Vector/Type: adeno-associated virus (AAV) *HIV component:* Env, Rev, Tat *Adjuvant:* IL-2
Species (MHC) mouse (H-2^d)
References Xin *et al.* 2001

- An AAV vector expressing HIV-1 env, tat, and rev genes (AAV-HIV vector) was used to vaccinate BALB/c mice.
- A single injection stimulated and long lasting serum IgG, fecal IgA, and HIV-specific CTL.
- Boosting enhanced the humoral response, and IL2 enhanced T-cell immunity.

HXB2 Location Rev
Author Location Rev
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Nef, Rev, Tat
Species (MHC) human
Keywords HAART, ART
References Calarota *et al.* 1999

- 9/9 HIV-1 + subjects were given one of three DNA vaccinations for nef, rev or tat, and novel proliferative and CTL responses were generated.
- The nef DNA immunization induced the highest and most consistent CTLp activity, IFN-gamma production, and IL-6 and IgG responses.
- Highly active antiretroviral treatment (HAART) did not induce new HIV-specific CTL responses but reduced viral load, while DNA vaccination induced new immune responses but did not reduce viral load – thus this is a potentially complementary and promising combination.

HXB2 Location Rev
Author Location (subtype C)
Epitope
Subtype C
Immunogen
Species (MHC) human
References Novitsky *et al.* 2001

- This study is provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort.
- Anti-Rev CTL responses were distributed throughout the protein and 27 of 47 subjects (57%) demonstrated HIV-1C Rev-specific ELISPOT CTL responses of more than 100 SFC/106 PBMC.

HXB2 Location Rev
Author Location Rev
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *HIV component:* Nef, Rev, Tat *Adjuvant:* CpG immunostimulatory sequence (ISS)
Species (MHC) human
Keywords review
References Calarota & Wahren 2001

- This review discusses the cellular immune response, and comments on the stimulatory role of CpG motifs and how HIV-1 DNA vaccines can boost the CTL and Th proliferative responses in asymptomatic HIV+ individuals.

HXB2 Location Rev
Author Location Rev
Epitope
Immunogen HIV-1 infection, vaccine
Species (MHC) human
Keywords review, escape, early-expressed proteins
References Gruters *et al.* 2002

- This paper is a review that makes a case for using Tat and Rev as part of a vaccine strategy.
- CTL against Tat and Rev were found preferentially in long term non-progressors.
- Tat/Rev vaccinations of macaques provided protection or reduction in viremia, with high levels of CTL providing protection from challenge, lower levels of CTL having lower viremia, while Gag/Pol vaccinations with did not result in decreased viremia.
- Early expression of Tat/Rev may in part explain the enhanced benefit of a CTL response directed at these proteins, and CTL escape is more prominent in these proteins.

HXB2 Location Rev
Author Location Rev
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type T-cell Elispot
References Wang *et al.* 2006b

- The association between T cell response and CD4+ T cell counts or CD4+ was investigated, using overlapping peptides corresponding to natural B clade and C consensus sequences.
- T cell responses and CD4+ count were correlated for Gag p24 and Gag p17 (B and C clades)and for Pol (C clade). CD4+ counts were higher in patients with Tat and /or Rev T cell response than in patients without Tat and Rev response.

II-B-20 Vpu CTL/CD8+ epitopes

HXB2 Location Vpu (4–13)
Author Location Vpu
Epitope `LVILAIVALV`
Immunogen
Species (MHC) human (B7)
References De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conservered regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFNγ production in an ELISPOT assay.
- LVILAIVALV was newly identified as an HLA-B7 epitope in this study using ELISPOT, but could not be shown to bind to B7.

HXB2 Location Vpu (4–13)
Author Location Vpu
Epitope `LVILAIVALV`
Epitope name 1300
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A03, A24, B07, B38, Cw07, Cw12/13
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for LVILAIVALV: 6%

HXB2 Location Vpu (5–13)
Author Location Vpu (5–13)
Epitope `YRLGVGALI`
Epitope name YI9
Subtype C
Immunogen
Species (MHC) human (Cw*18)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a Cw18 epitope.
- YRLGVGALI has weak similarity to subtype B gp41. However, its correct localization is Vpu 5-13, where its sequence matches subtype C well.

HXB2 Location Vpu (5–13)
Author Location Vpu (C consensus)
Epitope `YRLGVGALI`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*1801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- YRLGVGALI is an optimal epitope in Vpu.

HXB2 Location Vpu (5–13)
Author Location gp41 (1–8)
Epitope `YRLGVGALI`
Subtype C
Immunogen peptide-HLA interaction
Species (MHC) human (Cw*1801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords optimal epitope
References Honeyborne *et al.* 2006

- Novel epitopes are defined for four HLA-alleles common in South African Zulu/Xhosa populations: B*3910, B*4201, B*8101 and Cw*1801, by motif inference. HLA-A*2902 was found to overlap those of A1 and A24 supertypes.
- YRLGVGALI was the optimal epitope for HLA-Cw*1801 with variants YRLGVGAL, RLGVGALI, YRLGVGALIi, dYRLGVGALI having been tested.
- YRLGVGALI has weak similarity to subtype B gp41. However, its correct localization is Vpu 5-13, where its sequence matches subtype C well.

HXB2 Location Vpu (7–15)
Author Location Vpu (7–15)
Epitope `LAIVALVVA`
Subtype B
Immunogen HIV-1 infection, peptide-HLA interaction
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance
References Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, LAIVALVVA, is similar to human protein Trypsin-domain protein, sequence alVALVVApL, and human small inducible cytokine 28 protein, sequence LAIVALaV.

HXB2 Location Vpu (13–21)
Author Location Vpu (13–)
Epitope `VVAAIIAIV`
Epitope name Vpu13

CTL CD8+

Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* Vpu
Adjuvant: Incomplete Freund's Adjuvant (IFA)
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was an intermediate A2 binder that did not induce CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 2/17 HIV+ HLA-A2 subjects.

HXB2 Location Vpu (13–21)
Author Location
Epitope VVAAIIAIV
Epitope name Vpu 13
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Only 1 of 2 patients with the Vpu 13 VVAAIIAIV epitope was reactive to it.

HXB2 Location Vpu (25–40)
Author Location Vpu
Epitope IVFIEYRKLRQRKID
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot – only 2% (2/70) targeted one or more Vpu peptides, including this peptide.
- The regulatory proteins Rev and Tat combined contributed to 3%, and the accessory proteins Vif, Vpr and Vpu to 7%, of the total magnitude of HIV-1 specific CTL responses in a subset of 22 HIV-1 infected individuals in whom all HIV-1 proteins were studied.

HXB2 Location Vpu (29–37)
Author Location Vpu (29–37)
Epitope EYRKILRQR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*3303)
Keywords early-expressed proteins
References Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

HXB2 Location Vpu (29–37)
Author Location Vpu (29–37)
Epitope EYRKILRQR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*3303)
Keywords early-expressed proteins
References Addo *et al.* 2002a

- Detection of HIV CTL epitopes is rare in Vpu, and this is the first optimally defined Vpu epitope.
- This CTL response was first detected in a long term non-progressor, and 3/6 HLA A*3303 positive individuals were found to have a CTL response to this epitope.
- HLA A*3303 is common in West Africa and Asia.

HXB2 Location Vpu (29–37)
Author Location Vpu (29–37)
Epitope EYRKILRQR
Immunogen HIV-1 infection
Species (MHC) human (A*3303)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Vpu (29–37)
Author Location Vpu
Epitope EYRKILRQR
Epitope name ER9(Vpu)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A33)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.

- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A33-restricted epitope EYRKILRQR elicited an immune response in Chinese HIV-1 positive subjects as part of peptide IVFIEYRKILRQRKIDRL.
- 3 of the 20 HLA-A33 carriers responded to EYRKILRQR-containing peptide with average magnitude of CTL response of 403 SFC/million PBMC.

HXB2 Location Vpu (29–43)
Author Location
Epitope EYRKILRQRKIDRLI
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade MN *HIV component:* gp160
Species (MHC) human
Donor MHC A1, A33; B44, B8
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location Vpu (48–63)
Author Location
Epitope ERAEDSGNESEGDTEELSA
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*2301, A*2902, B*4101, B*4201, Cw*1701
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression, optimal epitope
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- ERAEDSGNESEGDTEELSA is of unknown restriction. Response was detected in 1 rapid progressor 12 weeks post-infection.

HXB2 Location Vpu (62–82)
Author Location Vpu (65–81)
Epitope AALVEMGHDAPWVVDDL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A2, B44, B7, Cw5, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Novel unmapped epitope. The third position was found to vary over time to AAfVEMGHDAPWVVDDL.

HXB2 Location Vpu (64–82)
Author Location (C consensus)
Epitope STMVDMGHLRLLDVNDL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*6801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location Vpu (67–75)
Author Location
Epitope ALVEMGHHA
Epitope name Vpu 66
Immunogen HIV-1 infection
Species (MHC) human
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords variant cross-recognition or cross-neutralization
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.

CTL CD8+

- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Vpu 66 ALVEMGHHA was found in 5 patients, being most conserved of Vpu epitopes. It was poorly immunogenic however, with no HLA-A2+ subjects responding to it and recognition by only 1 HLA-A2- patient.
- Anchor optimization to the Vpu66(9Vmod) variant, ALVEMGHHv, induced a very strong immune response, cross-reacting to natural Vpu66(9A).
- One patient reactive to Vpu 66 was not responsive as measured by IC-IFNgamma-FACS but by IC-TNFalpha and IC-IL-2-FACS.

HXB2 Location Vpu (74–82)
Author Location Vpu
Epitope HAPWDVNDL
Epitope name HL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*01)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords binding affinity
References Cao *et al.* 2008

- For the first time, viral immune evasion is reported via an insertion mutation, in an ART-naive patient. A 3 aa repeat, SPT inserted within p6<sup>Pol<sup> epitope NL8 is reported. This insertion is associated often with ART drug resistance to NRTI drugs. Thus immune pressure and drug resistance may cause HIV-1 to select the same variation.
- A concomitant insertion mutation APP, is seen in p6<sup>Gag<sup>, permitting viral budding.
- Epitope HAPWDVNDL bound its MHC I significantly less strongly than NL8, NSPTRREL, did its MHC I molecule.

HXB2 Location Vpu (74–82)
Author Location Vpu (74–82 2001 HIV-1 subtype B cons)
Epitope HAPWDVNDL
Epitope name HL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*0102)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Last position (9) in the epitope had potentially experienced positive selection. HAPWD-VNDm escape variant was found.

HXB2 Location Vpu
Author Location Vpu
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Nef, Vif, Vpu
Species (MHC) mouse (H-2^{d})
Keywords subtype comparisons, Th1
References Ayyavoo *et al.* 2000

- Splenocytes from BALB/c mice immunized with pVVN-P DNA were incubated with Vif, Vpu or Nef antigens for 3 days and assayed for IL-4 and IFN-gamma levels.
- Antigen stimulation increased IFN-gamma production in pVVN-P immunized mice, indicating a Th1 response.
- IL-4 production was not significantly changed after antigen stimulation compared to control levels.
- Cross-clade CTL activity was also observed: A, B clade, CRF01(AE) clade antigens could serve as targets for the B clade immunization-stimulated CTL – an HIV-1 AC recombinant, however, did not stimulate a CTL response, but was expressed at lower levels on the target cell.

II-B-21 gp160 CTL/CD8+ epitopes

HXB2 Location gp160 (2–10)
Author Location gp160 (2–10 IIIB)
Epitope RVKEKYQHL
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*0801 epitope.

HXB2 Location gp160 (2–10)
Author Location gp160 (2–10 IIIB)
Epitope RVKEKYQHL
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords subtype comparisons
References Sipsas *et al.* 1997

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB.
- Type-specific epitope, unique to the LAI and IIIB because of a deletion of three amino acids that are present in all other subtype B HIV-1s.
- RVKGIRKNYQHL, a variant found in JRCSF, was not recognized.
- This epitope is in the signal sequence of gp120.

HXB2 Location gp160 (2–10)
Author Location gp120 (2–10)
Epitope RVKEKYQHL
Immunogen HIV-1 infection
Species (MHC) human (B8)

References Day *et al.* 2001

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual.

HXB2 Location gp160 (2–10)
Author Location
Epitope RVKEKYQHL
Immunogen
Species (MHC) (B8)
Keywords review, immunodominance, escape, vaccine antigen design
References Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection.

HXB2 Location gp160 (5–20)
Author Location Env (5–19)
Epitope GIRKNYQHLWRGGTL
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized by mice co-immunized with Env and Tat, but not by mice immunized with Env alone.

HXB2 Location gp160 (6–12)
Author Location gp120 (6–15 CM243 subtype CRF01)
Epitope TQMNWPNLWK
Epitope name E6-15
Subtype CRF01_AE
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A11)
Keywords HIV exposed persistently seronegative (HEPS)
References Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope after a second stimulation *in vitro* gave a weak response in HEPS study subject 186 who was HLA A2/A11.

HXB2 Location gp160 (6–12)
Author Location gp120 (6–15 CM243 subtype CRF01)
Epitope TQMNWPNLWK
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords subtype comparisons
References Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This is one of the new A11 epitopes identified through the streamlined EpiMatrix method, and 2/8 tested FSWs recognized it.
- This epitope was not conserved in other subtypes, and exact matches were rare.

HXB2 Location gp160 (18–32)
Author Location Env (17–31)
Epitope GTLLLGMLMICSAVE
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized by mice co-immunized with Env and Tat, but not by mice immunized with Env alone.

HXB2 Location gp160 (22–36)
Author Location Env (21–35)
Epitope LGMLMICSAVEKLWV
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized by mice co-immunized with Env and Tat, but not by mice immunized with Env alone.

HXB2 Location gp160 (29–40)
Author Location gp160
Epitope AENLVWTVYY
Epitope name B44-AY10(gp160)
Immunogen HIV-1 infection
Species (MHC) human (B44)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location gp160 (30–40)
Author Location Env (29–39)
Epitope AAENLWVTVYY
Immunogen HIV-1 infection
Species (MHC) human (B44)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load..
- Less than 2 of 11 patients recognized this epitope.

HXB2 Location gp160 (30–44)
Author Location Env (29–43)
Epitope AVEKLWVTVYYGVPA
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized by mice co-immunized with Env and Tat, but not by mice immunized with Env alone.

HXB2 Location gp160 (30–46)
Author Location Env
Epitope AAENLWVTVYYGVPVWK
Epitope name ENV-05
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, aaeNLWVTVYYGVPVWK differs from the consensus C sequence vggNLWVTVYYGVPVWK at 3 amino acid positions, i.e. by 17.6%.

HXB2 Location gp160 (30–49)
Author Location gp120
Epitope `AAEQLWVTVYYGVPVWKEAT`
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords TCR usage
References Weekes *et al.* 1999b

- Peptide 7035.1: Almost all CD8+ T cells are CD28+ at birth, and the proportion of CD28-CD8+ cells increases with age – this study examines the contribution of CD8+CD28- cells to CTL memory pools for CTL clones specific for two persistent human viruses, CMV and HIV – clones were found to be similarly distributed in the CD28 depleted cell population.
- HIV CTL responses to 3 Env and 2 Gag peptides were studied.
- The clonal composition of the TCR Vβ responses was studied and was found to be highly focused, with one TCR beta-chain sequence tending to dominate the peptide-specific response – clones to this epitope were Vβ6.

HXB2 Location gp160 (30–49)
Author Location gp120 (30–49)
Epitope `AAEQLWVTVYYGVPVWKEAT`
Epitope name Peptide 7035.1
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A29, B44, B8
Country United Kingdom
Assay type Flow cytometric T-cell cytokine assay, Other
Keywords HAART, ART, immunodominance, TCR usage, memory cells
References Weekes *et al.* 2006

- The effect of HAART on the population size, phenotype and function of HIV- and HCMV-specific CTL clones was analyzed. It was determined that the clonal composition of gag and env HIV-specific CD8 T-cells did not change after HAART. Following HAART, the size of immunodominant HIV-specific CD8 T-cell clones was found to diminish even with the relative preservation of functional memory responses. Maintainance of such strong functional responses implied the preferential loss of HIV-specific cells that have reduced cloning efficiency in vitro. HCMV-specific CTL clones had different kinetics and phenotypes than HIV-specific CTL clones in the same subject.

HXB2 Location gp160 (30–49)
Author Location gp120 (1–20)
Epitope `ATEKLWVTVYYGVPVWKEAT`
Epitope name ATE
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A2, A68.1, B*07, B*3503, Cw*0401, Cw*0702, DQ2, DQ6, DR15, DR17, DR51, DR52
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ
Keywords rate of progression, escape
References Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses,and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relatively efficiency of the variant eptiopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- This was one of 8 reactive peptides found not to vary over time. It was one of four epitopes that were not precisely defined.

HXB2 Location gp160 (31–39)
Author Location
Epitope `AENLWVTVY`
Epitope name AY9
Immunogen
Species (MHC) human (B*1801)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*1801 epitope.

HXB2 Location gp160 (31–39)
Author Location gp120 (31–39 HIV-MN)
Epitope `AENLWVTVY`
Epitope name AY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1801)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203

CTL CD8+

Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Position 1 in the epitope had potentially experienced positive selection. AdNLWVTVY, tdNLWVTVY, tEdLWVTVY, eEdLWVTVY and AEdsWVTVY escape variants were found.

HXB2 Location gp160 (31–39)
Author Location gp160 (30–38 WEAU)
Epitope AENLWVTVY
Epitope name gp160 AY9
Immunogen HIV-1 infection
Species (MHC) human (B*4403)
Donor MHC A*2902, B*0801, B*4403
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, immunodominance, escape, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.
- This was the immunodominant response in acute infection in WEAU, and there was rapid escape in the epitope AENLWVTVY, with three variants observed by day 30 from the onset of symptoms. Additional mutations continued to develop, so that there were 9 different forms observed through the course of sampling. The variants all conferred different levels of reduction in CTL response, double mutations or anchor mutations tended to cause the greatest reduction: AaNLWVTaY, tNkWVTVY, AgNLWVTVY, AkNLWVTVY, although the double mutant tENLWVTiY elicted a very strong CTL response, suggesting it might not be an escape form.

HXB2 Location gp160 (31–39)
Author Location gp120 (30–38 SF2)
Epitope AENLWVTVY
Immunogen HIV-1 infection
Species (MHC) human (B44)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B44+ individuals that had a CTL response to this epitope broken down by group: 1/8 group 1, 2/3 group 2, and 3/4 group 3.

HXB2 Location gp160 (31–39)
Author Location gp120 (30–38)
Epitope AENLWVTVY
Immunogen HIV-1 infection
Species (MHC) human (B44)
References Day *et al.* 2001

HXB2 Location gp160 (31–39)
Author Location gp120
Epitope AENLWVTVY
Immunogen HIV-1 infection
Species (MHC) human (B44)
Keywords epitope processing
References Cao *et al.* 2002

- AC2 is a B44 restricted CTL clone that recognizes AENLWVTVY.
- CTL could be activated by a fusion protein of an HIV protein and anthrax lethal factor (LFn-HIV) that promotes antigen presenting cell uptake of exogenous protein and allows processing through the MHC class I pathway. This strategy for CTL detection could allow antigen presentation without generation of cells by the standard methods of using live viral vectors carrying a protein, or by loading the cells with peptides and by-passing processing.

HXB2 Location gp160 (31–39)
Author Location (B consensus)
Epitope AENLWVTVY
Epitope name AY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B44)
Donor MHC A11, A29, B08, B44, Cw4, Cw7
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location gp160 (31–39)
Author Location
Epitope AENLWVTVY
Epitope name AY9
Immunogen
Species (MHC) human (B44)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B44 epitope.

HXB2 Location gp160 (31–39)
Author Location
Epitope AENLWVTVY
Immunogen HIV-1 infection
Species (MHC) human (B44)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope AENLWVTVY elicited a magnitude of response of 160 SFC with a functional avidity of 5nM.

HXB2 Location gp160 (31–39)
Author Location gp120
Epitope AENLWVTVY
Epitope name AY9(gp120)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B44)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B44-restricted epitope AENLWVTVY elicited an immune response in Chinese HIV-1 positive subjects as part of peptides LGMLMICSAAENLWVTVY and AAENLWVTVYYGVPVWK.
- 1 of the 6 HLA-B44 carriers responded to AENLWVTVY-containing peptide, AAENLWVTVYYGVPVWK, with average magnitude of CTL response of 620 SFC/million PBMC (author communication and Fig.1).

HXB2 Location gp160 (31–39)
Author Location gp160 (31–39)
Epitope AENLWVTVY
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A1, A29, B44, B8
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, AENLWVTVY, was found to be 0.048/day (upper bound on rate of escape = 0.053), with SE of 0.022.
- Mutations at position 30 (E30G and E30A) were shown to confer escape.

HXB2 Location gp160 (31–40)
Author Location gp160 (30–39 WEAU)
Epitope AENLWVTVYY
Immunogen HIV-1 infection
Species (MHC) human (B*4402)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*4402 epitope.

HXB2 Location gp160 (31–40)
Author Location gp160 (30–39 WEAU)
Epitope AENLWVTVYY
Immunogen HIV-1 infection

CTL CD8+

Species (MHC) human (B44)
Keywords immunodominance, escape
References Borrow *et al.* 1997; Borrow & Shaw 1998; Goulder *et al.* 1997a

- Two CTL lines from the patient WEAU were studied – one had an optimal peptide of (A)AENLWVTVYY, and the other (A)AENLWVTVY, and both responded equally well with one or two N-term Alanines.
- Rapidly post-infection, a strong immunodominant response was observed against this epitope.
- The naturally occurring forms of the peptide found in WEAU were tested as targets for early WEAU CTLs – the form TENLWVTVY was as reactive as the wild type AENLWVTVY – but the forms AKNLWVTVY, AGNLWVTVY, AANLWVTVY did not serve as targets.
- The glutamic acid in the second position is a B44 anchor residue.
- Goulder *et al.* [1997a] and Borrow & Shaw [1998] are reviews of immune escape that summarizes this study in the context of CTL escape to fixation.

CTL CD8+

HXB2 Location gp160 (31–55)
Author Location gp120 (32–56 LAI)
Epitope TEKLWVTVYYGVPVWKEATTTLFCA
Subtype B
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* gp160
Species (MHC) human (B18)
References Johnson *et al.* 1994a

- HLA restricted CTL response to epitope in HIV-1 vaccinia-env vaccinees.

HXB2 Location gp160 (31–55)
Author Location gp120 (32–56 LAI)
Epitope TEKLWVTVYYGVPVWKEATTTLFCA
Subtype B
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* gp160
Species (MHC) human (B18)
References Ferris *et al.* 1999; Hammond *et al.* 1995

- This peptide can be processed for HLA-B18 presentation by both TAP-1/2 independent and dependent pathways.

HXB2 Location gp160 (32–40)
Author Location Env (92TH023)
Epitope DNLWVTVYY
Subtype B, CRF01_AE
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost, canarypox, canarypox prime with gp160 boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* Gag, gp120, gp41, Pol
Species (MHC) human (B44)
Country Thailand
Assay type Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Paris *et al.* 2004

- 21% (40/187) of Thai adults that recieved ALVAC-HIV with or without gp120 or oligomeric gp160 had a CD8+ T-cell response. HLA-B44 was positively associated with CTL responses, and A33 had a borderline significance association with response. A33/B44/DRB1*0701 is the most common haplotype in Thailand. B46, present in 30% of the population, was negatively associated with CTL responses, although it did not reach significance. HLA class I serotypes A11, A24, A33, B46 and B75 were the most common found in 245 Thai volunteers.
- 9/11 cases of pCTL activity to Env were in people with B44. The authors suggest some of the response may be directed at the previously mapped B44 Env epitope AENLWVTVYY in HXB2, DNLWVTVYY in their CRF01 ALAVC vaccine 92TH023. B*4403 is the most common B44 allele among Thais, while B*4402 is more common among Caucasians; a prior study had shown that B*4403 may be able to present a broader spectrum of epitopes than B*4402.

HXB2 Location gp160 (32–40)
Author Location gp160 (29–37 SUMA)
Epitope ENLWVTVYY
Epitope name GP160 EY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*1103, A*2402, B*1402, B*1501, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, acute/early infection, characterizing CD8+ T cells
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape muations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

HXB2 Location gp160 (33–42)
Author Location Env (32–41 subtype B)
Epitope KLWVTVYYGV
Subtype B

Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade MN *HIV component:* gp160
Species (MHC) human (A*0201)
Keywords binding affinity
References Kundu *et al.* 1998a

- Ten HIV-1 + HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period.
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity.
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual.
- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses.

HXB2 Location gp160 (33–42)
Author Location gp120 (33–42)
Epitope NLWVTVYYGV
Immunogen
Species (MHC) human (A02)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 37/51 Brazilian HIV sequences; present in 100% of subtype C and F sequences.

HXB2 Location gp160 (33–42)
Author Location gp120 (32–41 LAI)
Epitope KLWVTVYYGV
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN *HIV component:* gp160
Species (MHC) human (A2)
References Dupuis *et al.* 1995

- CTL from HLA-A2 positive subject react with this peptide.

HXB2 Location gp160 (33–42)
Author Location Env
Epitope NLWVTVYYGV
Epitope name 1256
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A02, A30, B39
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for NLWVTVYYGV: 84%

HXB2 Location gp160 (33–42)
Author Location Env
Epitope KLWVTVYYGV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2, A2.1)
Donor MHC A1, A19, B*3501, B44, Cw16, Cw7; A*0201, A19, B14, B44, Cw16, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
References Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than interperson sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-A2/A2.1 restricted epitope, KLWVTVYYGV was mutated to nwWVTVYYGV in the daughter D2 isolate.

HXB2 Location gp160 (34–42)
Author Location
Epitope LWVTVYYGV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Assay type Cytokine production, proliferation, Tetramer binding, Intracellular cytokine staining, Chromium-release assay
References Dagarag *et al.* 2003

- Telomer length is short in the CD8+ T-cell compartment of HIV-1 infected people, indicating excessive CTL activation and premature senescense. Here human telomerase RT (hTERT) transduction of HIV-1-specific CTL was used to

CTL CD8+

study the functional impact of telomerase. Telomerase expression enhanced proliferative capacity, as well as cytolytic and antiviral capabilities; cytokine production was unchanged. hTERT transduced CTLs were 10-fold more efficient in controlling HIV-1 replication in culture. Thus telomerase transduction can restore CTL mediated cytolysis, and may have therapeutic potential.
- Three polyclonal CD8+ T-cell lines derived from an HIV-1, HLA A*0201 positive patient were used in this study, including one specific for this epitope.

HXB2 Location gp160 (34–42)
Author Location gp120 (34–42)
Epitope LWVTVYYGV
Immunogen
Species (MHC) human (A*0201)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007
- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 50/51 Brazilian HIV sequences.

HXB2 Location gp160 (34–55)
Author Location gp120 (25–46 BRU)
Epitope LWVTVYYGVPVWKEATTTLFCA
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Dadaglio *et al.* 1991
- Defined through peptide blocking of CTL activity, and Env deletions.

HXB2 Location gp160 (34–55)
Author Location Env
Epitope LWVTVYYGVPVWKEATTTLFCA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A1, A19, B*3501, B44, Cw16, Cw7; A*0201, A19, B14, B44, Cw16, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
References Reinis *et al.* 2007
- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than interperson sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-A2 restricted epitope, LWVTVYYGVPVWKEATTTLFCA was mutated to wWVTVYYGVPVWKEATnTLFCA in the daughter D2 isolate.

HXB2 Location gp160 (36–44)
Author Location gp120 (36–44)
Epitope VTVYYGVPV
Immunogen
Species (MHC) human (A02)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007
- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 51/51 Brazilian HIV sequences.

HXB2 Location gp160 (36–44)
Author Location Env (35–)
Epitope VTVYYGVPV
Epitope name Env35
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* Env *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human (A2)
Assay type CD4 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003
- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced a CD8+ T-cell IFN gamma response in 1/6 mice. Responses to the peptide were not detected in 17 HIV+ HLA-A2 subjects.

HXB2 Location gp160 (36–44)
Author Location
Epitope VTVYYGVPV
Epitope name Env 35
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Previously defined Env 35 VTVYYGVPV epitope was found in all 11 patients but none had CTL immune responses to it.

HXB2 Location gp160 (36–46)
Author Location Env (47–)
Epitope VTVYYGVPVWK
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (A*0301)
Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008

- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location gp160 (36–46)
Author Location Env
Epitope VTVYYGVPVWK
Epitope name Env 47
Subtype M
Immunogen vaccine, in vitro stimulation or selection, computer prediction
Vector/Type: DNA, peptide *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, mouse (A*1101)
Assay type Cytokine production, T-cell Elispot
Keywords subtype comparisons, computational epitope prediction, escape, TCR usage, variant cross-recognition or cross-neutralization
References McKinney *et al.* 2004

- This study examined variant recognition of epitopes presented by A*0201 and A*1101. Numerous amino acid substitutions can be introduced into epitopes without disrupting their recognition by CTLs, although epitopes with multiple substitutions were less recognized. An algorithm was constructed for prediction of epitopes capable of inducing responses to a great number of variant epitopes.
- A total of 9 variant forms of Env 47 were identified. More than 95% of the variant epitopes were recognized by CTLs from mice immunized with the parental form.
- Env 47 epitope (parent or variant form) was present in 82% of HIV sequences of many M group subtypes.

HXB2 Location gp160 (36–46)
Author Location gp120 (36–46)
Epitope VTVYYGVPVWK
Immunogen
Species (MHC) human (A*6801)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 47/51 Brazilian HIV sequences.

HXB2 Location gp160 (36–46)
Author Location gp120 (36–46 CM243 subtype CRF01)
Epitope VTVYYGVPVWR
Epitope name E36-4
Subtype CRF01_AE
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A11)
Keywords HIV exposed persistently seronegative (HEPS)
References Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope after a second stimulation *in vitro* gave a weak response in HEPS study subject 186 who was HLA A2/A11.

HXB2 Location gp160 (36–46)
Author Location gp120 (36–46 CM243 subtype CRF01)
Epitope VTVYYGVPVWR
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords subtype comparisons
References Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This epitope was not predicted by the EpiMatrix method to be likely to bind to A11, though it served as an epitope in the FSWs, and it was one of the six A11 epitopes that had been previously defined.
- 1/8 tested FSWs recognized this epitope.
- This epitope was only conserved in CRF01 and subtypes B and C, and exact matches were uncommon.

CTL CD8+

HXB2 Location gp160 (36–46)
Author Location gp120
Epitope VTVYYGVPVWK
Immunogen HIV-1 infection
Species (MHC) human (A*6801, A11)
References Threlkeld *et al.* 1997

- Study of the fine specificity of an A3-like-HLA-super-type epitope (the A3-super-type includes A*0301, A*1101, A*3101, A*3301, and A*6801)
- The A3 super-type is characterized as a hydrophobic or hydroxyl containing anchor residue at position 2, and a positive charge in the C-term position.
- While most lines were specific, a promiscuous cloned CTL line was derived from an HIV+ donor that could recognize this epitope presented by either A11 or A*6801.

HXB2 Location gp160 (36–46)
Author Location Env
Epitope VTVYYGVPVWK
Epitope name Env47
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (A3)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- VTVYYGVPVWK is an Env epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location gp160 (36–46)
Author Location Env
Epitope VTVYYGVPVWK
Epitope name Env47
Subtype A, B, C, D
Immunogen HIV-1 infection
Species (MHC) human, mouse (A3 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope VTVYYGVPVWK of the HLA-A3 supertype bound most strongly to HLA-A*1101, -A*0301 and -A*6801 and also to -A*3301 but not -A*0301. It was conserved 25% in subtype A, 95% in B, 100% in C and 75% in subtype D. 3/23 HLA-A3 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Env47.

HXB2 Location gp160 (37–45)
Author Location gp120 (37–45)
Epitope TVYYGVPVW
Epitope name TW9
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (A*03, A*11)
Country Kenya
Assay type Cytokine production, proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2007

- The authors suggest that epitope variation has different effects on the HIV- specific immune responses of effector memory T cells (Tem) and central memory T cells (Tcm). They show a lack of correlation between IFN-gamma ELISPOT (Tem typical) and proliferation (Tcm typical) assays for specific epitopes in subjects. Since proliferating CTL also correlate with high intracellular IFN-gamma levels, they surmise that proliferating Tcm differentiate to express Tem functions.
- They also show that proliferating CTL numbers correlate with higher CD4 cell counts.
- Several patients responded strongly to epitope variants that were not part of their autologous HIV-1 sequences. Thus they suggest more comprehensive functional characterizations than the usual overnight IFN-gamma ELISPOTs as well as assessments of Tem versus Tcm specific responses rather than general CTL immune responses.
- 4 variants of this index epitope TVYYGVPVW, TW9, were tested - TiYYGVPVW, TVYYGiPVW, TVYYGVPrW, TVYYGVPmW. This index peptide, TW9, and its variants show a high proportion of instances where IFN-gamma ELIspot and proliferation correspond well.
- TW9 has previously published restrictions to HLA-A*11, -A*03 and -B*03.

HXB2 Location gp160 (37–45)
Author Location gp160
Epitope TVYYGVPVW
Subtype A, B, C, D
Immunogen HIV-1 infection, vaccine
Vector/Type: vaccinia *Strain:* A clade, B clade, D clade NDK, C clade consensus *HIV component:* Env
Species (MHC) human
Donor MHC A*2902A*2902, B*1503, B*1801, Cw*0202, Cw*1203; A*3001, A*6601, B*5703, B*5801, Cw*0401, Cw*1801
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References McKinnon *et al.* 2005

- Interclade cross-reactivity of clades A, B, C, and D was tested using recombinant vaccinia-based IFN-gamma Elispot assay. 47/74 women had a positive Elispot response to at least one clade, and cross-clade responses were frequent. Clade A responses were most frequent, as expected, as clade A dominates the Kenyan epidemic (85% of the 47 women responded to clade A Env, 74% to B, 62% to C, and 43% to D). Cross-clade CD8 T-cell responses were common and directed at conserved epitopes.
- There was a greater magnitude of response to A clade peptides in individuals who responded to more than 1 clade; a 2-fold higher response was observed in clade A in 36% (9/25) of these individuals, and the response to A peptides was never lower. TVYYGVPVW responses were detected in 2 women who reacted to all clades tested, A, B, C, and D, and the sequence was identical in all clades.

HXB2 Location gp160 (37–45)
Author Location Env
Epitope TVYYGVPVW
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101, A*2902, B*4201, B*8101, Cw*1701, Cw*1801; B*0702, B*1503, Cw*0202, Cw*0702; A*6802, A*7401, B*1510, B*4901, Cw*0304, Cw*0701; A*0201, B*4504, B*5301, Cw*1601
Country Kenya
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2008

- To evaluate the use of IFN-gamma ELISpot and proliferation assays, the two were compared in a cohort of HIV-1-infected Kenyan sex-workers. ELISpot does not always correlate with viral load and replication or disease progression. The exclusive use of these assays makes definition of CTL response in disease incomplete, especially for memory T cells.
- Despite assaying for 24 INF-gamma and 41 proliferative responses, only 5 of these responses overlapped in the same subject. 18 peptide-epitopes including 10 epitopes and their variants were used in this study.
- TVYYGVPVW elicited proliferation responses in 3 subjects; ELISpot response in 1 subject; both proliferation and ELISpot in 1 subject.

HXB2 Location gp160 (37–46)
Author Location gp120 (37–46 LAI)
Epitope TVYYGVPVWK
Subtype B
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* gp160
Species (MHC) human (A*0301)
References Johnson *et al.* 1994b

- Multiple CTL clones obtained from two vaccinees.
- C. Brander notes that this is an A*0301 epitope in the 1999 database.

HXB2 Location gp160 (37–46)
Author Location gp120 (38–41 LAI)
Epitope TVYYGVPVWK
Subtype B
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* gp160
Species (MHC) human (A*0301)
References Johnson *et al.* 1994a

- Highly conserved epitope recognized by multiple CTL clones from vaccinee.

HXB2 Location gp160 (37–46)
Author Location gp120 (37–46 LAI)
Epitope TVYYGVPVWK
Subtype B
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* gp160
Species (MHC) human (A*0301)
References Ferris *et al.* 1999; Hammond *et al.* 1995

- This peptide can be processed for HLA-A3.1 presentation by TAP-1/2 independent and dependent pathways.

HXB2 Location gp160 (37–46)
Author Location gp120 (37–46 LAI)
Epitope TVYYGVPVWK
Subtype B
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* gp160
Species (MHC) human (A*0301)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*0301 epitope.

HXB2 Location gp160 (37–46)
Author Location gp120 (37–46 LAI)
Epitope TVYYGVPVWK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords acute/early infection
References Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B2705; and A*0201, A*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK.
- The subject with A*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705.

- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

HXB2 Location gp160 (37–46)
Author Location gp120
Epitope TVYYGVPVWK
Subtype A, B, C, D
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human (A*0301)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location gp160 (37–46)
Author Location gp120 (430–440)
Epitope TVYYGVPVWK
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag
Species (MHC) human (A*0301)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords vaccine antigen design
References Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.
- 3/5 subjects with CD8+ T-cell responses responded to this epitope.

HXB2 Location gp160 (37–46)
Author Location Env (37–46)
Epitope TVYYGVPVWK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
References Liang *et al.* 2008

- 1100 unique full-length Env sequences were analyzed and the positive selection (PS) pressure determined. The QUASI method was used across Clades A, B, C and D, to find PS sites dispersed across Env.
- Frequency of PS sites is stable over time.
- 25% to 61% PS sites are shared between subtypes A, B, C and D, so it is inferred that immune responses are targeted against the same general regions.
- Significant correlations between PS sites and neutralizing antibody response, helper response, antibody plus CTL response are found. This suggests that the NAb response might be the driving force behind HIV-1 Env evolution.
- PS-free sites that are targeted greatly by NAb and CTL were found. Functional reasons for the lack of positive selection in such regions must exist.
- PS-site-rare regions (conserved regions of Env) were examined for PS, and epitopes located in such regions. Epitope TVYYGVPVWK, restricted by HLA-A*0301, is on a region free from positive selection. It is found in European populations and has no known association with progression to AIDS.
- Overlapping conserved NAb 4E10 epitope LWVTVYYGVPVWK was also found and thought to be protective against HIV-1.

HXB2 Location gp160 (37–46)
Author Location gp120 (37–46)
Epitope TVYYGVPVWK
Immunogen
Species (MHC) human (A*0301, A*6801)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 47/51 Brazilian HIV sequences.

HXB2 Location gp160 (37–46)
Author Location Env
Epitope TVYYGVPVWK
Immunogen vaccine
Vector/Type: DNA
Species (MHC) transgenic mouse (A11)
References Ishioka *et al.* 1999

- A minigene vaccine construct encoding 6 HLA 2.1 and 3 HLA A11 restricted CTL epitopes, the universal Th cell epitope PADRE (pan-DR epitope) and an ER translocating signal sequence was constructed.
- The epitopes were chosen for dominant recognition by CTLs during HBV and HIV infections in humans.

- HLA transgenic mice were used for quantitating *in vivo* immunogenicity of DNA vaccines encoding HLA-restricted CTL epitopes.

HXB2 Location gp160 (37–46)
Author Location Env
Epitope TVYYGVPVWK
Epitope name 1283
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A*6801, A11, A2, A3, B18)
Donor MHC A25, A68, B18, B27; A03, A11, B14, B51, Cw08, Cw13
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for TVYYGVPVWK:18% Promiscuous epitope binding to A02, A03, A11, A6801 and B18.

HXB2 Location gp160 (37–46)
Author Location gp120 (37–46)
Epitope TVYYGVPVWK
Immunogen vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Protease
Species (MHC) human (A3)
References Carruth *et al.* 1999

- The vaccine used was a live recombinant canarypox (CP) virus vaccine containing multiple HIV-1 genes (HIV-1 MN gp120, HIV-1 LAI gp41, HIV-1 LAI Gag, HIV-1 LAI protease)
- CD4+ and CD8+ Gag and Env specific CTL responses were detected in only 1/5 vaccinated volunteers, and were not detectable 1 year after vaccination.
- CTL responses to epitopes SLYNTVATL and TVYYGVPVWK from HIV+ control patients were used as positive controls.
- The study explored why vaccinees were non-responsive – non-response was not due to inherent defects or differences in the ability of these individuals to process and present antigen.

HXB2 Location gp160 (37–46)
Author Location gp120 (37–46 LAI)
Epitope TVYYGVPVWK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords review, escape
References Goulder *et al.* 1997e; Goulder *et al.* 1997a

- HLA-identical sibling hemophiliac brothers were both infected with the same batch of factor VIII.
- One had a response to this epitope, the other did not. They were tested 6-8 years after infection.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

HXB2 Location gp160 (37–46)
Author Location gp120 (36–45)
Epitope TVYYGVPVWK
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location gp160 (37–46)
Author Location gp120 (37–46)
Epitope TVYYGVPVWK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant.

HXB2 Location gp160 (37–46)
Author Location
Epitope TVYYGVPVWK
Epitope name Env-VK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A03, 0/20 (0%) recognized this epitope.

HXB2 Location gp160 (37–46)
Author Location gp160 (37–46)
Epitope TVYYGVPVWK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these eptiopes, but this increased over time.

HXB2 Location gp160 (37–46)
Author Location gp120
Epitope TVYYGVPVWK
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A3)
Donor MHC A01, A03, B39, B44, Cw4, Cw6
Assay type T-cell Elispot
Keywords HIV exposed persistently seronegative (HEPS)
References Missale *et al.* 2004

- HIV-specific T-cell response was tested in patients exposed to blood from a patient with highly replicating HIV; these patients were nosocomially infected with HBV, but uninfected with HIV. HIV-specific T-cell responses were directed to structural and non-structural HIV proteins in 2 patients, suggesting that the virus replicated in these patients sufficiently to prime a cell-mediated immune response that protected them from HIV infection.
- This patient responded to 3/11 HIV epitopes tested in an IFNgamma EliSpot assay. Responses were detected 16 and 20 weeks after exposure, but were lost by week 80.

HXB2 Location gp160 (37–46)
Author Location gp120
Epitope TVYYGVPVWK
Epitope name A3-TK11(gp120)
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location gp160 (37–46)
Author Location gp160
Epitope TVYYGVPVWK
Epitope name TK10(gp160)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A3-restricted epitope TVYYGVPVWK elicited an immune response in Chinese HIV-1 positive subjects as part of peptides AAENLWVTVYYGVPVWK and TVYYGVPVWKEATTTLF.
- 2 of the 3 HLA-A3 carriers responded to a TVYYGVPVWK-containing peptide, TVYYGVPVWKEATTTLF, with average magnitude of CTL response of 200 SFC/million PBMC (author communication and Fig.1).

HXB2 Location gp160 (37–46)
Author Location Env (49–58)
Epitope TVYYGVPVWK
Immunogen HIV-1 infection
Species (MHC) human (A3 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801).

HXB2 Location gp160 (37–46)
Author Location Env (37–46)
Epitope TVYYGVPVMK
Immunogen peptide-HLA interaction
Species (MHC) (A11, A3, A68)
Assay type HLA binding
Keywords binding affinity, immunodominance
References Racape *et al.* 2006

- Interaction between purified HLA-A3 molecules and several dominant CD8 epitopes was characterized. Amplitude, stability, and kinetic parameters of the interaction between HLA-A3, peptides, and anti-HLA mAbs were tested.
- Epitopes tested bound strongly to HLA-A3 and formed very stable complexes.
- Gag epitope RLRPGGKKK and Nef epitope RLAFHHVAR complexes with HLA-A3 were not recognized by the A11.1 mAb specific to HLA-A3 alleles. The proposed explanation was that Arg at position P1 of the peptide may push the α2 helix residue and affect mAb recognition.

HXB2 Location gp160 (37–53)
Author Location (C consensus)
Epitope TVYYGVPVWKEAKTTLF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*3201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location gp160 (37–53)
Author Location (C consensus)
Epitope TVYYGVPVWKEAKTTLF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*4301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location gp160 (37–53)
Author Location (C consensus)
Epitope TVYYGVPVWKEAKTTLF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location gp160 (37–53)
Author Location Env
Epitope TVYYGVPVWKEATTTLF
Epitope name ENV-06
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, TVYYGVPVWKEAtTTLF differs from the consensus C sequence TVYYGVPVWKEAkTTLF at 1 amino acid position, i.e. by 5.9%.

HXB2 Location gp160 (37–53)
Author Location gp120
Epitope TVYYGVPVWKEATTTLF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most

CTL CD8+

differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, TVYYGVPVWKEATTTLF, had an overall frequency of recognition of 22.7% - 25.4% AA, 19.2% C, 18.2% H, 28.6% WI. This peptide is included in a 41 aa gp120 highly reactive region to be used for vaccine design.

HXB2 Location gp160 (38–48)
Author Location gp120 (45–55)
Epitope VYYGVPVWKEA
Immunogen HIV-1 infection
Species (MHC) human (Cw7)
References Nehete *et al.* 1998a
- Three long-term non-progressors and one asymptomatic HIV+ individual were studied and found to have HLA class I C-restricted CD8+ Env-specific CTLs – Cw7 specific CTL were found against three peptides, including this one.
- HLA-C antigens are expressed on lymphoid cells to a lesser extent than either HLA-A or -B.
- HLA-C confers protection against lysis by natural killer cells and by non-MHC-restricted effector T cells and Cw7 directly governs this resistance to lysis – the authors hypothesize that pathogens that inhibit antigen expression and class I expression may particularly down regulate Cw7, thus triggering non-MHC restricted killing.

HXB2 Location gp160 (38–48)
Author Location gp120 (38–48)
Epitope VYYGVPVWKEA
Immunogen
Species (MHC) (Cw7)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007
- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 46/51 Brazilian HIV sequences.

HXB2 Location gp160 (38–52)
Author Location
Epitope VYYGVPVWKEATTTL
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* gp140
Species (MHC) mouse
Assay type proliferation, T-cell Elispot
References Kumar *et al.* 2006c
- A recombinant plasmid DNA construct expressing env gp140 from B clade isolate 6101 was developed.
- The construct was highly immunogenic in mice and cross-reacted with clade C peptides. 3 immunodominant peptides were mapped out. Proliferation was observed in CD4+, CD8+ and CCR+ memory T cells.
- Immunodominant peptide VYYGVPVWKEATTTL overlapped with the SYFPEITHI database predicted epitope YGVPVWKEA for the Balb/C mouse H2-Kd loci.

HXB2 Location gp160 (38–52)
Author Location Env (37–51)
Epitope VYYGVPVWKEATTTL
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008
- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized by mice co-immunized with Env and Tat, but not by mice immunized with Env alone.

HXB2 Location gp160 (42–51)
Author Location gp120 (42–51 PV22)
Epitope VPVWKEATTT
Immunogen HIV-1 infection
Species (MHC) human (B*5501)
Keywords optimal epitope
References Llano *et al.* 2009
- C. Brander notes this is a B*5501 epitope.

HXB2 Location gp160 (42–51)
Author Location gp120 (42–51)
Epitope VPVWKEATTT
Immunogen
Species (MHC) human (B*5501, B55)

CTL CD8+

Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 32/51 Brazilian HIV sequences; variant VPVWKEAkTT present in all Brazilian subtype C sequences.

HXB2 Location gp160 (42–51)
Author Location gp120 (42–51 PV22)
Epitope VPVWKEATTT
Immunogen HIV-1 infection
Species (MHC) human (B55)
References Brander & Walker 1995

- P. Johnson, unpublished.

HXB2 Location gp160 (42–51)
Author Location gp120 (41–55)
Epitope VPVWKEATTT
Immunogen HIV-1 infection
Species (MHC) human (B55)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location gp160 (42–52)
Author Location gp120 (42–52)
Epitope VPVWKEATTTL
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*3501 epitope.

HXB2 Location gp160 (42–52)
Author Location gp120 (42–52)
Epitope VPVWKEATTTL
Immunogen
Species (MHC) human (B*3501)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 32/51 Brazilian HIV sequences; variant VPVWKEAkTTL present in all Brazilian subtype C sequences.
- This epitope is associated with the rapid-progression HLA, B35; epitope has low variation in non-C subtypes, but high variability in BF recombinants suggests that CTL may be exerting selective pressure on BF viruses.

HXB2 Location gp160 (42–52)
Author Location (C consensus)
Epitope VPVWKEAKTTL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location gp160 (42–52)
Author Location (C consensus)
Epitope VPVWKEAKTTL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- VPVWKEAKTTL is an optimal epitope.

HXB2 Location gp160 (42–52)
Author Location gp120 (42–52 PV22)
Epitope VPVWKEATTTL
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords subtype comparisons
References Cao *et al.* 1997a

- VPVWKEATTTL is the consensus sequence for clades B and D.
- VPVWKDAETTL is the consensus sequence for clade A and it is cross-reactive.
- VPVWKEADTTL is the consensus sequence for clade C and it is cross-reactive.
- VPVWKEADTTL is the consensus sequence for clade E and even with three substitutions still retains some cross-reactivity.

HXB2 Location gp160 (42–52)
Author Location gp120 (41–51)
Epitope VPVWKEATTTL
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Ferrari *et al.* 2000

CTL CD8+

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location gp160 (42–52)
Author Location Env (41–50)
Epitope VPVWKEATTTL
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 4/9 patients recognized this epitope.

HXB2 Location gp160 (42–52)
Author Location gp120
Epitope VPVWKEATTTL
Epitope name B35-VL11(gp120)
Immunogen HIV-1 infection
Species (MHC) human (B35)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location gp160 (42–52)
Author Location
Epitope VPVWKEATTTL
Immunogen HIV-1 infection
Species (MHC) human (B35)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope VPVWKEATTTL elicited a magnitude of response of 310 SFC with a functional avidity of 0.1nM and binding affinity of 10730nM.

HXB2 Location gp160 (42–52)
Author Location gp120
Epitope VPVWKEATTTL
Epitope name VL11(gp120)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B35-restricted epitope VPVWKEATTTL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide TVYYGVPVWKEATTTLF.
- 3 of the 12 HLA-B35 carriers responded to a VPVWKEATTTL-containing peptide with average magnitude of CTL response of 167 SFC/million PBMC (author communication and Fig.1).

HXB2 Location gp160 (42–52)
Author Location Env (43–52 BH10, LAI)
Epitope VPVWKEATTTL
Immunogen HIV-1 infection
Species (MHC) human
References Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this peptide is PVWKEATTTL) has similarity with the platelet membrane glycoprotein IIIA precursor (GLIIIA) (integrin beta-3) (CD61): PLYKEATSTF.

HXB2 Location gp160 (42–56)
Author Location Env (41–55)
Epitope VPVWKEATTTLFCAS

CTL CD8+

Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized both by mice co-immunized with Env and Tat, and by mice immunized with Env alone.

HXB2 Location gp160 (42–61)
Author Location gp120 (49–68)
Epitope `VPVWKEATTTLFCASDAKAY`
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

HXB2 Location gp160 (42–61)
Author Location gp120 (49–68 SF2)
Epitope `VPVWKEATTTLFCASDAKAY`
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- Three of these 11 had CTL response to this peptide.
- The responding subjects were HLA-A2, A3, B8, B62; HLA-A3, A24, B7, B38.

HXB2 Location gp160 (42–61)
Author Location gp120 (49–68 SF2)
Epitope `VPVWKEATTTLFCASDAKAY`
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

HXB2 Location gp160 (42–61)
Author Location gp120 (11–30)
Epitope `VPVWKEATTTLFCASDAKAY`
Epitope name VPV
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A2, A68.1, B*07, B*3503, Cw*0401, Cw*0702, DQ2, DQ6, DR15, DR17, DR51, DR52
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ
Keywords rate of progression, escape
References Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses,and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relatively efficiency of the variant eptiopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- This was one of 8 reactive peptides found not to vary over time. It was one of four epitopes that were not precisely defined.

HXB2 Location gp160 (44–53)
Author Location Env
Epitope `VWKEAKTTLF`
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0103, A*0201, B*4901, B*5702, Cw*0708, Cw*1801; A*6802, A*7401, B*1510, B*4901, Cw*0304, Cw*0701
Country Kenya
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2008

- To evaluate the use of IFN-gamma ELISpot and proliferation assays, the two were compared in a cohort of HIV-1-infected Kenyan sex-workers. ELISpot does not always correlate with viral load and replication or disease progression. The exclusive use of these assays makes definition of CTL response in disease incomplete, especially for memory T cells.
- Despite assaying for 24 INF-gamma and 41 proliferative responses, only 5 of these responses overlapped in the same subject. 18 peptide-epitopes including 10 epitopes and their variants were used in this study.
- VWKEAKTTLF elicited proliferation alone in 1 subject; and ELISpot response in another subject.

HXB2 Location gp160 (44–53)
Author Location Env
Epitope `VWKDAETTLF`
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101, B*3701, B*8101, Cw*0602, Cw*1801
Country Kenya

CTL CD8+

Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2008

- To evaluate the use of IFN-gamma ELISpot and proliferation assays, the two were compared in a cohort of HIV-1-infected Kenyan sex-workers. ELISpot does not always correlate with viral load and replication or disease progression. The exclusive use of these assays makes definition of CTL response in disease incomplete, especially for memory T cells.
- Despite assaying for 24 INF-gamma and 41 proliferative responses, only 5 of these responses overlapped in the same subject. 18 peptide-epitopes including 10 epitopes and their variants were used in this study.
- VWKDAETTLF elicited an ELISpot response in one subject.

HXB2 Location gp160 (44–53)
Author Location Env
Epitope `VWKEATTTLF`
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101, A*2301, B*0702, B*4501, Cw*0702, Cw*1601
Country Kenya
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2008

- To evaluate the use of IFN-gamma ELISpot and proliferation assays, the two were compared in a cohort of HIV-1-infected Kenyan sex-workers. ELISpot does not always correlate with viral load and replication or disease progression. The exclusive use of these assays makes definition of CTL response in disease incomplete, especially for memory T cells.
- Despite assaying for 24 INF-gamma and 41 proliferative responses, only 5 of these responses overlapped in the same subject. 18 peptide-epitopes including 10 epitopes and their variants were used in this study.
- VWKEATTTLF elicited an ELISpot response in one subject.

HXB2 Location gp160 (46–60)
Author Location Env (45–59)
Epitope `KEATTTLFCASDAKA`
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized by mice co-immunized with Env and Tat, but not by mice immunized with Env alone.

HXB2 Location gp160 (50–59)
Author Location Env (61–)
Epitope `TTLFCASDAK`
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (A*0301)
Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008

- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location gp160 (50–59)
Author Location gp120 (50–59)
Epitope `TTLFCASDAK`
Immunogen
Species (MHC) human (A3)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 46/51 Brazilian HIV sequences.

HXB2 Location gp160 (50–59)
Author Location Env
Epitope `TTLFCASDAK`
Epitope name Env61
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (A3)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

CTL CD8+

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- TTLFCASDAK is an Env epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location gp160 (50–59)
Author Location Env (62–71)
Epitope `TTLFCASDAK`
Immunogen HIV-1 infection
Species (MHC) human (A3 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801).

HXB2 Location gp160 (50–59)
Author Location Env
Epitope `TTLFCASDAK`
Epitope name Env61
Subtype A, B, C, D
Immunogen HIV-1 infection
Species (MHC) human, mouse (A3 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope TTLFCASDAK of the HLA-A3 supertype bound most strongly to HLA-A*1101, and -A*0301 and -A*6801 also to -A*3101 but not to -A*3301. It was conserved 100% in subtype A, 84% in B, 75% in C and 100% in subtype D. 2/23 HLA-A3 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Env61.

HXB2 Location gp160 (51–59)
Author Location gp160 (51–59)
Epitope `TLFCASDAK`
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to published restriction above, epitope TLFCASDAK was predicted to be restricted by HLA A*0301, A*1101, A*3101, A*3301, A*6601 and A*6801.

HXB2 Location gp160 (51–59)
Author Location gp120 (51–59)
Epitope `TLFCASDAK`
Immunogen
Species (MHC) human (A3)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 47/51 Brazilian HIV sequences.

HXB2 Location gp160 (51–59)
Author Location Env (51–59)
Epitope `TLFCASDAK`
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Liang *et al.* 2008

- 1100 unique full-length Env sequences were analyzed and the positive selection (PS) pressure determined. The QUASI method was used across Clades A, B, C and D, to find PS sites dispersed across Env.
- Frequency of PS sites is stable over time.
- 25% to 61% PS sites are shared between subtypes A, B, C and D, so it is inferred that immune responses are targeted against the same general regions.
- Significant correlations between PS sites and neutralizing antibody response, helper response, antibody plus CTL response are found. This suggests that the NAb response might be the driving force behind HIV-1 Env evolution.

CTL CD8+

- PS-free sites that are targeted greatly by NAb and CTL were found. Functional reasons for the lack of positive selection in such regions must exist.
- PS-site-rare regions (conserved regions of Env) were examined for PS, and epitopes located in such regions. Epitope TLFCASDAK, restricted by HLA-A3 is on a region free from positive selection. It is found in North American and European populations and is associated with Long Term Nonprogression to AIDS.

HXB2 Location gp160 (51–59)
Author Location Env (63–71)
Epitope TLFCASDAK
Immunogen HIV-1 infection
Species (MHC) human (A3 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801).

HXB2 Location gp160 (52–61)
Author Location gp120 (59–68 HXB2)
Epitope LFCASDAKAY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
References Lieberman *et al.* 1992

- CTL epitope defined by T cell line and peptide mapping.
- C. Brander notes that this is an A*2402 epitope in the 1999 database.

HXB2 Location gp160 (52–61)
Author Location gp120 (53–62 LAI)
Epitope LFCASDAKAY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*2402 epitope.

HXB2 Location gp160 (52–61)
Author Location gp120 (53–62)
Epitope LFCASDAKAY
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A24)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location gp160 (52–61)
Author Location gp120 (53–62)
Epitope LFCASDAKAY
Immunogen HIV-1 infection
Species (MHC) human (A24)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, T-cell Elispot, CD8 T-cell Elispot granzyme B
Keywords characterizing CD8+ T cells
References Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- Two of seven patients responded to this peptide with GzB producing cells, and a different patient with IFN-gamma producing cells.

HXB2 Location gp160 (52–61)
Author Location gp120
Epitope LFCASDAKAY
Epitope name A24-LY10(gp120)
Immunogen HIV-1 infection
Species (MHC) human (A24)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location gp160 (52–61)
Author Location
Epitope LFCASDAKAY
Immunogen HIV-1 infection
Species (MHC) human (A24)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope LFCASDAKAY elicited a magnitude of response of 240 SFC with a functional avidity of 5nM.

HXB2 Location gp160 (52–61)
Author Location gp120
Epitope LFCASDAKAY
Epitope name LY10(gp120)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A24)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide sequence (VQKEATTTLFCASDAKAY) contains the exact sequence of a previously described HLA-A24 optimal epitope, LFCASDAKAY, none of the 30 HLA-A24 carriers responded to it (author communication and Fig.1).

HXB2 Location gp160 (52–61)
Author Location gp120 (53–62 LAI)
Epitope LFCASCAKAY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B38)
References Shankar *et al.* 1996

- Uncertain whether optimal, binds A24 as well.

HXB2 Location gp160 (52–71)
Author Location gp120 (59–78)
Epitope LFCASDAKAYDTEVHINVWAT
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

HXB2 Location gp160 (52–71)
Author Location gp120 (59–78 SF2)
Epitope LFCASDAKAYDTEVHINVWAT
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-A2 and B-21.

HXB2 Location gp160 (54–68)
Author Location Env (53–67)
Epitope CASDAKAYDTEVHNV
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized by mice co-immunized with Env and Tat, but not by mice immunized with Env alone.

HXB2 Location gp160 (58–69)
Author Location Env
Epitope AKAYETEKHNVW
Subtype A, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.

CTL CD8+

- 1 subject responded to peptide AKAYETEKHNVW from subtype A.

HXB2 Location gp160 (59–69)
Author Location (C consensus)
Epitope KAYETEVHNVW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- KAYETEVHNVW is an optimal epitope.

HXB2 Location gp160 (59–69)
Author Location
Epitope KAYETEVHNVW
Epitope name KW11
Immunogen
Species (MHC) human (B58)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B58 epitope.

HXB2 Location gp160 (59–69)
Author Location gp120
Epitope KAYDTEVHNVW
Epitope name KW11(gp120)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope KAYDTEVHNVW elicited an immune response in Chinese HIV-1 positive subjects as a part of peptide KAYDTEVHNVW. The epitope differs from the previously described HLA-B58-restricted epitope sequence, KAYETEVHNVW, at 1 residue, KAYdTEVHNVW.
- 6 of the 14 HLA-B58 carriers responded to KAYdTEVHNVW-containing peptide with average magnitude of CTL response of 235 SFC/million PBMC (author communication and Fig.1).

HXB2 Location gp160 (61–69)
Author Location
Epitope YETEVHNVW
Epitope name YW9
Immunogen
Species (MHC) human (B*1801)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*1801 epitope.

HXB2 Location gp160 (61–69)
Author Location gp120 (61–69 HIV-MN)
Epitope YETEVHNVW
Epitope name YW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1801)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Positions 2 and 5 in the epitope had potentially experienced positive selection. YgTEVHNVW, YdTEVHNVW, YETEaHNVW and YdTEaHNVW escape variants were found.

HXB2 Location gp160 (62–76)
Author Location Env (61–75)
Epitope DTEVHNVWATHACVP
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.

- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized both by mice co-immunized with Env and Tat, and by mice immunized with Env alone.

HXB2 Location gp160 (62–80)
Author Location gp120 (69–88 SF2)
Epitope DTEVHNVWATHACVPTDPN
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-A2 and B-21.

HXB2 Location gp160 (64–73)
Author Location Env (63–72 SF2)
Epitope EVHNVWATHA
Subtype A, B, C, CRF01_AE, D
Immunogen HIV-1 infection
Species (MHC) human (A*2603)
Country Japan
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay, HLA binding
Keywords binding affinity, subtype comparisons, computational epitope prediction, rate of progression, escape, variant cross-recognition or cross-neutralization
References Kawashima *et al.* 2005

- A*26 is associated with slow progression to disease and is common in Asian populations (about 20%). 31/110 HIV peptides that carried the A*2603 motif ([VTILP] at P2, [ML] at the C-terminus) bound to HLA-A*2603. Only 2 of these were epitopes and could induce specific CD8 T-cell responses in PBMC from HLA-A*2603 positive subjects.
- This epitope induced specific CD8+ T cells in chronically infected individuals with A*2603, but not A*2601.
- 5 common B clade variants were synthesized. EVHNVWATHA and EVHNiWATHA bound to A*2603 with equal affinity. EiHNVWATHA and EaHNVWATHA bound to A*2603 with reduced affinity. EmHNVWATHA and EkHNVWATHA could not bind to A*2603. A CTL clone that recognized EVHNVWATHA was able kill cells prepulsed with the 3 peptide variants that could bind to A*2602.
- EVHNVWATHA is the most common form in clades A, B, C, and E (CRF01), but EaHNiWATHA is the most common form in clade D.

HXB2 Location gp160 (67–75)
Author Location Env (67–)
Epitope NIWATHACV
Epitope name Env67(2I)
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* gp120 *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 1/17 HIV+ HLA-A2 subjects.
- The variant nVwathacv was also immunogenic in transgenic mice, but was not recognized in the 17 people tested.

HXB2 Location gp160 (67–75)
Author Location
Epitope NVWATHACV
Epitope name Env 67(2V)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords variant cross-recognition or cross-neutralization
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Previously described Env 67(2V) epitope, NVWATHACV, was found in 10 patients but none had CTL immune responses to it. Response to the Env 67(2I)var, NiWATHACV, was however detected in one case.
- Env 67 is one of the most conserved epitopes in Env. Its variant Env 67(2V) was less targeted and immunogenic. Rare variant Env 67(2I) was more immunogenic and was also recognized by 1 in 16 HLA-A2- patients.

HXB2 Location gp160 (67–75)
Author Location Env (67–)
Epitope NIWATHACV
Epitope name Env67(2I)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark

CTL CD8+

Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Env epitope NIWATHACV, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients. DK1 had sequence variant NvWATHACV.

HXB2 Location gp160 (73–81)
Author Location gp41 (73–81)
Epitope `ACVPTDPNP`
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*2902, B*1402
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, ACVPTDPNP, was found to be 0.023/day, with SE of 0.016.
- Five mutations at the fifth position of Env gp41 73-81 were all shown to confer limited CTL escape.

HXB2 Location gp160 (75–84)
Author Location gp120
Epitope `VPTDPNPPEV`
Immunogen computer prediction
Species (MHC) human (A*02)
Keywords TCR usage
References Frankild *et al.* 2008

- TCR can recognize multiple and distinct ligands. A model of TCR peptide recognition using amino acid similarity matrices is developed here, to predict cross-reactivity within diverse CTL epitopes. The ability of TCRs to recognize unrelated peptides with high specificity is termed "poly-specificity" here.
- Non-immunogenic HIV peptides were found to be similar to human self-antigens, suggesting that sequence similarity to self-antigens is what discriminates between immunodominant and cryptic epitope-elicited CTL responses.
- One example of cross-reactivity of TCR for different epitopes in the literature is cited here. HIV Env epitope, VPTDPNPPEV and Tuberculosis VLTDGNPPEV are cross-recognized by the same TCR.

HXB2 Location gp160 (75–84)
Author Location gp120
Epitope `VPTDPNPPEV`
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Tetramer binding
References Höhn *et al.* 2003

- The M. tuberculosis HLA-A2 restricted epitope VLTDGNPPEV and this HLA-A2 HIV-1 gp120 VPTDPNPPEV epitope are cross-recognized. HLA-A2+ patients with pulmonary tuberculosis exhibit cross-reactivity with the HIV gp160 epitope, and those with HIV-1 infection have cross-reactive responses to M.tuberculosis antigen.

HXB2 Location gp160 (75–84)
Author Location Env
Epitope `VPTDPNPQEI`
Epitope name Env1129
Subtype C
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Novel Env epitope VPTDPNPQEI elicits IFN-gamma ELISpot responses in 1/7 subjects; and bound HLA-B7 with low affinity in cell-based assays.

HXB2 Location gp160 (78–86)
Author Location gp120 (77–85)
Epitope `DPNPQEVVL`
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
References Ogg *et al.* 1998b

- This epitope was included to illustrate the specificity of HIV-tetrameric staining, in a cross-sectional study correlating HLA A*0201 CTL effector cells and low viral load.

HXB2 Location gp160 (78–86)
Author Location gp120 (77–85 SF2)
Epitope DPNPQEVVL
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Keywords optimal epitope
References Llano *et al.* 2009
- C. Brander notes this is a B*3501 epitope.

HXB2 Location gp160 (78–86)
Author Location gp120 (77–85 SF2)
Epitope DPNPQEVVL
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
References Tomiyama *et al.* 1997
- A CTL clone responsive to this epitope was obtained.
- 2/7 B35-positive individuals have a CTL response to this epitope.
- This epitope is highly variable.
- The substitutions: 1N, 3S and 7I, 7L and 9M, 8I, 8K all abrogate specific CTL lysis, while only 8K reduces binding to B*3501.
- The substitution 8V to 8E does not reduce specific CTL activity.

HXB2 Location gp160 (78–86)
Author Location Env (77–85)
Epitope DPNPQEVVL
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Keywords HAART, ART
References Ogg *et al.* 1999
- CTL effector levels were measured after potent ARV therapy using HLA-tetramer complexes for the A*0201 epitopes SYLVANTVATL and ILKEPVHGV in seven patients, and the B*3501 epitope DPNPQEVVL in one additional patient.
- Levels of CTL effectors typically decline for 5-7 days and then rebound, fluctuating during the first two weeks of therapy.
- After the early fluctuation, there was a steady exponential decay with a median half-life of 45 days.

HXB2 Location gp160 (78–86)
Author Location Env (77–85)
Epitope DPNPQEVVL
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Country Japan
Assay type Cytokine production, Tetramer binding, CTL suppression of replication, Other, HLA binding
Keywords class I down-regulation by Nef
References Ueno *et al.* 2008
- The balance between Nef selective pressures to modulate HLA I or its escape mutations reducing Nef HLA I down-regulating activity is studied.
- Nef mutations had the effect of increasing cytolytic activity of CTL clones with other specificities like CTLs specific for Env-DPNPQEVVL.

HXB2 Location gp160 (78–86)
Author Location Env (77–85)
Epitope DPNPQEVVL
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Dyer *et al.* 1999
- CTL specific responses were measured over a 1.3 to 1.5 year period in members of the Sydney Blood Bank Cohort (SBBC) who had been infected with a natural attenuated strain of HIV-1 which was Nef-defective.
- Some of these patients had prolonged high levels of CTL effector and memory cells despite low viral load.

HXB2 Location gp160 (78–86)
Author Location
Epitope DPNPQEVVL
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords acute/early infection
References Wilson *et al.* 2000a
- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T cells and viral load.
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B2705; and A*0201, A*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK.
- The subject with A*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705.
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

HXB2 Location gp160 (78–86)
Author Location (SF2)
Epitope DPNPQEVVL
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords rate of progression
References Kawana *et al.* 1999
- HLA B35 is associated with rapid disease progression.
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals.

- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals, but this was one of the six that had no B35 associated pattern of mutation.

HXB2 Location gp160 (78–86)
Author Location gp120 (77–85 SF2)
Epitope DPNPQEVVL
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 1/2 group 1, 0/2 group 2, and 0/1 group 3.

HXB2 Location gp160 (78–86)
Author Location
Epitope DPNPQEVVL
Epitope name Env-DL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B35, 3/20 (15%) recognized this epitope.

HXB2 Location gp160 (78–86)
Author Location gp120 (78–86)
Epitope DPNPQEVVL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC A3, A33, B14, B35, Cw*0401, Cw*0802
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

HXB2 Location gp160 (78–86)
Author Location (C consensus)
Epitope DPNPQEMVL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location gp160 (78–86)
Author Location gp120 (47–55)
Epitope DPNPQEVAL
Epitope name DPN
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC A2, A68.1, B*07, B*3503, Cw*0401, Cw*0702, DQ2, DQ6, DR15, DR17, DR51, DR52
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, escape
References Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses,and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relatively efficiency of the variant eptiopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody

titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- This epitope was one of six epitopes found to be under positive selection for escape mutations, and was mostly replaced by an escape variant between days 66 and 369 (dpnpqeAal)and,then replaced by a new escape variant (dpnpqevPl) by day 635.

HXB2 Location gp160 (78–86)
Author Location gp120
Epitope DPNPQEVVL
Epitope name B35-DL9(gp120)
Immunogen HIV-1 infection
Species (MHC) human (B35)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006
- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location gp160 (78–86)
Author Location gp120
Epitope DPNPQEVVL
Epitope name DL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a
- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- Epitope DPNPQEVVL varied to DPNPQEVaL or DPsPQEVVL or DPsPQEVaL in an untreated patient. Previously published HLA-restriction for DL9 is HLA-B35.

HXB2 Location gp160 (78–86)
Author Location gp120
Epitope DPNPQEVVL
Epitope name DL9(gp120)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008
- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B35-restricted epitope DPNPQEVVL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide VPTDPNPQEVVLGNV.
- 4 of the 12 HLA-B35 carriers responded to a DPNPQEVVL-containing peptide with average magnitude of CTL response of 442 SFC/million PBMC (author communication and Fig.1).

HXB2 Location gp160 (78–86)
Author Location gp120 (77–85 SF2)
Epitope DPNPQEVVL
Immunogen HIV-1 infection
Species (MHC) human (B35, B51)
References Shiga *et al.* 1996
- Binds HLA-B*3501 and B*5101 – binds and kills gp120-vaccinia virus infected cells carrying B35 or B51.

HXB2 Location gp160 (78–86)
Author Location gp120 (77–85)
Epitope DPNPQEVVL
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B51)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location gp160 (78–86)
Author Location gp160 (78–86)
Epitope DPNPQEVVL
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these eptiopes, but this increased over time.

HXB2 Location gp160 (88–96)
Author Location gp120 (88–96 HIV-MN)
Epitope `NVTENFNMW`
Epitope name NW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2501)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Positions 5 and 7 in the epitope had potentially experienced positive selection. NVTEdFdMW, NVTEeFdMW and NVTEsFdMW escape variants were found.

HXB2 Location gp160 (89–97)
Author Location gp160
Epitope `VTEEFNMWK`
Subtype A, B, C, D
Immunogen HIV-1 infection, vaccine
Vector/Type: vaccinia *Strain:* A clade, B clade, D clade NDK, C clade consensus *HIV component:* Env
Species (MHC) human
Donor MHC A*3201, A*3601, B*5301, B*8101, Cw*0401, Cw*0804; A*2402, A*3201, B*5101, B*5301, Cw*0401, Cw*0602
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References McKinnon *et al.* 2005

- Interclade cross-reactivity of clades A, B, C, and D was tested using recombinant vaccinia-based IFN-gamma Elispot assay. 47/74 women had a positive Elispot response to at least one clade, and cross-clade responses were frequent. Clade A responses were most frequent, as expected, as clade A dominates the Kenyan epidemic (85% of the 47 women responded to clade A Env, 74% to B, 62% to C, and 43% to D). Cross-clade CD8 T-cell responses were common and directed at conserved epitopes.
- There was a greater magnitude of response to A clade peptides in individuals who responded to more than 1 clade; a 2-fold higher response was observed in clade A in 36% (9/25) of these individuals, and the response to A peptides was never lower. VTEEFNMWK responses were detected in 2 women who had Env responses to all 4 clades, and clade A gave the highest responses; a VnEEFNMWK variant was in clade B and D, and the clade C Env carried VnEEFNMWe. One woman also reacted with RAIEAQQHL, the other with KNCSFNMTT.
- Both women that reacted with VTEEFNMWK carried HLA-B*5301, the only common HLA allele.

HXB2 Location gp160 (89–98)
Author Location Env
Epitope `VTENFNMWKN`
Epitope name 1284
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A11, A68 supertype)
Donor MHC A01, A68, B15, B40, Cw03; A03, A11, B14, B51, Cw08, Cw13
Country United States
Assay type T-cell Elispot
Keywords binding affinity, supertype, computational epitope prediction, cross-presentation by different HLA
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for VTENFNMWKN:17%. This epitope can be presented by the A11, A68 supertype.

HXB2 Location gp160 (90–104)
Author Location
Epitope `TENFNMWKNNMVEQM`
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A*2501, A*3002; B*0702, B*1801
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.

- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location gp160 (103–111)
Author Location Env (102–110)
Epitope QMHEDIISL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords binding affinity, TCR usage
References Kmieciak *et al.* 1998a

- CTL responses in six patients to four Env epitopes were studied: D2: LLNATAIAV, 5.3: RLRDLLLIV, D1: KLTPLCVTL, and 4.3: QMHEDIISL – all have A2 anchor residues.
- The C terminal epitopes (D2 and 5.3) were highly variable and the variability was considered responsible for limited CTL response, while D1 and 4.3, N-terminal epitopes, were much more conserved and gave evidence of high levels of CTL response *in vitro*.
- Peptides 4.3 and D1 bound HLA-A*0201 molecules with high affinity.
- Peptides 4.3 and D1 stimulated CTL with a relatively limited TCR Vβ repertoire.

HXB2 Location gp160 (104–112)
Author Location gp160 (104–112)
Epitope MHEDIISLW
Immunogen HIV-1 infection
Species (MHC) human (B*3801)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location gp160 (104–112)
Author Location gp120 (104–112)
Epitope MHEDIISLW
Immunogen HIV-1 infection
Species (MHC) human (B*3801)
Donor MHC A26, A3, B*3801, B7, Cw*0702, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

HXB2 Location gp160 (104–112)
Author Location gp120
Epitope MHEDIISLW
Epitope name MW9(gp120)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B38)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B38-restricted epitope MHEDIISLW elicited an immune response in Chinese HIV-1 positive subjects as part of peptides WKNNMVEQMHEDIISLW and QMHEDIISLWDQSLKPCV.

HXB2 Location gp160 (104–112)
Author Location
Epitope MHEDIISLW
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A3, A32; B38, B64
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was recognized by a placebo patient after infection.

HXB2 Location gp160 (104–112)
Author Location
Epitope MHEDIISLW
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A1, A2; B38, B8
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location gp160 (104–119)
Author Location gp120 (111–126 IIIB)
Epitope MQEDIISLWDQSLKPC
Immunogen in vitro stimulation or selection
Species (MHC) human
References Macatonia *et al.* 1991

- Primary CTL response with cells from non-infected donors stimulated by the peptide.

HXB2 Location gp160 (105–117)
Author Location gp120 (112–124 IIIB)
Epitope HEDIISLWDQSLK
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Clerici *et al.* 1991a

- Helper and cytotoxic T cells can be stimulated by this peptide (T2)

HXB2 Location gp160 (105–117)
Author Location gp120 (MN)
Epitope HEDIISLWDQSLK
Immunogen HIV-1 infection
Species (MHC) chimpanzee
References Lubeck *et al.* 1997

- No epitope-specific CTL were detected in chimpanzees immunized with adenovirus-HIV-1 MN gp160 recombinant despite a response to peptides P18 and T1.
- Helper and cytotoxic T cells have been found to be stimulated by this peptide (T2)

HXB2 Location gp160 (105–117)
Author Location gp120 (112–124 IIIB)
Epitope HEDIISLWDQSLK
Immunogen HIV-1 exposed seronegative
Species (MHC) human
References Pinto *et al.* 1995

- CTL and T helper cell reactivity in healthcare workers exposed to HIV.

HXB2 Location gp160 (108–116)
Author Location Env (107–115 subtype B)
Epitope IISLWDQSL
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN *HIV component:* gp160
Species (MHC) human (A*0201)
Keywords binding affinity
References Kundu *et al.* 1998a

- Ten HIV-1 + HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period.
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity.
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual.
- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses.

HXB2 Location gp160 (108–116)
Author Location gp120 (108–116)
Epitope IISLWDQSL
Immunogen
Species (MHC) human (A2.1)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 46/51 Brazilian HIV sequences.

HXB2 Location gp160 (109–117)
Author Location Env (109–117 CM243 subtype CRF01)
Epitope ISLWDQSLK
Epitope name E109-117
Subtype CRF01_AE
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A11)
Keywords HIV exposed persistently seronegative (HEPS)
References Bond *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.

- This epitope was weakly reactive in the HEPS study subject 265 who was HLA A2/A11, and had been predicted to be a possible A11 epitope using Epimer in Bond *et al.* [2001]

HXB2 Location gp160 (109–117)
Author Location gp120 (109–117)
Epitope ISLWDQSLK
Immunogen
Species (MHC) human (A11)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 48/51 Brazilian HIV sequences.

HXB2 Location gp160 (110–118)
Author Location gp120 (110–118)
Epitope SLWDQSLKP
Immunogen
Species (MHC) human (A03)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 48/51 Brazilian HIV sequences.

HXB2 Location gp160 (110–118)
Author Location Env
Epitope SLWDQSLKP
Epitope name 1328
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A02, A03, B08, B51, Cw01, Cw07
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction, immunodominance
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for SLWDQSLKP: 50%.Immunodominant epitope.

HXB2 Location gp160 (112–130)
Author Location gp120 (119–139 SF2)
Epitope WDQSLKPCVKLTPLCVSLK
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-A2 and B-21.

HXB2 Location gp160 (112–131)
Author Location gp120 (MN)
Epitope WDQSLKPCVKLTPLCVTLNC
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A2
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, HAART, ART
References Chitnis *et al.* 2003

- 17 perinatally HIV-1 infected children (0.08-16 years) were evaluated for HLA-A2-restricted IFN-gamma CD8+ CTL responses against 4 immunodominant peptides that carry HLA-A2 epitopes. Two peptides were from gp120 (one at position 112, one from the V3 loop), and one each was from gp41 and Gag. 15/17 patients responded to the Gag peptide, 13/17 to the gp41 and the non-V3 gp120 peptides, and 11/17 responded to the V3 loop. 4 children recognized all 4 peptides.

HXB2 Location gp160 (117–126)
Author Location Env (117–126)
Epitope KPCVKLTPLC
Immunogen HIV-1 infection
Species (MHC) human (B*07)
References Liang *et al.* 2008

- 1100 unique full-length Env sequences were analyzed and the positive selection (PS) pressure determined. The QUASI method was used across Clades A, B, C and D, to find PS sites dispersed across Env.
- Frequency of PS sites is stable over time.
- 25% to 61% PS sites are shared between subtypes A, B, C and D, so it is inferred that immune responses are targeted against the same general regions.
- Significant correlations between PS sites and neutralizing antibody response, helper response, antibody plus CTL response are found. This suggests that the NAb response might be the driving force behind HIV-1 Env evolution.
- PS-free sites that are targeted greatly by NAb and CTL were found. Functional reasons for the lack of positive selection in such regions must exist.
- PS-site-rare regions (conserved regions of Env) were examined for PS, and epitopes located in such regions. Epitope KPCVKLTPLC, restricted by HLA-B*07 is on a region free from positive selection. It is found in European populations and is associated with fast progression to AIDS.
- Conserved NAb 4E10 epitope LWVTVYYGVPVWK was also found and thought to be protective against AIDS.

HXB2 Location gp160 (117–126)
Author Location Env (72–81)
Epitope KPCVKLTPLC
Immunogen HIV-1 infection

CTL CD8+

Species (MHC) human (B7)
References Jin *et al.* 2000b

- This B7 epitope is one of three subdominant CTL responses detected in a long-term non-progressor.
- A dominant B7 epitope was defined using conventional methods, and three additional sub-dominant HLA B7 epitopes were defined by first using a non-anchor based strategy, EpiMatrix, to identify 2078 possible epitopes in the autologous HIV-1, followed by B7 anchor residue prediction to narrow the set to 55 peptides for experimental testing.

HXB2 Location gp160 (117–126)
Author Location Env
Epitope KPCVKLTPLC
Epitope name 1295
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for KPCVKLTPLC: 27%. This epitope was previously reported but not confirmed in this study.

HXB2 Location gp160 (117–126)
Author Location gp120 (117–126)
Epitope KPCVKLTPLC
Immunogen
Species (MHC) human (B7)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 47/51 Brazilian HIV sequences.

HXB2 Location gp160 (121–129)
Author Location Env (121–129)
Epitope KLTPLCVTL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- One patient developed a response to epitope KLTPLCVTL after primary infection at early chronic infection. This was one of the epitopes targeted by broad HLA-A2-restricted CTL responses.

HXB2 Location gp160 (121–129)
Author Location Env
Epitope KLTPLCVTL
Immunogen vaccine
Vector/Type: DNA
Species (MHC) transgenic mouse (A*0201)
References Ishioka *et al.* 1999

- A minigene vaccine construct encoding 6 HLA 2.1 and 3 HLA A11 restricted CTL epitopes, the universal Th cell epitope PADRE (pan-DR epitope) and an ER translocating signal sequence was constructed.
- The epitopes were chosen for dominant recognition by CTLs during HBV and HIV infections in humans.
- HLA transgenic mice were used for quantitating *in vivo* immunogenicity of DNA vaccines encoding HLA-restricted CTL epitopes – strong responses were observed to all nine epitopes, and CTL memory persisted up to four months after a single injection.

HXB2 Location gp160 (121–129)
Author Location Env (120–128 subtype B)
Epitope KLTPLCVTL
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN
HIV component: gp160
Species (MHC) human (A*0201)
Keywords binding affinity
References Kundu *et al.* 1998a

- Ten HIV-1 + HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period.
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity.
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual.

- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses.

HXB2 Location gp160 (121–129)
Author Location Env (120–128)
Epitope KLTPLCVTL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords binding affinity, TCR usage
References Kmieciak *et al.* 1998a

- CTL responses in six patients to four Env epitopes were studied: D2: LLNATAIAV, 5.3: RLRDLLLIV, D1: KLTPLCVTL, and 4.3: QMHEDIISL—all have A2 anchor residues.
- The C terminal epitopes (D2 and 5.3) were highly variable and the variability was considered responsible for limited CTL response, while D1 and 4.3, N-terminal epitopes, were much more conserved and gave evidence of high levels of CTL response *in vitro*.
- Peptides 4.3 and D1 bound HLA-A*0201 molecules with high affinity.
- Peptides 4.3 and D1 stimulated CTL with a relatively limited TCR Vβ repertoire.
- In a longitudinal study, the CTL response to the variable D2 epitope diminished over time, while the response to the conserved epitope D1 stayed higher over time.

HXB2 Location gp160 (121–129)
Author Location Env (134–)
Epitope KLTPLCVTL
Epitope name Env-134
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords binding affinity, subtype comparisons, supertype, computational epitope prediction
References Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- 2/22 individuals with chronic HIV-1 infection recognized this epitope in ELISPOT.
- 0/12 acutely infected individuals recognized this epitope.
- KLTPLCVTL binds to four HLA-A2 supertype alleles: A*0201, A*0202, A*0203 and A*6802 (highest affinity).

HXB2 Location gp160 (121–129)
Author Location Env
Epitope KLTPLCVTL
Epitope name Env 134
Immunogen vaccine, in vitro stimulation or selection, computer prediction
Vector/Type: DNA
Species (MHC) human, humanized mouse (A*0201)
Assay type Cytokine production, T-cell Elispot
Keywords subtype comparisons, computational epitope prediction, escape, TCR usage, variant cross-recognition or cross-neutralization
References McKinney *et al.* 2004

- This study examined variant recognition of epitopes presented by A*0201 and A*1101. Numerous amino acid substitutions can be introduced into epitopes without disrupting their recognition by CTLs, although epitopes with multiple substitutions were less recognized. An algorithm was constructed for prediction of epitopes capable of inducing responses to a great number of variant epitopes.
- A total of 19 variant forms of Env 134 were identified of which 10 were recognized by CTLs from transgenic mice immunized with the parental form.
- Env 134 epitope was present in 80% of HIV sequences of diverse M group HIV-1 subtypes.

HXB2 Location gp160 (121–129)
Author Location Env
Epitope KLTPLCVTL
Epitope name K9L
Immunogen vaccine
Vector/Type: measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140ΔV3
Species (MHC) transgenic mouse (A*0201)
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells
References Lorin *et al.* 2005a

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

HXB2 Location gp160 (121–129)
Author Location Env
Epitope KLTPLCVSL
Epitope name P10L
Immunogen vaccine
Vector/Type: measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140ΔV3
Species (MHC) transgenic mouse (A*0201)
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells
References Lorin *et al.* 2005a

CTL CD8+

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

HXB2 Location gp160 (121–129)
Author Location Env (134–)
Epitope KLTPLCVTL
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (A*0201)
Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008

- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location gp160 (121–129)
Author Location gp120 (120–128 LAI)
Epitope KLTPLCVTL
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN *HIV component:* gp160
Species (MHC) human (A2)
References Dupuis *et al.* 1995

- CTL from HLA-A2 positive subject react with this peptide.

HXB2 Location gp160 (121–129)
Author Location gp120 (120–128)
Epitope KLTPLCVTL
Immunogen vaccine
Vector/Type: vaccinia
Species (MHC) human (A2)
References Woodberry *et al.* 1999

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2.
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D^d – this transgene is the only MHC molecule expressed in the mice.
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost.
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFD-SRL)
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested.
- KLTPLCVTL was recognized by 3 of the patients.

HXB2 Location gp160 (121–129)
Author Location gp120 (120–128)
Epitope KLTPLCVTL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords dendritic cells
References Kundu *et al.* 1998b

- Allogeneic dendritic cells (DCs) were obtained from HLA-identical siblings, pulsed with rgp160 MN or A2-restricted HIV-1 epitope peptides, and infused monthly into six HIV-infected patients.
- 1/6 showed increased env-specific CTL and increased lymphoproliferative responses, 2/6 showed increase only in proliferative responses, and 3/6 showed no change – pulsed DCs were well tolerated.
- KLTPLCVTL is a conserved HLA-A2 epitope included in this study – all six patients had this sequence as their HIV direct sequence, and a detectable CTL response.
- CTL demonstrated against peptide-coated target, epitope is naturally processed and enhancible with vaccine.

HXB2 Location gp160 (121–129)
Author Location gp120 (120–128)
Epitope KLTPLCVTL
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Kmieciak *et al.* 1998b

- Increased CTL response to cells expressing a VV construct Δv3 mutant compared with a full-length env gene product.

HXB2 Location gp160 (121–129)
Author Location gp120 (121–129)
Epitope KLTPLCVSL
Immunogen in vitro stimulation or selection
Species (MHC) human (A2)
Keywords dendritic cells
References Zarling *et al.* 1999

- This study compares the ability of macrophages and dendritic cells to stimulate primary responses in CD8+ lymphocytes isolated from HLA-appropriate HIV-uninfected donors using peptide-pulsed APC – the dendritic cells performed better as APC for the stimulation of primary responses.
- Strong CTL responses were elicited by the epitopes DRFYKTLRA and GEIYKRWII when presented by either immature or mature dendritic cells – macrophages were not able to prime a CTL response against DRFYKTLRA.
- A weak response to KLTPLCVSL was stimulated using macrophages as the APC.
- No detectable response was observed for the following previously-defined HIV epitopes: KIRLRPGGK, ILKEPVHGV, IRLRPGGK, GPKVKQWPL.

HXB2 Location gp160 (121–129)
Author Location gp120 (120–128)
Epitope KTLPLCVTL
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location gp160 (121–129)
Author Location gp120 (121–129 IIIB)
Epitope KLTPLCVTL
Epitope name D1
Subtype B
Immunogen vaccine
Vector/Type: DNA, DNA with protein boost *Strain:* B clade IIIB *HIV component:* gp160, gp160ΔV3 *Adjuvant:* IL-12
Species (MHC) mouse (A2)
Keywords vaccine-specific epitope characteristics
References Kiszka *et al.* 2002

- Transgenic mice expressing a HLA-A2/Kb chimeric protein were vaccinated with a full length gp160 or with gp160deltaV3, with the V3 loop deleted. Mice given gp160deltaV3 had a broader immune response than those given gp160, with increased responses to conserved HLA-A2 epitopes in the C1 region of gp120, KLTPLCVTL, and the C-term region of gp41, SLLNATAIAV.
- Greater resistance was conferred by the gp160deltaV3 than the gp160 vaccine to a challenge of vaccinia expressing heterologous gp160 from primary isolates (VI-06 and 89.6), and the resistance was conferred by CD8+ T-cells.

HXB2 Location gp160 (121–129)
Author Location Env (121–)
Epitope KLTPLCVTL
Epitope name Env121
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This epitope was one of the previously identified HLA-A2 epitopes studied.
- 3/17 HIV-infected HLA-A2+ people recognized this epitope.

HXB2 Location gp160 (121–129)
Author Location gp160 (121–129)
Epitope KLTPLCVTL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords acute/early infection, optimal epitope
References Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was recognized both during acute and chronic infection, but more often during chronic infection.

HXB2 Location gp160 (121–129)
Author Location Env (121–129 HXB2)
Epitope KLTPLCVTL
Epitope name D1
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* multiple epitope immunogen *HIV component:* p17/p24 Gag, Pol *Adjuvant:* IL-12
Species (MHC) transgenic mouse (A2)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-specific epitope characteristics, vaccine antigen design
References Bolesta *et al.* 2005

- Immunization of transgenic mice with a codon-optimized hGagp17p24-Polp51 DNA plasmid, consisting of clusters of highly conserved CTL epitopes presented by multiple MHC class I alleles, induced 2- to 5-fold higher CD8+ T-cell responses than the corresponding full-length proteins. The modified proteins had the ribosomal frameshift deleted, as well as the potentially immunosuppressive p15, and protease and integrase. This correlated with higher protection against challenge with Gag and Pol expressing recombinant vaccinia virus. Mice immunized with the hGagp17p24-Polp51 also showed an elevated level of type 1 cytokine production as well as an increased titer of p24- and RT-specific IgG2 antibody responses.
- Four A2 gag/pol epitopes were tested, and this Env A2 epitope was used as a negative control.

HXB2 Location gp160 (121–129)

CTL CD8+

Author Location gp160
Epitope KLTPLCVTL
Epitope name A2-KL9(gp160)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location gp160 (121–129)
Author Location
Epitope KLTPLCVTL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope KLTPLCVTL elicited a magnitude of response of 530 SFC with a functional avidity of 0.1nM.

HXB2 Location gp160 (121–129)
Author Location
Epitope KLTPLCVTL
Epitope name Env 121
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords immunodominance
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Env 121 KLTPLCVTL epitope was used as an immunodominant control. It was found in 8 patients but only 3 had a CTL immune response to it.
- Considerable variation was found in Env 121 variants in the TCR-interacting residues 3-8.

HXB2 Location gp160 (121–129)
Author Location gp120
Epitope KLTPLCVTL
Epitope name KL9(gp120)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A2-restricted epitope KLTPLCVTL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide PCVKLTPLCVTLNCTDL.
- 3 of the 55 HLA-A2 carriers responded to KLTPLCVTL-containing peptide with average magnitude of CTL response of 110 SFC/million PBMC (author communication and Fig.1).

HXB2 Location gp160 (121–129)
Author Location Env (121–)
Epitope KLTPLCVTL
Epitope name Env121
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.

CTL CD8+

- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Env control epitope KLTPLCVTL, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients.

HXB2 Location gp160 (121–129)
Author Location Env
Epitope KLTPLCVTL
Epitope name Env134
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- KLTPLCVTL is a Pol epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location gp160 (121–129)
Author Location Env (134–142)
Epitope KLTPLCVTL
Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind four of the five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802).

HXB2 Location gp160 (121–129)
Author Location Env
Epitope KLTPLCVTL
Epitope name Env134
Subtype A, B, C, D
Immunogen HIV-1 infection
Species (MHC) human, mouse (A2 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope KLTPLCVTL of the HLA-A2 supertype bound most strongly to HLA-A*0203, -A*0201, -A*0202 and -A*0206, but not to -A*6802. It was conserved 75% in subtype A, 95% in B, 88% in C and 95% in subtype D. 5/22 HLA-A2 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Env134.

HXB2 Location gp160 (123–132)
Author Location Env
Epitope TPLCVTLNCT
Epitope name Env1148
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Novel Env epitope TPLCVTLNCT elicits IFN-gamma ELISpot responses in 2/7 subjects; and bound HLA-B7 with low affinity in cell-based assays.

HXB2 Location gp160 (146–154)
Author Location Env
Epitope TYNETYNEI
Epitope name Env T-I
Subtype BC
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost *Strain:* Other *HIV component:* Env, Gag, Nef, Pol, Tat
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ

CTL CD8+

Keywords vaccine-specific epitope characteristics, vaccine antigen design
References Huang *et al.* 2008b

- 2 dual promoter candidate vaccines were constructed: ADVAX-I containing env and gag; ADVAX-II containing pol and nef-tat. The combined vaccine, ADVAX, showed equal immunogenicity in mice to single-gene plasmid vaccines, and elicited dose-dependent T-cell responses. Sequences were based on the Yunnanese subtype C/B' recombinant form of HIV-1.
- Both vaccine components induced dose-dependent IFN-gamma responses to epitope Env T-I
- IFN-gamma response was also elicited by 2 CD4 epitope-containing 20mers.

HXB2 Location gp160 (155–163)
Author Location gp160
Epitope KNCSFNMTT
Subtype A, B, C, D
Immunogen HIV-1 infection, vaccine
Vector/Type: vaccinia *Strain:* A clade, B clade, D clade NDK, C clade consensus *HIV component:* Env
Species (MHC) human
Donor MHC A*2402, A*3201, B*5101, B*5301, Cw*0401, Cw*1604
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References McKinnon *et al.* 2005

- Interclade cross-reactivity of clades A, B, C, and D was tested using recombinant vaccinia-based IFN-gamma Elispot assay. 47/74 women had a positive Elispot response to at least one clade, and cross-clade responses were frequent. Clade A responses were most frequent, as expected, as clade A dominates the Kenyan epidemic (85% of the 47 women responded to clade A Env, 74% to B, 62% to C, and 43% to D). Cross-clade CD8 T-cell responses were common and directed at conserved epitopes.
- There was a greater magnitude of response to A clade peptides in individuals who responded to more than 1 clade; a 2-fold higher response was observed in clade A in 36% (9/25) of these individuals, and the response to A peptides was never lower. VTEEFNMWK responses were detected in 2 women who had Env responses to all 4 clades, and clade A gave the highest responses; a VnEEFNMWK variant was in clade B and D, and the clade C Env carried VnEEFNMWe. One woman also reacted with RAIEAQQHL, the other one with KNCSFNMTT. KNCSFNMTT was identical in clades A and C, while clade B carried KNCSFNMis, clade D carried KNiSFNMTT.

HXB2 Location gp160 (156–165)
Author Location gp120 (156–165)
Epitope NCSFNISTSI
Immunogen HIV-1 infection
Species (MHC) human (Cw*08)
Keywords epitope processing
References Ferris *et al.* 1999

- Recognized by CTL clone LWF A5, isolated from a lab worker exposed to HIV-1 in 1985.
- The processing of this epitope is TAP1/2-dependent, as are most Env epitopes, and it contains two N-linked glycosylation sites that are glycosylated in Env.
- Only peptide that has been deglycosylated, a process that changes asparagine (N) to aspartic acid (D) was recognized: the aspartic acid at position 5 was critical, position 1 could be either D or N.
- This peptide also contains a Cys involved in a disulfide linkage but reducing conditions did not effect recognition by CTL clone LWF A5.
- The HIV-1 Env epitopes are typically processed by a TAP1/2 dependent mechanism, which involves cotranslational translocation into the ER, glycosylation, export back into the cytosol, and deglycosylation for processing, and retransport into the ER for the association with class I molecules.
- The particular pathway of generating an epitope may have an impact on the presentation of that epitope, quantitatively as well as qualitatively.

HXB2 Location gp160 (156–165)
Author Location gp120 (156–165 IIIB)
Epitope NCSFNISTSI
Immunogen HIV-1 infection
Species (MHC) human (Cw8)
References Sipsas *et al.* 1997

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB.
- NCSFNITTSI, a variant found in HIV-1 MN, was not recognized, thus this epitope was type-specific.
- NCSFNISTSI contains two potential N-linked glycosylation sites and cysteine residue, possibly related to the requirement for a high sensitizing dose of peptide for CTL activity.

HXB2 Location gp160 (156–165)
Author Location Env (162–171 BH10, LAI)
Epitope NCSFNISTSI
Immunogen HIV-1 infection
Species (MHC) human
References Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is STSIRGKVQK) has similarity with the macrophage colony stimulating factor I receptor fragment SISIRLKVQK.

HXB2 Location gp160 (165–173)
Author Location Env
Epitope IRDKVQKEY
Epitope name IY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- IY9, IRDKVQKEY, is a novel HLA-B27-restricted epitope that elicits a CTL IFN-gamma response in the same range as Los Alamos database peptides.

HXB2 Location gp160 (183–191)
Author Location Env
Epitope `YSENSSEYY`
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human (A*01)
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- An optimal CTL Env epitope YSENSSEYY, not previously described elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (183–191)
Author Location Env (173–177)
Epitope `YSENSSEYY`
Subtype B, C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA) *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland, United States
Assay type Tetramer binding, Flow cytometric T-cell cytokine assay, Other
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Precopio *et al.* 2007

- Vaccines against vaccinia (MVA or Dryvax) or HIV-1 clade C (NYVAC, a recombinant vaccinia virus) induce a similar polyfunctional CTL profile, secreting IFN-gamma, IL-2, MIP-1beta and TNF-alpha, as well as being CD107a+. CD45RO-CD27intermediate phenotype-polyfunctional CTLs secrete more IFN-gamma than monofunctional CTLs.

HXB2 Location gp160 (188–207)
Author Location gp120 (193–212 BRU)
Epitope `TTSYTLTSCNTSVITQACPK`
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Dadaglio *et al.* 1991

- Defined through blocking CTL activity, and Env deletions.

HXB2 Location gp160 (190–208)
Author Location gp41 (190–208)
Epitope `SYKLTSCNTSVITQACPKV`
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A3, A32, B15, B51
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, SYKLTSCNTSVITQACPKV, was found to be 0.005/day, with SE of 0.001.
- In the subject studied, the monotonic outgrowth of a Q199K mutation in Env gp41 was observed over a period of 1,028 days.

HXB2 Location gp160 (191–200)
Author Location gp120 (194–202 CM243 subtype CRF01)
Epitope `YRLINCNTSV`
Epitope name E191-200
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HIV exposed persistently seronegative (HEPS)
References Sriwanthana *et al.* 2001

CTL CD8+

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was reactive in HIV+ control study subject 144 who carried HLA-A2.

HXB2 Location gp160 (191–200)
Author Location gp120 (194–202 CM243 subtype CRF01)
Epitope `YRLINCNTSV`
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords subtype comparisons
References Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- 1/4 tested FSWs recognized the E clade version of this epitope, which differs from the previously defined B clade version by four amino acids, KLTSCNTSV.
- This epitope was somewhat conserved in 4/8 subtypes: CRF01 (E), B, C, and D.

HXB2 Location gp160 (191–208)
Author Location gp120
Epitope `YRLISCNTSVITQACPKV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, YRLISCNTSVITQACPKV, had an overall frequency of recognition of 15.3% - 11.9% AA, 23.1% C, 18.2% H, 9.5% WI.

HXB2 Location gp160 (192–200)
Author Location gp120 (192–199)
Epitope `KLTSCNTSV`
Epitope name SL9
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Keywords HAART, ART
References Rinaldo *et al.* 2000

- Administration of triple-drug antiretroviral therapy (IDV, 3TC and ZDV) sometimes showed a transient increase and other times failed to increase CTL responses in patients with advanced HIV disease, but there is a stable population of tetramer stained HIV-specific CD8+ CD45RO+ cells that persist after therapy and long periods of virus being below the level of detection.

HXB2 Location gp160 (192–200)
Author Location Env (192–200)
Epitope `RLISCNTSV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

HXB2 Location gp160 (192–200)
Author Location gp120 (199–207)
Epitope `TLTSCNTSV`
Immunogen HIV-1 infection

Species (MHC) human (A*0201)
References Brander *et al.* 1996

- This epitope was recognized by PBMC from 6/14 HIV+ asymptomatic patients.
- This epitope was used along with pol CTL epitope ALQDSGLEV and a tetanus toxin T helper epitope for a synthetic vaccine.
- This vaccine failed to induce a CTL response, although a helper response was evident.

HXB2 Location gp160 (192–200)
Author Location gp120 (192–199 HXB2R)
Epitope KLTSCNTSV
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Brander *et al.* 1995

- Epitope predicted on HLA binding motif, and studied in the context of inclusion in a synthetic vaccine.

HXB2 Location gp160 (192–200)
Author Location gp120 (192–199)
Epitope KLTSCNTSV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HAART, ART
References Huang *et al.* 2000

- The single cell ELISPOT assay was optimized and highly specific, and found to work well even after the primary cells had been frozen and thawed.
- Increases in gamma interferon producing cells were observed in response to anti-retroviral therapy using single cell IFN-gamma-production ELISPOT.

HXB2 Location gp160 (192–200)
Author Location gp120 (197–205)
Epitope TLTSCNTSV
Immunogen peptide-HLA interaction
Species (MHC) human (A2)
References Garboczi *et al.* 1992

- Crystallization of HLA-A2 molecules complexed with antigenic peptides – refers to Dadaglio *et al.* 1991.

HXB2 Location gp160 (192–200)
Author Location gp120 (161–169)
Epitope ILRSCNTSV
Epitope name ILR
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, A68.1, B*07, B*3503, Cw*0401, Cw*0702, DQ2, DQ6, DR15, DR17, DR51, DR52
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ
Keywords rate of progression, escape
References Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses,and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relatively efficiency of the variant eptiopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- This was one of 8 reactive epitopes found not to vary over time.

HXB2 Location gp160 (192–211)
Author Location gp120 (199–219 SF2)
Epitope SLTSCNTSVITQACPKVSFE
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-A2, -B21.

HXB2 Location gp160 (196–210)
Author Location Env
Epitope CNTSTITQACPKVSF
Epitope name Peptide37
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human, mouse
Country United States
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, epitope processing, optimal epitope
References Zhan *et al.* 2007

- By studying 4 subjects and surveying the database, it was found that for Env protein, some CTL epitopes cluster in similar "hotspots" as CD4 T-cell epitopes. This is not subtype-specific and shows that regions rather than specific peptides are targeted by T cells.
- Peptide37, CNTSTITQACPKVSF, was targeted by CTLs of one HIV-1 positive subject.

HXB2 Location gp160 (199–207)
Author Location gp160 (202–210)
Epitope SVITQACPK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*11)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This putative epitope, SVITQACPK, was detected and confirmed within overlapping peptide YRLISCNTSVITQACPKV.

HXB2 Location gp160 (199–207)
Author Location Env (202–210)
Epitope SVITQACPK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Keywords subtype comparisons, TCR usage
References Fukada *et al.* 2002

- Counterparts for eight known clade B HLA A*1101 epitopes were generated for clade E (CRF01). Three epitopes, identical among clade A-E, were cross-reactive and recognized by clade E infected individuals. The clade E and B analogs to three more HLA A*1101 epitopes was recognized in a clade specific manner. Two other HLA A*1101 clade B defined epitopes were found not to have stimulated a response in clade E infected individuals.
- SVITQACPK was found to elicit clade-specific responses in clade B (SVITQACPK is most common, sAitqacpk is most common variant in clade A, C and D) and clade E (saiKqacpk is most common). SVITQACPK was recognized by CTL from 3/5 B clade infected Japanese subjects, and aiKqacpk by CTL from 0/7 E clade infected Thai subjects, so this seems to be a B clade exclusive epitope.
- The binding of the three variant peptides to HLA A*1101 was comparable, implicating TCR interaction differences.

HXB2 Location gp160 (199–207)
Author Location gp160 (199–207)
Epitope SVITQACPK
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location gp160 (199–207)
Author Location gp160
Epitope SVITQACPK
Epitope name SK9(gp169)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A11-restricted epitope SVITQACPK elicited an immune response in Chinese HIV-1 positive subjects as part of peptide SVITQACPKVSFEPIPIH.
- 2 of the 28 HLA-A11 carriers responded to a SVITQACPK-containing peptide with average magnitude of CTL response of 150 SFC/million PBMC (author communication and Fig.1).

HXB2 Location gp160 (201–215)
Author Location Env
Epitope ITQACPKVSFEPIPI
Subtype A, B, C, D
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost, protein *Strain:* B clade 1007, B clade 1035 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse
Country United States
Assay type Cytokine production
Keywords subtype comparisons, immunodominance
References Brown *et al.* 2006

- A vaccine study with B clade Envs in mice was unertaken to assess a subtype-specificity of responses. Four T-cell hybridomas responsive to subtype B envelope proteins were tested against 20 different subtype B envelope proteins and a protein each from subtypes A, C and D. IL-2 production was measured.
- No consistent correlation was found between T cell specificity towards epitopes from a certain (B) subtype or lack of specificity towards other (A, C, D) subtype.
- Not only did T-cell specificity not vary with subtype, but pairwise sequence comparisons of HIV gp120 envelope sequences showed that some US-derived sequences were more similar to sequences from distant countries than to each other.
- Changes in core epitopes, flanking and distant regions, all affected responsiveness of the hybridomas to different subtype Env epitopes, showing that it is not only core changes that can eliminate T cell reactivity to an epitope.
- The above findings were substantiated by database analyses showing that epitope distributions are not necessarily dictated by subtype.
- This paper lists several variants of the epitope above, ITQACPKVSFEPIPI.

HXB2 Location gp160 (201–225)
Author Location gp120 (201–225 LAI)
Epitope ITQACPKVSFEPIPHYCAPAGFAI
Subtype B
Immunogen vaccine

Vector/Type: vaccinia *HIV component:* gp160
Species (MHC) human
Keywords CD4+ CTL
References Johnson *et al.* 1994b; Johnson *et al.* 1994a
- CD4+ CTL isolated from LAI IIIB gp160 vaccinees.

HXB2 Location gp160 (202–221)
Author Location gp120 (209–228)
Epitope TQACPKVSFEPIPIHYCAPA
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1995
- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

HXB2 Location gp160 (202–221)
Author Location gp120
Epitope TQACPKVSFEPIPIHYCAPA
Immunogen HIV-1 infection
Species (MHC) human
Keywords TCR usage
References Weekes *et al.* 1999b
- Peptide 740.18: Almost all CD8+ T cells are CD28+ at birth, and the proportion of CD28-CD8+ cells increases with age – this study examines the contribution of CD8+CD28- cells to CTL memory pools for CTL clones specific for two persistent human viruses, CMV and HIV – clones were found to be similarly distributed the CD28 depleted cell population.
- HIV CTL responses to 3 Env and 2 Gag peptides were studied.
- The clonal composition of the TCR Vβ responses were studied and was found to be highly focused, with one TCR beta-chain sequence tending to dominate the peptide-specific response – clones to this epitope were Vβ13.1.

HXB2 Location gp160 (202–221)
Author Location gp120
Epitope TQACPKVSFEPIPIHYCAPA
Immunogen HIV-1 infection
Species (MHC) human
References Weekes *et al.* 1999a
- Peptide 740.18: Memory CTL specific for HIV-1 may contribute to oligoclonal expansions within the CD57+ CD28- CD8+ CTLp populations.

HXB2 Location gp160 (202–221)
Author Location gp120 (209–228 SF2)
Epitope TQACPKVSFEPIPIHYCAPA
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a
- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- One of these 11 had CTL response to this peptide.

HXB2 Location gp160 (202–221)
Author Location gp120 (209–228 SF2)
Epitope TQACPKVSFEPIPIHYCAPA
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997b
- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

HXB2 Location gp160 (202–221)
Author Location gp120 (173–192)
Epitope TQACPKVSFEPIPIHYCAPA
Epitope name Peptide 740.18
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A11, A29, B44, B8
Country United Kingdom
Assay type Flow cytometric T-cell cytokine assay, Other
Keywords HAART, ART, immunodominance, TCR usage, memory cells
References Weekes *et al.* 2006
- The effect of HAART on the population size, phenotype and function of HIV- and HCMV-specific CTL clones was analyzed. It was determined that the clonal composition of gag and env HIV-specific CD8 T-cells did not change after HAART. Following HAART, the size of immunodominant HIV-specific CD8 T-cell clones was found to diminish even with the relative preservation of functional memory responses. Maintainance of such strong functional responses implied the preferential loss of HIV-specific cells that have reduced cloning efficiency in vitro. HCMV-specific CTL clones had different kinetics and phenotypes than HIV-specific CTL clones in the same subject.

HXB2 Location gp160 (205–213)
Author Location Env (250–)
Epitope CPKVSFEPI
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (B*0702)
Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008
- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location gp160 (205–213)
Author Location Env
Epitope CPKVSFEPI
Epitope name Env250
Subtype B
Immunogen vaccine

CTL CD8+

Vector/Type: polyepitope *HIV component:* Other
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- CPKVSFEPI is an Env epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location gp160 (205–213)
Author Location Env
Epitope `CPKVSFEPI`
Epitope name Env250
Subtype A, B, D
Immunogen HIV-1 infection
Species (MHC) human, mouse (B7 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope CPKVSFEPI of the HLA-B7 supertype bound most strongly to HLA-B*5401, -B*0702 and -B*5101 and also to -B*5301 and -B*3501. It was conserved 75% in subtype A, 79% in B, 50% in subtype D. 3/16 HLA-B7 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Env250.

HXB2 Location gp160 (205–219)
Author Location
Epitope `CPKVSFEPIPIHYCA`
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* gp140
Species (MHC) mouse
Assay type proliferation, T-cell Elispot
References Kumar *et al.* 2006c

- A recombinant plasmid DNA construct expressing env gp140 from B clade isolate 6101 was developed.
- The construct was highly immunogenic in mice and cross-reacted with clade C peptides. 3 immunodominant peptides were mapped out. Proliferation was observed in CD4+, CD8+ and CCR+ memory T cells.
- Immunodominant peptide CPKVSFEPIPIHYCA overlapped with the SYFPEITHI database predicted epitope CPKMSFEPI for the Balb/C mouse H2-Kd loci.

HXB2 Location gp160 (206–220)
Author Location Env
Epitope `PKVSFEPIPIHYCAP`
Subtype A, B, C, D
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost, protein *Strain:* B clade 1007, B clade 1035
Species (MHC) mouse
Assay type Cytokine production
Keywords subtype comparisons, immunodominance
References Brown *et al.* 2006

- A vaccine study with B clade Envs in mice was unertaken to assess a subtype-specificity of responses. Four T-cell hybridomas responsive to subtype B envelope proteins were tested against 20 different subtype B envelope proteins and a protein each from subtypes A, C and D. IL-2 production was measured.
- No consistent correlation was found between T cell specificity towards epitopes from a certain (B) subtype or lack of specificity towards other (A, C, D) subtype.
- Not only did T-cell specificity not vary with subtype, but pairwise sequence comparisons of gp120 envelope sequences showed that some US-derived sequences were more similar to sequences from distant countries than to each other.
- Changes in core epitopes, flanking and distant regions, all affected responsiveness of the hybridomas to different subtype Env epitopes, showing that it is not only core changes that can eliminate T cell reactivity to an epitope.
- The above findings were substantiated by database analyses showing that epitope distributions are not necessarily dictated by subtype.
- This paper lists several variants of the epitope above, PKVSFEPIPIHYCAP.

HXB2 Location gp160 (206–220)
Author Location Env
Epitope `PKVSFEPIPIHYCAP`
Epitope name Peptide39
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human, mouse
Country United States
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, epitope processing, optimal epitope
References Zhan *et al.* 2007

- By studying 4 subjects and surveying the database, it was found that for Env protein, some CTL epitopes cluster in similar "hotspots" as CD4 T-cell epitopes. This is not subtype-specific and shows that regions rather than specific peptides are targeted by T cells.
- Peptide39, PKVSFEPIPIHYCAP, was targeted by CTLs of one HIV-1 positive subject.

HXB2 Location gp160 (207–216)
Author Location gp120 (subtype A)
Epitope KMTFEPIPIH
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (A29)
Keywords subtype comparisons
References Cao *et al.* 2000

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, Pol, RT or Nef from HIV-1 clades A, B, and D.
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype.
- CTL derived from subtype A clade infection (patient SP 528), recognized the subtype A version of the peptide (KMSFEPIPIH), had a slightly reduced specific lysis using the B clade version of the peptide (KVSFEPIPIH), and no lysis using the D clade version of the epitope (KVTFEPIPIH)
- Patient SP 528 is HLA A1, A29, B57, B81, Bw4, Bw6.

HXB2 Location gp160 (207–224)
Author Location (C consensus)
Epitope KVSFDPIPIHYCAPAGYA
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0401)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location gp160 (208–216)
Author Location Env
Epitope VSFEPIPIH
Epitope name 1329
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, A23, B49, B57; A03, A24, B27, B57, Cw13, Cw18
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for VSFEPIPIH: 58%

HXB2 Location gp160 (208–217)
Author Location gp120 (subtype B)
Epitope VSFEPIPIHY
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A29)
References Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T cell epitopes: DTVLEDINL (3 individuals), SLYNTVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

HXB2 Location gp160 (208–217)
Author Location gp120 (263–272)
Epitope VSFEPIPIHY
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A29)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location gp160 (208–217)
Author Location gp120
Epitope VSFEPIPIHY
Immunogen HIV-1 infection
Species (MHC) human (A29)
Assay type Intracellular cytokine staining
Keywords immunodominance, genital and mucosal immunity
References Kaul *et al.* 2003

- Predefined immunodominant peptide responses were used to compare CD8+ T cells responses in the blood and cervix of 16 HIV+ Kenyan sex workers. Cervical responses were detected in 8/10 women from whom adequate samples could be obtained. The frequency of the CD8+ T cell response in the genital tract was comparable to the blood, with a trend toward being slightly higher.

- The immunodominant response was to this epitope in the PBMC of 1/16 patients (Kaul *et al.* 2001, AIDS, 107:1303).

HXB2 Location gp160 (208–219)
Author Location Env
Epitope VSFEPIPPHYCA
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords epitope processing
References Cao *et al.* 2002

- SP 511 is an A2 restricted CTL clone generated from a Ugandan subject that recognizes VSFEPIPPHYCA.
- CTL could be activated by a fusion protein of an HIV protein and anthrax lethal factor (LFn-HIV) that promotes antigen presenting cell uptake of exogenous protein and allows processing through the MHC class I pathway. This strategy for CTL detection could allow antigen presentation without generation of cells by the standard methods of using live viral vectors carrying a protein, or by loading the cells with peptides and by-passing processing.

HXB2 Location gp160 (208–219)
Author Location Env
Epitope VSFEPIPPHYCA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A*0202, A*0301, B*0702, B*1516
Country United States
Keywords escape, acute/early infection
References Bernardin *et al.* 2005

- Full HIV genomes from nine individuals were analyzed for mutations prior to seroconversion and 7 to 28 days later. It was found that the influence of the host's HLA type was reflected within weeks of infection; a statistically significant number of early nonsynonymous mutations were observed within previously reported CTL epitopes.
- K to E mutation was observed in position 4.

HXB2 Location gp160 (209–217)
Author Location (C consensus)
Epitope SFDPIPIHY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*29)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the S1 residue of SFDPIPIHY are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location gp160 (209–217)
Author Location (LAI)
Epitope SFEPIPIHY
Subtype B
Immunogen
Species (MHC) human (A*2902)
Keywords optimal epitope
References Altfeld 2000; Llano *et al.* 2009

HXB2 Location gp160 (209–217)
Author Location gp160 (207–215 BORI, WEAU)
Epitope SFEPIPIHY
Epitope name gp160 SY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2902)
Donor MHC A*2902, B*1402, Cw*0802; A*2902, B*0801, B*4403
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, immunodominance, escape, acute/early infection, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined, WEAU and BORI, had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape. This epitope was recognized in both patients.
- The patient BORI had high viral loads and rapid CD4 decline. BORI mounted 8 detected responses. BORI did not control viral replication well, and escape mutations occurred early and in most epitopes, 6/7 that were precisely identified. The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.
- Four escape variants to the SFEPIPIHY epitope were found in the patient BORI. SFdPIPIHY came up first, at day 55 from onset of symptoms, and caused a reduced cytotoxic response. By day 218, two rare forms were found, SIEPIPIHf and SiEPIPIHf. By day 556, only tFEPIPIHY was found. The weakest response was detected in the double mutant,SiEPIPIHf, yet tFEPIPIHY was the form that persisted.
- In WEAU, a minor variant, SsEPIPIHY was present at day 41. The SIEPIPIHf variant first came up day 136, gave a reduced CTL response, and then came to be the dominant form. Other variants were SFEPIPInY and SFEPIPIdf.

HXB2 Location gp160 (209–217)
Author Location gp120 (213–221 SF2)
Epitope SFEPIPIHY

Immunogen HIV-1 infection
Species (MHC) human (A29)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A29+ individuals that had a CTL response to this epitope broken down by group: 1/3 group 1, 0/0 group 2, and 0/0 group 3.

HXB2 Location gp160 (209–217)
Author Location gp120 (209–217)
Epitope SFEPIPIHY
Immunogen HIV-1 infection
Species (MHC) human (A29)
Donor MHC 1261: A*0201, A29, B58, B62, Cw*0304, Cw*1601; 1168: A*0201, A29, B44, B60, Cw16, Cw3
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- Two subjects recognized this epitope during primary infection, both in the context of A29.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

HXB2 Location gp160 (209–217)
Author Location (C consensus)
Epitope SFDPIPIHY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A29)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location gp160 (209–217)
Author Location (B consensus)
Epitope SFEPIPIHY
Epitope name SY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A29)
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope

HXB2 Location gp160 (209–217)
Author Location gp120
Epitope SFEPIPIHY
Epitope name SY9(gp120)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A29)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.

CTL CD8+

- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A29-restricted epitope SFEPIPIHY elicited an immune response in Chinese HIV-1 positive subjects as part of peptide KVSFEPIPIHYCAPAGFA.
- 2 of the 8 HLA-A29 carriers responded to SFEPIPIHY-containing peptide with average magnitude of CTL response of 100 SFC/million PBMC (author communication and Fig.1).

HXB2 Location gp160 (209–217)
Author Location
Epitope SFDPIPIHY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A29)
Donor MHC A*2301, A*2902, B*4101, B*4201, Cw*1701
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- Known epitope SFDPIPIHY is HLA-A29-restricted. Response to a peptide containing this epitope was detected in a rapid progressor 12 weeks post-infection.

HXB2 Location gp160 (209–217)
Author Location gp160 (209–217)
Epitope SFEPIPIHY
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*2902, B*1402; A*2902, B*0801, B*4403
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimates of escape rate for this epitope, SFEPIPIHY, were found to be 0.072 and 0.041/day (optimistic escape rate = 0.13), with SEs of 0.041 and 0.005 respectively, in 2 subjects.
- In the first subject, rapid loss of wild type at this epitope (primarily due to a E211D mutation) was observed. In the second subject, a Y217F mutation grew out over time.

HXB2 Location gp160 (209–217)
Author Location Env
Epitope SFEPIPIHY
Subtype B, D
Immunogen HIV-1 infection
Species (MHC) human, mouse
Country United States
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, epitope processing, optimal epitope
References Zhan *et al.* 2007

- By studying 4 subjects and surveying the database, it was found that for Env protein, some CTL epitopes cluster in similar "hotspots" as CD4 T-cell epitopes. This is not subtype-specific and shows that regions rather than specific peptides are targeted by T cells.
- SFEPIPIHY was targeted by the human subject with a positive IFN-gamma response to Peptide39, PKVSFEPIPIHYCAP. This epitope is shifted by one residue compared to the immunodominant murine CD4 T-cell eptiope, FEPIPIHYC.

HXB2 Location gp160 (209–217)
Author Location gp160
Epitope SFEPIPIHY
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Garrison *et al.* 2007

- The study examined the influence of HIV-1 infection on human endogenous retroviruses (HERVs) activity and explored T cells cross-reactivity in regions of HIV-1/HERV similarity.
- T cell responses to HERV peptides were identified in HIV-1 positive individuals. There was an inverse correlation between anti-HERV T cell responses and HIV-1 viral load.
- HIV-1 epitope SFEPIPIHY has a corresponding HERV peptide TLEPIPPGE. These 2 peptides were used in measuring IFN-γ ELISPOT responses in HIV-1-positive and -negative individuals.

HXB2 Location gp160 (212–226)
Author Location
Epitope PIPIHYCAPAGFAIL
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human

Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location gp160 (212–231)
Author Location gp120
Epitope `PIPIHYCAPAGFAILKCNNK`
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords TCR usage
References Weekes *et al.* 1999b

- Peptide 740.19: Almost all CD8+ T cells are CD28+ at birth, and the proportion of CD28-CD8+ cells increases with age – this study examines the contribution of CD8+CD28- cells to CTL memory pools for CTL clones specific for two persistent human viruses, CMV and HIV – clones were found to be similarly distributed in the CD28 depleted cell population.
- HIV CTL responses to 3 Env and 2 Gag peptides were studied.
- The clonal composition of the TCR Vβ responses was studied and was found to be highly focused, with one TCR beta-chain sequence tending to dominate the peptide-specific response – clones to this epitope were Vβ13.6.

HXB2 Location gp160 (212–231)
Author Location gp120 (183–202)
Epitope `PIPIHYCAPAGFAILKCNNK`
Epitope name Peptide 740.19
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A2, A24, B27, B62
Country United Kingdom
Assay type Flow cytometric T-cell cytokine assay, Other
Keywords HAART, ART, immunodominance, TCR usage, memory cells
References Weekes *et al.* 2006

- The effect of HAART on the population size, phenotype and function of HIV- and HCMV-specific CTL clones was analyzed. It was determined that the clonal composition of gag and env HIV-specific CD8 T-cells did not change after HAART. Following HAART, the size of immunodominant HIV-specific CD8 T-cell clones was found to diminish even with the relative preservation of functional memory responses. Maintainance of such strong functional responses implied the preferential loss of HIV-specific cells that have reduced cloning efficiency in vitro. HCMV-specific CTL clones had different kinetics and phenotypes than HIV-specific CTL clones in the same subject.

HXB2 Location gp160 (212–231)
Author Location gp120
Epitope `PIPIHYCAPAGFAILKCNNK`
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Jin *et al.* 1998b

- Progressive HIV-1 infection and CD4 decline was associated decreased the IL-2-expandable HIV-1 CTL response in 10 asymptomatic HIV-infected patients – this observation may be partially due to a reduction and impaired function of T helper cells, CTL exhaustion and APC dysfunction.
- Continued presence of HIV-1 specific memory cells (CTLp) was observed in three patients, one to GIWGCSGKLICTTAV, one to ALIWEDLRSLCLFSY, and one to PIPIHYCAPAGFAILKCNNK.

HXB2 Location gp160 (212–231)
Author Location gp120
Epitope `PIPIHYCAPAGFAILKCNNK`
Immunogen HIV-1 infection
Species (MHC) human
References Weekes *et al.* 1999a

- Peptide 740.19: Memory CTL specific for HIV-1 may contribute to oligoclonal expansions within the CD57+ CD28- CD8+ CTLp populations.

HXB2 Location gp160 (212–231)
Author Location gp120 (219–238 HXB2)
Epitope `PIPIHYCAPAGFAILKCNNK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1992

- CTL epitope defined by T cell line and peptide mapping.

HXB2 Location gp160 (212–231)
Author Location gp120 (219–238)
Epitope `PIPIHYCAPAGFAILKCNNK`
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

HXB2 Location gp160 (213–221)
Author Location Env (259–)
Epitope `IPIHYCAPA`
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (B*0702)
Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008

CTL CD8+

- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location gp160 (213–221)
Author Location Env
Epitope IPIHYCAPA
Epitope name Env1161
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Epitope IPIHYCAPA elicits IFN-gamma ELISpot responses in 1/7 subjects; and bound HLA-B7 with medium and high affinities in soluble and cell-based assays respectively. Previously published HLA restrictions of this epitope include A3 (LANL database), B*0702 and DRB4*0101, DRB1*0101, DRB1*0401, DRB1*0701, DRB1*0901 (Immune Epitope Database).

HXB2 Location gp160 (213–221)
Author Location Env
Epitope IPIHYCAPA
Epitope name Env259
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- IPIHYCAPA is an Env epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location gp160 (213–221)
Author Location Env
Epitope IPIHYCAPA
Epitope name Env259
Subtype A, B, C, D
Immunogen HIV-1 infection
Species (MHC) human, mouse (B7 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope IPIHYCAPA of the HLA-B7 supertype bound most strongly to HLA-B*5101 and -B*5401 and also to -B*0702, -B*3501 but not to -B*5301. It was conserved 75% in subtype A, 42% in B, 38% in C and 75% in subtype D. 0/17 HLA-B7 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Env259.

HXB2 Location gp160 (216–226)
Author Location gp120 (216–226)
Epitope HYCAPAGFAIL
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008

- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.
- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.
- CTL immune response to consensus sequence HYCAPAGFAIL was elicited in subject 00015.

HXB2 Location gp160 (217–226)
Author Location Env
Epitope YCAPAGFAIL
Epitope name YL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*01)

Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords binding affinity
References Cao *et al.* 2008

- For the first time, viral immune evasion is reported via an insertion mutation, in an ART-naive patient. A 3 aa repeat, SPT inserted within p6<sup>Pol<sup> epitope NL8 is reported. This insertion is associated often with ART drug resistance to NRTI drugs. Thus immune pressure and drug resistance may cause HIV-1 to select the same variation.
- A concomitant insertion mutation APP, is seen in p6<sup>Gag<sup>, permitting viral budding.
- Epitope YCAPAGFAIL bound its MHC I less strongly than NL8 (NSPTRREL) did its MHC I molecule.

HXB2 Location gp160 (217–226)
Author Location gp120 (217–226 HIV-MN)
Epitope `YCAPAGFAIL`
Epitope name YL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*0102)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Last position (10)in the epitope had potentially experienced positive selection. YCAPAGFAIi escape variant was found.

HXB2 Location gp160 (218–226)
Author Location gp120
Epitope `CAPAGFAIL`
Epitope name CL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw1)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords immunodominance, escape, superinfection
References Streeck *et al.* 2008b; Zuniga 2008

- Loss of viral replication control by an elite controller after superinfection was found to coincide with rapid recombination events in 2, ∼50 residue regions of Gag and Env that include immunodominant epitopes KK10 (KRWIILGLNK) and CL9 (CAPAGFAIL). Viral escape was seen at both epitopes and consequent CTL responses against the epitope-variants.
- Epitope CAPAGFAIL (CL9) is previously described, with restriction to HLA-A2. Env CL9 developed variants - CtPAGFAIL at A217T that recombined the superinfecting virus to its variant sequence, CtPAGFtIL, and CtPAGFvIL.
- This epitope appears on the A list of optimal epitopes, added June 2009.

HXB2 Location gp160 (218–226)
Author Location
Epitope `CAPAGFAIL`
Epitope name CL9
Immunogen
Species (MHC) human (Cw1)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a Cw1 epitope.

HXB2 Location gp160 (218–228)
Author Location Env (218–228)
Epitope `CTPAGYAILKC`
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Thailand
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords optimal epitope
References Kantakamalakul *et al.* 2006

- T cell responses in CRF01_AE infected individuals from Thailand were studied.
- Based on two overlapping peptide sequences that were both reactive, as well as conserved anchor residues, this peptide is suggested to contain an epitope, CTPAGYAILKC.
- CTPAGYAILKC may be a novel epitope that is promiscuously presented by HLA-A*0201, -A*0206 and -A*0207 as it matches the published binding motifs for the HLA, and is present in subjects recognizing the epitope.

HXB2 Location gp160 (237–245)
Author Location Env
Epitope `GPCTNVSTV`
Epitope name Env1158
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Novel Env epitope GPCTNVSTV elicits IFN-gamma ELISpot responses in 2/7 subjects; and bound HLA-B7 with low and medium affinities in soluble and cell-based assays respectively.

HXB2 Location gp160 (237–246)

Author Location Env
Epitope GPCKNVSTVQ
Immunogen
Species (MHC) human (B56)
References De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conservered regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFNγ production in an ELISPOT assay.
- GPCKNVSTVQ was newly defined as an epitope in this study, was shown to stimulate an ELISPOT response, and to bind to HLA-B7.

HXB2 Location gp160 (237–249)
Author Location Env
Epitope GTCKSVSTVQCTH
Subtype CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide GTCKSVSTVQCTH from subtype CRF02_AG.

HXB2 Location gp160 (239–247)
Author Location gp160 (237–245 BORI)
Epitope CKNVSTVQC
Epitope name gp160 CC9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*0802)
Donor MHC A*2902, B*1402, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, immunodominance, escape, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient BORI had high viral loads and rapid CD4 decline. BORI mounted 8 detected responses. BORI did not control viral replication well, and escape mutations occurred early and in most epitopes, 6/7 that were precisely identified.
- Four variants of the CKNVSTVQC epitope were found in the patient BORI. CeNVSTVQC and cCeNVSTVhC came up first, at day 6 from onset of symptoms. The CeNVSTVQC form was the form that persisted, with a second rare variant present at day 35, CgNVSTVQC.These variants were not tested for their impact on escape.

HXB2 Location gp160 (239–247)
Author Location gp120 (241–249 LAI)
Epitope CTNVSTVQC
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw8)
References Sipsas *et al.* 1997

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB.
- CTNVSTVQC contains a potential N-linked glycosylation site and cysteine residues, possibly related to a requirement for a high sensitizing dose of peptide for CTL activity.

HXB2 Location gp160 (239–247)
Author Location Env
Epitope CTNVSTVQC
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw8)
Donor MHC A1, A19, B*3501, B44, Cw16, Cw7; A*0201, A19, B14, B44, Cw16, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
References Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.

- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-Cw8 restricted epitope, CTNVSTVQC was mutated to CqNVSTVQC in the daughter D2 isolate.

HXB2 Location gp160 (242–261)
Author Location gp120 (249–268)
Epitope VSTVQCTHGIRPVVSTQLLL
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1995
- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

HXB2 Location gp160 (242–261)
Author Location gp120 (249–268 SF2)
Epitope VSTVQCTHGIRPVVSTQLLL
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a
- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-2, -B21.

HXB2 Location gp160 (242–261)
Author Location gp120 (249–268)
Epitope VSTVQCTHGIRPVVSTQLLL
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997b
- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

HXB2 Location gp160 (245–259)
Author Location Env (243–257)
Epitope VQCTHGIRPVVSTQL
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008
- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized both by mice co-immunized with Env and Tat, and by mice immunized with Env alone.

HXB2 Location gp160 (252–260)
Author Location gp120 (255–263 SF2)
Epitope RPIVSTQLL
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
References Tomiyama *et al.* 1997
- A CTL clone responsive to this epitope was obtained.
- Only 1/7 B35-positive individuals had a CTL response to this epitope.
- An I to V substitution at position 3 reduces specific lysis, but not binding to B*3501.
- A Q to H substitution at position 7 abrogates specific lysis, but not binding to B*3501.

HXB2 Location gp160 (252–260)
Author Location gp120 (255–263 SF2)
Epitope RPIVSTQLL
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Shiga *et al.* 1996
- Binds HLA-B*3501.

HXB2 Location gp160 (252–260)
Author Location (SF2)
Epitope RPIVSTQLL
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords rate of progression
References Kawana *et al.* 1999
- HLA B35 is associated with rapid disease progression.
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals.
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals, but this was one of the six that had no B35 associated pattern of mutation.

HXB2 Location gp160 (252–261)
Author Location gp120 (252–261)
Epitope KPVVSTQLLL
Immunogen
Species (MHC) human (B07, B08)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007
- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 36/59 Brazilian HIV sequences; a common variant is rPVVSTQLLL found in subtype B and BF sequences.

HXB2 Location gp160 (252–261)
Author Location Env

CTL CD8+

Epitope RPVVSTQLLL
Immunogen
Species (MHC) human (B7)
References De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conservered regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 of the predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFNγ production in an ELISPOT assay.
- RPVVSTQLLL was one of the 15, and had been previously identified as an HLA-B7 epitope, and was confirmed in this study.

HXB2 Location gp160 (252–261)
Author Location Env
Epitope KPVVSTQLLL
Epitope name 1298
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (B7, B8)
Donor MHC A01, A03, B07, B08, Cw03, Cw07; A29, A30, B08, B44, Cw07, Cw16
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for KPVVSTQLLL: 46% Promiscuous epitope binding to B08 and B07.

HXB2 Location gp160 (252–261)
Author Location Env
Epitope RPVVSTQLLL
Epitope name 1305
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (B7, B8)
Donor MHC A29, A30, B08, B44, Cw07, Cw16
Country United States
Assay type T-cell Elispot
Keywords binding affinity, supertype, computational epitope prediction, cross-presentation by different HLA
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for RPVVSTQLLL: 41%. Supertype epitope, published B07, responses by B08 subject.

HXB2 Location gp160 (252–271)
Author Location gp120 (256–275 LAI)
Epitope RPVVSTQLLLNGSLAEEEVV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Shankar *et al.* 1996

HXB2 Location gp160 (252–271)
Author Location Env (256–268 BH10, LAI)
Epitope RPVVSTQLLLNGSLAEEEVV
Immunogen HIV-1 infection
Species (MHC) human
References Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is STQLLLNGSLAEE) has similarity with the lymphatic endothelium-specific hyaluronan receptor LYVE-1 fragment TTRLLVQGSLRAEE.

HXB2 Location gp160 (269–281)
Author Location Env
Epitope KIAIRSENISNNA
Subtype CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide KIAIRSENISNNA from subtype CRF02_AG.

HXB2 Location gp160 (280–288)
Author Location Env
Epitope NAKTIIVHL
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (Cw*0602)
Country Thailand
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords immunodominance, optimal epitope
References Kantakamalakul *et al.* 2006

- T cell responses in CRF01_AE infected individuals from Thailand were studied.

CTL CD8+

- Fine mapping of the peptide NAKTIIVHL, revealed a novel Cw*0602-restricted epitope.

HXB2 Location gp160 (281–288)
Author Location (C consensus)
Epitope AKTIIVHL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0602)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the L8 residue of AKTIIVHL are associated with the presence of the HLA presenting molecule in the host.
- AKTIIVHL not optimized.

HXB2 Location gp160 (281–293)
Author Location Env
Epitope AKTIIVQLTEPVE
Subtype CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide AKTIIVQLTEPVE from subtype CRF02_AG.

HXB2 Location gp160 (289–303)
Author Location Env (287–301)
Epitope KESVEINCTRPNNNT
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized both by mice co-immunized with Env and Tat, and by mice immunized with Env alone.

HXB2 Location gp160 (291–307)
Author Location gp120 (295–312 BRU)
Epitope SVEINCTRPNNNTRKSI
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Dadaglio *et al.* 1991

- Defined through blocking CTL activity, and Env deletions.

HXB2 Location gp160 (291–307)
Author Location gp120 (291–307 IIIB)
Epitope SVEINCTRPNNNTRKRI
Subtype B
Immunogen vaccine
Vector/Type: DNA, DNA with protein boost *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* IL-12
Species (MHC) mouse (A2)
Keywords vaccine-specific epitope characteristics
References Kiszka *et al.* 2002

- Transgenic mice expressing a HLA-A2/Kb chimeric protein were vaccinated with a full length gp160 or with gp160deltaV3, with the V3 loop deleted. Mice given gp160deltaV3 had a broader immune response than those given gp160, with increased responses to conserved HLA-A2 epitopes in the C1 region of gp120, KLTPLCVTL, and the C-term region of gp41, SLLNATAIAV.
- Greater resistance was conferred by the gp160deltaV3 than the gp160 vaccine to a challenge of vaccinia expressing heterologous gp160 from primary isolates (VI-06 and 89.6), and the resistance was conferred by CD8+ T-cells.
- The most intense CTL responses to the intact gp160 vaccine were directed at three V3 peptides.

HXB2 Location gp160 (291–307)
Author Location Env (292–301 BH10, LAI)
Epitope SVEINCTRPNNNTRKSI
Immunogen HIV-1 infection
Species (MHC) human
References Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.

- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is VEINCTRPNN) has similarity with the FasI receptor precursor (Apptosis-mediating surface antigen fas) (APO-1 antigen) (CD95 antigen) fragment VEINCTRQN.

HXB2 Location gp160 (296–305)
Author Location gp120 (296–305)
Epitope CTRPNNNTRK
Immunogen
Species (MHC) human (A02, A03)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 283/515 Brazilian HIV sequences; a common variant is CTRPgNNTRK found in subtype B sequences.

HXB2 Location gp160 (296–305)
Author Location Env (296–305 B1 and B2)
Epitope CTRPNNNTRK
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A3, A32, B62, B8, Cw3
Country Netherlands
Assay type Other
Keywords subtype comparisons, computational epitope prediction, superinfection
References Kozaczynska *et al.* 2007

- The influence of superinfection upon changes in HIV-1 strains was studied in a triple infected subject. While continuous expression of all three strains was observed, the LTR promoters of subtype AE had highest activity of all 3 strains, and subtype B2 had the lowest. Env-V3 sequences were present in higher numbers in strains B2 and CRF01_AE. Recombination was seen between viruses B1/B2 in gag and vpr genes.
- This HLA-A03 restricted epitope, CTRPNNNTRK, varied to CTRPsNNTRK in B1 and B2, and CTRPsNNTRt in AE by the earliest time point taken, with no changes over time.

HXB2 Location gp160 (296–305)
Author Location Env
Epitope CTRPNNNTRK
Epitope name 1265
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A2, A3)
Donor MHC A03, A23, B49, B57
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for CTRPNNNTRK: 51% Promiscuous epitope binding to A02 and A03.

HXB2 Location gp160 (297–322)
Author Location gp120 (297–322 IIIB)
Epitope TRPNNNTRKRIRIQRGPGRAFVTIGK
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB
HIV component: V3 *Adjuvant:* liposome
Species (MHC) mouse (H-2D^d)
References Chang *et al.* 1999

- Induction of peptide-specific CTLs in BALB/c mice was dependent on immunization with peptide encapsulated liposomes containing MPL as adjuvant.
- T26K (26mer) elicited a stronger AB and CTL response than R15K (a V3 15mer, RIQRGPGRAFVTIGK)

HXB2 Location gp160 (297–330)
Author Location Env (303–335 BX08)
Epitope TRPNNNTRKSIHIGPGRAFYATGEIIGDIRQAH
Immunogen vaccine
Vector/Type: lipopeptide
Species (MHC) human
References Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long amino acid peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 6/10 reacted to this peptide.
- 9/12 tested mounted a CTL response to at least one of the six peptides; each of the six peptides elicited a CTL response in at least one individual – this peptide was particularly immunogenic, eliciting a CTL response in five vaccinees.
- None of the 12 tested had an IgG response to gp120 or gp160 and vaccinees could be differentiated from HIV-1 seropositive individuals with a commercial HIV detection kit – no neutralizing antibodies were observed.

HXB2 Location gp160 (298–306)
Author Location gp120 (298–306)
Epitope RPNNNTRKS
Epitope name RS9
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (B*07)
Country Kenya
Assay type Cytokine production, proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2007

- The authors suggest that epitope variation has different effects on the HIV- specific immune responses of effector memory T cells (Tem) and central memory T cells (Tcm). They show a lack of correlation between IFN-gamma ELISPOT (Tem typical) and proliferation (Tcm typical) assays for specific epitopes in subjects. Since proliferating CTL also correlate with high intracellular IFN-gamma levels, they surmise that proliferating Tcm differentiate to express Tem functions.
- They also show that proliferating CTL numbers correlate with higher CD4 cell counts.
- Several patients responded strongly to epitope variants that were not part of their autologous HIV-1 sequences. Thus they suggest more comprehensive functional characterizations than the usual overnight IFN-gamma ELISPOTs as well as assessments of Tem versus Tcm specific responses rather than general CTL immune responses.
- 4 variants of this index epitope RPNNNTRKS, RS9, were tested in vitro - RPsNNTRKS, RPyNNTRKS, RPyNNTRqS, RPNNNTRrS. Autologous variants RPNNNTRrg and RPNNNTRtS were also detected. The rare variant RPyNNTRqS, found almost exclusively in clade B HIV (but absent in all subjects in this study), showed both proliferative as well as ELIspot responses. However, the intermediate RPyNNTRKS showed only a slight increase in proliferation but not in ELIspot detection.
- RS9 has previously published restriction to HLA-B*07.

HXB2 Location gp160 (298–306)
Author Location Env
Epitope `RPNNNTRKS`
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0201, A*0205, B*1503, B*5801, Cw*0401, Cw*0701; A*3001, A*6802, B*1801, B*4201, Cw*0304, Cw*1701
Country Kenya
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2008

- To evaluate the use of IFN-gamma ELISpot and proliferation assays, the two were compared in a cohort of HIV-1-infected Kenyan sex-workers. ELISpot does not always correlate with viral load and replication or disease progression. The exclusive use of these assays makes definition of CTL response in disease incomplete, especially for memory T cells.
- Despite assaying for 24 INF-gamma and 41 proliferative responses, only 5 of these responses overlapped in the same subject. 18 peptide-epitopes including 10 epitopes and their variants were used in this study.
- RPNNNTRKS elicited proliferation alone in 2 subjects; and ELISpot response in no subjects.

HXB2 Location gp160 (298–306)
Author Location Env
Epitope `RPYNNTRQS`
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0201, B*4504, B*5301, Cw*1601; A*0101, A*2301, B*0702, B*4501, Cw*0702, Cw*1601
Country Kenya
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2008

- To evaluate the use of IFN-gamma ELISpot and proliferation assays, the two were compared in a cohort of HIV-1-infected Kenyan sex-workers. ELISpot does not always correlate with viral load and replication or disease progression. The exclusive use of these assays makes definition of CTL response in disease incomplete, especially for memory T cells.
- Despite assaying for 24 INF-gamma and 41 proliferative responses, only 5 of these responses overlapped in the same subject. 18 peptide-epitopes including 10 epitopes and their variants were used in this study.
- RPYNNTRQS elicited proliferation in 2 subjects; ELISpot responses in none.

HXB2 Location gp160 (298–307)
Author Location gp120 (298–307)
Epitope `RPNNNTRKSI`
Immunogen HIV-1 infection
Species (MHC) human (B*07)
Keywords epitope processing, TCR usage
References Ferris *et al.* 1999; Hammond *et al.* 1995

- The processing of this epitope is TAP1/2-dependent, as are most Env epitopes, and it contains an N-linked glycosylation site that is glycosylated in Env.
- Peptide that had been deglycosylated, a process that changes asparagine (N) to aspartic acid (D) (RPNDNTRKSI) was recognized a 100-fold more efficiently than either glycosylated or non-glycosylated RPNNNTRKSI.
- Position 5 is not involved with HLA B*07 binding, so is probably important for TCR recognition.
- HIV-1 Env epitopes are typically processed by a TAP1/2 dependent mechanism, which involves cotranslational translocation into the ER, glycosylation, export back into the cytosol, and deglycosylation for processing, and retransport into the ER for the association with class I molecules.
- The particular pathway of generating an epitope may have an impact on the presentation of that epitope, quantitatively as well as qualitatively.

HXB2 Location gp160 (298–307)
Author Location gp120 (302–312 HXB2)
Epitope `RPNNNTRKSI`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*0702 epitope.

HXB2 Location gp160 (298–307)
Author Location (C consensus)
Epitope `RPNNNTRKSI`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ

CTL CD8+

Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location gp160 (298–307)
Author Location
Epitope RPNNNTRKSI
Immunogen HIV-1 infection
Species (MHC) human (B07)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope RPNNNTRKSI elicited a magnitude of response of 1075 SFC with a functional avidity of 1nM and binding affinity of 23nM.

HXB2 Location gp160 (298–307)
Author Location gp120 (302–312 HXB2)
Epitope RPNNNTRKSI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Safrit *et al.* 1994b

- CTL from two acute seroconversion cases.

HXB2 Location gp160 (298–307)
Author Location gp120 (302–312 HXB2)
Epitope RPNNNTRKSI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Hammond *et al.* 1995

- Peptide processed by a TAP-1/2-dependent pathway only.
- CTL from an acute seroconverter.

HXB2 Location gp160 (298–307)
Author Location gp120 (302–312 HXB2)
Epitope RPNNNTRKSI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Wolinsky *et al.* 1996

- Longitudinal study of epitope variation *in vivo*.

HXB2 Location gp160 (298–307)
Author Location gp120 (302–311 subtype B)
Epitope RPNNNTRKSI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords subtype comparisons, immunodominance
References Wilson *et al.* 1998b

- The extent of CTL interclade cross-reactivity from CTL isolated from individuals newly infected with B clade virus was studied, and extensive cross-reactivity was observed.
- Two HLA B7 individuals had CTL response to B_LAI, A_92UG037 and C_92BR025 gp160, but were B clade strain MN non-responders – the authors note that the B7 epitope RPNNNTRKSI is immunodominant, conserved between the LAI and clade A and C strains, but is very divergent in MN (RPNYNKRKRI), and that this epitope might be dominating the specificity of the response in the HLA B7 individuals.

HXB2 Location gp160 (298–307)
Author Location gp120 (303–312 SF2)
Epitope RPNNNTRKSI
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 0/4 group 1, 1/3 group 2, and 1/1 group 3.

HXB2 Location gp160 (298–307)
Author Location gp120 (298–307)
Epitope RPNNNTRKSI
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes.
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

HXB2 Location gp160 (298–307)
Author Location gp120 (298–307)
Epitope RPNNNTRKSI
Epitope name B7-RI10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 4/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 1/4 individuals had detectable responses to this epitope after STI.

HXB2 Location gp160 (298–307)
Author Location gp120
Epitope RPNNNTRKSI
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A2, A3, B7, Bw6
Keywords HAART, ART
References Appay *et al.* 2002

- Four HIV patients with prolonged clinically successful anti-viral therapy but with ongoing evidence of replication and Nef mRNA transcription, showed specific T-cell responses by Elispot and Tetramer staining, maintained for 2-4 years after initiation of HAART.
- Nef epitope recognition was detected in all 4 subjects, gp120, Pol and Gag-specific in 1 or 2 subjects.
- The HIV-specific CD8+ T-cells had an intermediate maturation phenotype characterized by low levels of perforin and high levels of CD27 expression.

HXB2 Location gp160 (298–307)
Author Location gp160 (298–307)
Epitope RPNNNTRRGI
Epitope name B7-RI10 Env
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), escape, early treatment, superinfection
References Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The first infecting strain had the variant rpSnntrKSi, and the CTL response was higher to the second variant, RPNNNTRRGI.

HXB2 Location gp160 (298–307)
Author Location gp120
Epitope RPNNNTRKSI
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords HIV exposed persistently seronegative (HEPS)
References Koning *et al.* 2004

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A*11, A*31 and Cw*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
- No one pre-seroconversion, 0/9 HLA A2+ infection-resistant men, and 0/4 pre-seroconversion men who went on to become infected, reacted to this epitope.

HXB2 Location gp160 (298–307)
Author Location Env (302–311)
Epitope RPNNNTRKSI
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

CTL CD8+

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 3/7 patients recognized this epitope.

HXB2 Location gp160 (298–307)
Author Location Env
Epitope RPNNNTRKSI
Epitope name Env1146
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Epitope RPNNNTRKSI elicits IFN-gamma ELISpot responses in 2/7 subjects; and bound HLA-B7 with high affinities in soluble and cell-based assays. Previously published HLA restriction of this epitope is HLA-B7 (LANL database).

HXB2 Location gp160 (298–307)
Author Location gp120
Epitope RPNNNTRKSI
Epitope name RI10(gp120)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide sequence (NCTRPNNNTRKSITL) contains the exact sequence of a previously described HLA-B7 optimal epitope, RPNNNTRKSI, none of the 9 HLA-B7 carriers responded to it (author communication and Fig.1).

HXB2 Location gp160 (298–307)
Author Location gp120 (303–312 IIIB)
Epitope RPNNNTRKSI
Immunogen HIV-1 infection
Species (MHC) human (B7?)
Keywords responses in children, mother-to-infant transmission
References Wilson *et al.* 1996

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.
- RPNNNTRKDI and RPNNNTRKGI, naturally occurring variants, were found in non-transmitting mother – ability to recognize these variants has not yet been determined.

HXB2 Location gp160 (299–319)
Author Location Env (299–319)
Epitope PNNNTRKSIRIGPGQTFYA
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location gp160 (303–322)
Author Location gp120
Epitope TRKSIHIGPGRAFYTTGE
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *Strain:* B clade consensus *HIV component:* Gag, V3
Species (MHC) mouse
References Luo *et al.* 1998

- Intramuscular injection of chimeric gag-env virus-like particles (VLPs) containing V3 loop sequences into BALB/c mice induce V3 specific CTL – TRKSIHIGPGRAFYTTGE is a B subtype consensus that stimulated a cross-reactive CTL response.

HXB2 Location gp160 (304–318)
Author Location gp120 (304–318 IIIB)
Epitope RKSIRIQRGPGRAFV
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *Strain:* B clade IIIB, B clade MN, B clade RF, B clade SF2, HIV-2 VLP *HIV component:* Gag, V3
Species (MHC) mouse (H-2^d)
References Kang *et al.* 1999

- Virus-like particles could be formed from HIV-2 gag after deleting 143 amino acids at the C-terminal end – a proline rich region in positions 373-377 was critical to VLP formation.
- CTL responses in BALB/c mice were induced by chimeric gag-V3 particles against the V3 region of HIV-1 clade B isolates IIIB (SIRIQRGRAFVTI), MN (KRIHIGPGRAFYTTK), RF (SITKGPGRVIYATGQ), and SF2 (SIYIGPGRAFHTTGR)

- The vaccine induced CTL were cross-reactive with a broad spectrum of B clade isolates, with the exception of the RF V3 which did not induce CTL.

HXB2 Location gp160 (305–321)
Author Location gp120 (MN)
Epitope KRIHIGPGRAFYTTK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A2
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, HAART, ART
References Chitnis *et al.* 2003

- 17 perinatally HIV-1 infected children (0.08-16 years) were evaluated for HLA-A2-restricted IFN-gamma CD8+ CTL responses against 4 immunodominant peptides that carry HLA-A2 epitopes. Two peptides were from gp120 (one at position 112, one from the V3 loop), and one each was from gp41 and Gag. 15/17 patients responded to the Gag peptide, 13/17 to the gp41 and the non-V3 gp120 peptides, and 11/17 responded to the V3 loop. 4 children recognized all 4 peptides.

HXB2 Location gp160 (306–322)
Author Location gp160 (LAI)
Epitope SIRIQGPGRAFVTIGI
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160 *Adjuvant:* aluminum hydroxide, CpG immunostimulatory sequence (ISS)
Species (MHC) mouse (H-2D^{d})
Keywords immunodominance, Th1, Th2
References Deml *et al.* 1999

- Addition of CpG oligodeoxynucleotide to a gp160/alum vaccine given to BALB/c mice shifted the response to Th0/Th1 from Th2, but no still CTL response to this immunodominant epitope was induced.

HXB2 Location gp160 (307–324)
Author Location (C consensus)
Epitope IRIGPGQTFYATGDII
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*1801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location gp160 (308–321)
Author Location Env (IIIB)
Epitope RIQRGPGRAFVTIG
Epitope name P18IIIB
Subtype B
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* V3
Species (MHC) mouse (H-2D^{d})
Keywords binding affinity, Th1
References Ahlers *et al.* 2001

- BALB/c and A.AL were immunized with an Env-peptide vaccine construct containing the CTL epitope P18IIIB and the T helper epitope T1, KQIINMWQEVGKAMYA.
- Substitution of Glu (wt) to Ala in T1, kqiinmwqAvgkamya, caused increased affinity for MHC class II Ek, resulting in the upregulation of CD40L in the responding Th cells, and shifting the response towards Th1. Increased Th responses stimulated DCs to produce higher levels of IL-12, and B7-1 and B7-2, and enhanced CTL responses to P18.
- The modified epitope, T1A, elicited stronger protection against increasing doses of viral challenge with vaccinia expressing HIV-1 IIIB gp120 compared to the wt epitope T1.

HXB2 Location gp160 (308–321)
Author Location Env (gp160)
Epitope RIQRGPGRAFVTIK
Epitope name P18IIIB
Immunogen vaccine
Vector/Type: hemagglutinating virus of Japan (HVJ)-liposome *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) mouse
Donor MHC H-2d
Assay type Cytokine production, Chromium-release assay
Keywords genital and mucosal immunity
References Sakaue *et al.* 2003

- BALB/c mice were immunized nasally with HIVgp160-encapsulated hemagglutininating virus of Japan (HVJ)-liposome. Vaccination induced IgG in serum and IgA in nasal wash, saliva, fecal extract, and vaginal wash, with some ability to neutralize the primary field isolate HIV-MNp.
- Th1 and Th2-type responses were stimulated, as well as gp160 V3-specific MHC class I-restricted CTL responses.

HXB2 Location gp160 (308–322)
Author Location Env (315–329)
Epitope RIQRGPGRAFVTIGK
Epitope name P18
Subtype B
Immunogen vaccine
Vector/Type: DNA *HIV component:* HIV-1
Species (MHC) mouse (A*0201)
Keywords epitope processing, vaccine-specific epitope characteristics, immunodominance
References Singh *et al.* 2002; Sykes & Johnston 1999

- C3H (H-2k) transgenic mice carrying a fused HLA-A*0201 alpha1 and alpha2 and H-2Dk alpha3 hybrid class I molecule were immunized using an epidermal gene gun with an ubiquitin expression library of 32 plasmids that spanned the HIV-1 genome. Ubiquitin targets the expressed HIV-1 peptides to the proteasome.

CTL CD8+

- A single immunization with the UB-HIV-1 library vaccine induced potent, stable and multivalent CTL responses against all library members.
- Immunodominant epitopes SLYNTVATL (Gag), ILKEPVHGV (Pol), RIQRGPGRAFVTIGK (Env) and AFHHVAREK (Nef) elicited strong CD8+/IFN- responses and stimulated CTL that were functional in a Cr-release assay and against wild type antigen.
- The presence of multiple plasmids HLA-A*0201-restricted CTL epitopes did not decrease CTL immunogenicity, and CTL responses to single peptide immunizations were comparable to responses based on mixtures of either 16 or 32 peptides.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) human (A11)
References Achour *et al.* 1994
- One of 3 HLA type restrictions associated with this peptide.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 BRU)
Epitope RIQRGPGRAFVTIGK
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Dadaglio *et al.* 1991
- Defined through blocking CTL activity, and Env deletions.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Clerici *et al.* 1991a
- Helper and cytotoxic T cells can be stimulated by this peptide (P18)

HXB2 Location gp160 (308–322)
Author Location gp120 (308–322 IIIB)
Epitope RIQRGPGRAFVTIGK
Subtype B
Immunogen vaccine
Vector/Type: DNA, DNA with protein boost *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* IL-12
Species (MHC) mouse (A2)
Keywords vaccine-specific epitope characteristics
References Kiszka *et al.* 2002
- Transgenic mice expressing a HLA-A2/Kb chimeric protein were vaccinated with a full length gp160 or with gp160deltaV3, with the V3 loop deleted. Mice given gp160deltaV3 had a broader immune response than those given gp160, with increased responses to conserved HLA-A2 epitopes in the C1 region of gp120, KLTPLCVTL, and the C-term region of gp41, SLLNATAIAV.
- Greater resistance was conferred by the gp160deltaV3 than the gp160 vaccine to a challenge of vaccinia expressing heterologous gp160 from primary isolates (VI-06 and 89.6), and the resistance was conferred by CD8+ T-cells.
- The most intense CTL responses to the intact gp160 vaccine were directed at three V3 peptides.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* gp160
Species (MHC) human (A2, A3)
References Achour *et al.* 1993
- Two of 3 HLA type restrictions associated with this peptide.

HXB2 Location gp160 (308–322)
Author Location gp160 (308–322)
Epitope RIQRGPGRAFVTIGK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003
- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these eptiopes, but this increased over time.

HXB2 Location gp160 (308–322)
Author Location Env (308–322 B1 and B2)
Epitope RIQRGPGRAFVTIGK
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A3, A32, B62, B8, Cw3
Country Netherlands
Assay type Other
Keywords subtype comparisons, computational epitope prediction, superinfection
References Kozaczynska *et al.* 2007
- The influence of superinfection upon changes in HIV-1 strains was studied in a triple infected subject. While continuous expression of all three strains was observed, the LTR promoters of subtype AE had highest activity of all 3 strains, and subtype B2 had the lowest. Env-V3 sequences were present in higher numbers in strains B2 and CRF01_AE. Recombination was seen between viruses B1/B2 in gag and vpr genes.

- This HLA-A03 restricted epitope, RIQRGPGRAFVTIGK, varied to sIhiaPGRAFyatGe in B1, sIhmGPGkAFfTtGe in B2, and sIhmGPGqvFyrtGd in AE by the earliest time point taken, with no changes over time.

HXB2 Location gp160 (308–322)
Author Location gp120 (HXB2)
Epitope RIQRGPGRAFVTIGK
Subtype B
Immunogen vaccine
Vector/Type: protein *HIV component:* Gag, V3
Species (MHC) mouse (H-2^d)
References Griffiths *et al.* 1993

- Gag-V3 fusion protein immunization elicited V3 CTL response in mice.

HXB2 Location gp160 (308–322)
Author Location gp120 (HXB2)
Epitope RIQRGPGRAFVTIGK
Subtype B
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *HIV component:* Env, Gag
Species (MHC) mouse (H-2^d)
References Deml *et al.* 1997

- Env bound to virus-like particles (VLPs) can elicit a CTL response that is dependent on the amount of Env presented on the VLP.

HXB2 Location gp160 (308–322)
Author Location gp120 (313–327 MN)
Epitope RIHIGPGRAFYTTKN
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade MN *HIV component:* gp160, V3
Species (MHC) mouse (H-2^d)
References Fomsgaard *et al.* 1998a

- Enhanced B and CTL responses to the V3 region occur following epidermal immunization by gene gun with a chimeric DNA vaccine of V3-hepatitis B surface antigen relative to a gp160 plasmid vaccine.

HXB2 Location gp160 (308–322)
Author Location gp120 (313–327 MN)
Epitope RIHIGPGRAFYTTKN
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade MN *HIV component:* V3 *Adjuvant:* GM-CSF, IL-12
Species (MHC) mouse (H-2^d)
Keywords Th1
References Ahlers *et al.* 1996; Ahlers *et al.* 1997a

- Vaccine constructs containing helper, antibody and CTL peptide epitopes induce strong Th1, CTL and NAb responses against the autologous HIV-1 virus.
- The peptide CTL response was as cross-reactive as one elicited by a vaccinia construct expressing rgp160 MN.
- GM-CSF and IL-12 were the two cytokines most effective for inducing and boosting CTLs.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *Strain:* B clade IIIB *HIV component:* Gag, V3
Species (MHC) mouse (H-2^d)
References Layton *et al.* 1993

- V3-Ty-Virus-like particles can induce type-specific CTL in mice in the absence of adjuvant.

HXB2 Location gp160 (308–322)
Author Location gp120 (IIIB)
Epitope RIQRGPGRAFVTIGK
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* gp120 *Adjuvant:* IL-2, IL-2/Ig
Species (MHC) mouse (H-2^d)
References Barouch *et al.* 1998

- A discistronic IL-2 gp120 expression vector gave a weaker CTL response than gp120 alone in the expression vector, however co-administration of an Il-2/IgG fusion protein enhanced the immune response and administration of a Il-2/IgG plasmid had a response that depended on the timing of administration.
- This study showed that a response to an HIV-1 DNA vaccine could be either augmented or suppressed by plasmid Cytokine/Ig administration.

HXB2 Location gp160 (308–322)
Author Location Env (308–322 IIIB)
Epitope RIQRGPGRAFVTIGK
Epitope name P18
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* V3 *Adjuvant:* B7, CpG immunostimulatory sequence (ISS), in vivo electroporation
Species (MHC) mouse (H-2^d)
Keywords Th1
References Uno-Furuta *et al.* 2001

- Peptide immunization usually doesn't elicit a good CTL response because epitopes are not internalized and processed and presented, so vaccination with electric pulsing was tried (i.m. injection followed by 8 electric pulses), to enhance peptide uptake through electroporation.
- BALB/c immunized with HIV P18 or hepatitis C P17 peptides with an electric pulse elicited a CTL response, those that did not receive the pulse did not.
- The CTL response was enhanced by addition of immunostimulatory sequences ISS in the plasmid pCMV-LacZ, that contains hexamers GACGTC, AGCGCT, AACGCT, sequences common in prokaryotic genomes but rare in eukaryotic genomes that elicit Th1 cytokines and result in B cell and T-cell proliferation.
- The CTL response was also enhanced by addition of B7-1 cDNA – the B7 family of proteins transduce co-stimulatory signals through interaction with CD28.

HXB2 Location gp160 (308–322)
Author Location gp160 (MN)
Epitope RIHIGPGRAFYTTKN
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade MN *HIV component:* gp160
Species (MHC) mouse (H-2^b, H-2^d)
References Fomsgaard *et al.* 1998b

- CTL responses to a primary gene gun vaccination were rapid and strong for several methods of vaccinations: i.m., bupivacaine pretreatment, cardiotoxin pretreatment or gene gun – the CTL response was more rapid and consistent than the antibody response.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^d, H-2^p, H-2^q, H-2^u)
References Shirai *et al.* 1992; Shirai *et al.* 1993

- In a murine system multiple class I molecules can present this peptide, called P18, to CTL, including H-2D^d, H-2D^p, H-2D^q, H-2L^q
- The MHC class I molecule D^d as well as H-2^{u,p,q}, were found to present peptides P18 and HP53.
- The V-β usage in T cells showing cross-reaction between these two peptides was conserved for H-2^{d,u,p}, but not in H-2^q

HXB2 Location gp160 (308–322)
Author Location gp160 (IIIB)
Epitope GIHIGPGRAFYAARK
Immunogen vaccine
Vector/Type: peptide, protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse (H-2D^d)
Keywords Th1, Th2
References Morris *et al.* 2000

- LT(R192G) induces gp160-specific serum and mucosal IgG1 and IgG2a, systemic CTL activity and Th1 and Th2 cytokine responses upon internasal immunization.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* V3 *Adjuvant:* Cholera toxin (CT)
Species (MHC) mouse (H-2D^d)
References Porgador *et al.* 1997

- A intranasal peptide vaccine with cholera toxin as a mucosal adjuvant was given.
- IIIB peptide referred to as R15K.
- Peptide-specific CTLs were induced after *in vitro* restimulation with peptide-pulsed targets.
- R15K was superior at inducing CTL compared to the RGPGRAFVTI, in contrast to the findings of Nehete *et al.*
- Memory CTL responses were induced.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Immunogen vaccine
Vector/Type: vaccinia with H1 influenza HA gene cassette *Strain:* B clade IIIB *HIV component:* p18 Gag
Species (MHC) (H-2D^d)
References Chiba *et al.* 1999

- Vaccine was capable of priming P18IIIB specific CTL in BALB/c mice, but could not induce a P18IIIB-specific antibody response.

HXB2 Location gp160 (308–322)
Author Location gp120 (multiple)
Epitope RIHIGPGRAFYTTKN
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade MN, B clade SC *HIV component:* V3
Species (MHC) mouse (H-2D^d)
References Casement *et al.* 1995

- V3 peptides from MN and SC induce murine CTL that are cross-reactive with diverse strains.

HXB2 Location gp160 (308–322)
Author Location gp120 (313–327 MN)
Epitope RIHIGPGRAFYTTKN
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN *HIV component:* gp120 *Adjuvant:* QS21
Species (MHC) mouse (H-2D^d)
References Newman *et al.* 1997

- MN vaccine induced CTL reactive with MN, IIIB and RF vaccinia-expressed Env, but not this peptide.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp120 *Adjuvant:* QS21
Species (MHC) mouse (H-2D^d)
References Newman *et al.* 1997

- IIIB vaccine induced IIIB type-specific CTL to this peptide (P18), and an additional Env CTL response that was cross-reactive.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329)
Epitope RIQRGPGRAFVTIGK
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2D^d)
References Takahashi *et al.* 1988

- V3 loop CTL response in mice vaccinated with gp160.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* V3
Species (MHC) mouse (H-2D^{d})
References Takahashi *et al.* 1989a

- Positions R(8) and F(10) are important for MHC/peptide interaction.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* V3
Species (MHC) mouse (H-2D^{d})
References Sastry *et al.* 1992

- Free peptide injected into the footpad of a mouse could stimulate specific CTL.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade MN *HIV component:* V3
Species (MHC) mouse (H-2D^{d})
References Ahlers *et al.* 1997b

- PCLUS 3-18MN synthetic peptide vaccine construct contained T1 helper epitope covalently linked to truncated P18 CTL epitope.
- A substitution in the T1 peptide stimulated an enhanced Th response and class II binding specificity, which in turn enhanced CTL induction by vaccine.
- Construct PCLUS 3-18MN is currently in a phase I vaccine clinical trial.

HXB2 Location gp160 (308–322)
Author Location gp120 (313–327 MN)
Epitope RIHIGPGRAFYTTKN
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB, B clade MN *HIV component:* gp160
Species (MHC) mouse (H-2D^{d})
References Takahashi *et al.* 1989b

- Y(11 MN) exchange with V(11 IIIB) interchanges specificities.

HXB2 Location gp160 (308–322)
Author Location gp120 (313–327 IIIB, MN, RF)
Epitope SITKGPGRVIYATGQ
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade RF *HIV component:* gp160
Species (MHC) mouse (H-2D^{d})
References Takahashi *et al.* 1992

- Comparison of MN, IIIB, and RF specificities, position 11 is critical.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329)
Epitope RIQRGPGRAFVTIGK
Immunogen vaccine
Vector/Type: liposome *Strain:* B clade IIIB *HIV component:* V3 *Adjuvant:* oligomannose
Species (MHC) mouse (H-2D^{d})
References Fukasawa *et al.* 1998

- The peptide RIQRGPGRAFVTIGK was incorporated into liposomes and given as a subcutaneous injection, which induces a MHC class I restricted CTL response in mice.
- Liposomes coated with oligomannose show no toxicity and can elicit a potent CTL response upon a single subcutaneous infection, while non-coated liposomes do not, suggesting that oligomannose may be a good adjuvant for CTL responses.

HXB2 Location gp160 (308–322)
Author Location
Epitope RIQRGPGRAFVTIGK
Epitope name P18
Subtype B
Immunogen vaccine
Vector/Type: fusion protein with anthrax delivery domain *HIV component:* V3 *Adjuvant:* B. anthracia lethal toxin LF component
Species (MHC) mouse (H-2D^{d})
Keywords epitope processing, vaccine-specific epitope characteristics
References Lu *et al.* 2000a

- Bacillus anthrax lethal toxin (LFn)-HIV fusion proteins are candidate HIV vaccines that are safe in mice, and LFn-V3 region fusion proteins induce CD8 T cells in BALBc mice. LFn causes exogenous protein to be taken up and processed in a class I pathway. Expressed proteins from Gag p24 and nef fragments cloned into the LFn expression plasmid stimulate gag-specific CD4 proliferation and CTL responses in HIV-infected donor PBMCs *in vitro*.

HXB2 Location gp160 (308–322)
Author Location gp120 (V3) (MN)
Epitope RIHIGPGRAFYTTKN
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* V3 *Adjuvant:* Cholera toxin (CT), GM-CSF, IL-12, IL-18, IL-1α
Species (MHC) mouse (H-2D^{d})
References Staats *et al.* 2001

- Cholera toxin (CT) is a potent adjuvant used in animal studies that is not safe in humans, so combinations of cytokins were used in nasal immunization of BALB/c mice V3 peptides to attempt to replace CT as a potent adjuvant.
- Peptide vaccine induced CTL activity was significantly increased by IL-1alpha , IL-18, and GMCSF given alone as adjuvant, but CT gave more potent CTL activity than any single cytokine.
- Combinations of cytokins could be more potent that CT as an adjuvant. The highest tetramer binding of H-2Dd peptide-specific PBMC after nasal immunization was observed with IL-1alpha plus IL-18 as adjuvant.

CTL CD8+

- Nasal immunization with HIV peptide in the presence of IL-1alpha, IL-12 and GM- CSF induced IFN-gamma-secreting cells in the cervical lymph node, the lung and the spleen, and was associated with upregulation of MHC class II and B7.1 on nonlymphocytes in NALT/nasal mucosal cells.
- Consistent results were obtained for the IIIB and the MN peptides.

HXB2 Location gp160 (308–322)
Author Location gp160 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Epitope name P18
Immunogen in vitro stimulation or selection
Species (MHC) mouse (H-2D^{d})
Donor MHC H-2d
Keywords TCR usage
References Yokosuka *et al.* 2002

- The TCR repertoire and its specificity was studied through analyzing the spectrum of TCR-alpha and beta chains able to reconstitute a reaction to the H-2 Dd-restricted P18 peptide. The RT-1 TCR alpha chain was able to react with 1/3 of the tested TCR beta chains to create a specific response. Experiments in transgenic mice also supported the observation that a single TCR alpha chain would confer the specificity of the response and could interact with a large variety of TCR beta chains.

HXB2 Location gp160 (308–322)
Author Location gp160 (315–329 MN)
Epitope RIHIGPGRAFYTTKN
Epitope name P18
Immunogen in vitro stimulation or selection
Species (MHC) mouse (H-2D^{d})
Donor MHC H-2d
Keywords TCR usage
References Yokosuka *et al.* 2002

- The TCR repertoire and its specificity was studied through analyzing the spectrum of TCR-alpha and beta chains able to reconstitute a reaction to the H-2 Dd-restricted P18 peptide. The RT-1 TCR alpha chain was able to react with 1/3 of the tested TCR beta chains to create a specific response. Experiments in transgenic mice also supported the observation that a single TCR alpha chain would confer the specificity of the response and could interact with a large variety of TCR beta chains.

HXB2 Location gp160 (308–322)
Author Location Env (IIIB)
Epitope RIQRGPGRAFVTIGK
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp120 *Adjuvant:* poly(I:C), lipopolysaccharide (LPS)
Species (MHC) mouse (H-2D^{d})
Assay type Chromium-release assay
Keywords epitope processing, vaccine-induced epitopes, Th1, Th2, immunotherapy, adjuvant comparison
References Fujimoto *et al.* 2004

- When BALB/c mice were immunized with recombinant HIV-1 Env gp120 or Influenza HA protein together with polyriboinosinic polyribocytidylic acid (poly (I:C)), an epitope-specific CD8+ class I MHC-restricted CTL response was observed. This response was not observed when LPS was used as adjuvant instead of poly (I:C) indicating activation of cellular immunity by poly (I:C). In the presence of poly (I:C), immature DC presented processed external antigen in association with class I MHC.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* gp160
Species (MHC) mouse (H-2^{u}, H-2D^{d}, H-2D^{p}, H-2D^{q})
References Shirai *et al.* 1996b

- Multiple murine MHC can cross-present this epitope (P18) and HP53, DRVIEVVQGAYRAIR, to specific CTL.

HXB2 Location gp160 (308–322)
Author Location gp160 (MN)
Epitope RIHIGPGRAFYTTKN
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade MN *HIV component:* V3 *Adjuvant:* Montanide (ISA 51)
Species (MHC) human
References Pinto *et al.* 1999

- Peptide P18: Eight HIV+ individuals were vaccinated with peptides containing specific T helper, CTL and Ab epitopes in Montanide ISA 51 in a Phase I trial.
- Four displayed a 4-fold increase in PCLUS 3-18 MN-specific T helper responses.
- One patient developed a new, sustained P18MN-peptide-specific CTL response – the patient's HLA haplotype was A2,30; B53,7; Cw2,4, and anti-HLA A2 antibody did not inhibit the response, suggesting it was not A2.
- Patients with low baseline Ab levels developed an increase of neutralizing Ab titers.
- No significant change was observed in plasma HIV viral loads and CD4 cell counts.

HXB2 Location gp160 (308–322)
Author Location gp120 (MN)
Epitope RIHIGPGRAFYTTKN
Immunogen HIV-1 infection
Species (MHC) chimpanzee
References Lubeck *et al.* 1997

- Epitope-specific CTL detected in chimpanzees immunized with adenovirus-HIV-1 MN gp160 recombinant.
- CTL response may account for protection against subsequent HIV-1 SF2 challenge in a chimpanzee lacking neutralizing antibodies.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Immunogen HIV-1 exposed seronegative

Species (MHC) human
References Pinto *et al.* 1995
- CTL and T helper cell reactivity in healthcare workers exposed to HIV.

HXB2 Location gp160 (308–322)
Author Location gp120 (313–327 MN)
Epitope RIHIGPGRAFYTTKN
Immunogen HIV-1 exposed seronegative
Species (MHC) human
References Pinto *et al.* 1995
- CTL and T helper cell reactivity in healthcare workers exposed to HIV.

HXB2 Location gp160 (308–322)
Author Location gp120 (110–122)
Epitope RIQRGPGRAFVTIGK
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *Adjuvant:* FLt3 ligand (FL), GM-CSF, IL-12, IL-15, IL-2
Species (MHC) mouse
Keywords vaccine-specific epitope characteristics
References Moore *et al.* 2002a
- Intramuscular immunization of BALB/c mice with DNA vaccines carrying either gp160 or Nef in the expression vector plasmid pNGVL gave different responses – gp160 induced strong gp160-specific CTL and IFN-responses and low-titer humoral responses, and Nef generated humoral (IgG1, IgG2a) responses and IFN-responses but little CTL activity.
- Co-injection of DNA plasmids encoding cytokines and/or hematopoietic growth factors, IL2, IL-12, IL-15, Flt3 ligand (FL), and GMCSF tended to give responses that were enhanced quantitatively, but not altered qualitatively.
- Co-administration of GMCSF most strongly enhanced CTL and IFN-responses against pNGVL-gp160.
- Repeated immunization with pNGVL-Nef failed to induce CTL responses. Co-administration of IL-12 most strongly enhanced humoral and IFNgamma responses.
- FL, which enhances innate immune responses, in combination with IL-2, IL-12 or IL-15 generated with most potent Nef responses.

HXB2 Location gp160 (308–322)
Author Location gp140 (iiib)
Epitope RIQRGPGRAFTIGK
Subtype B
Immunogen vaccine
Vector/Type: liposome, protein *Strain:* B clade IIIB *HIV component:* oligomeric gp140 *Adjuvant:* liposome
Species (MHC) mouse
Donor MHC H-2d
Assay type proliferation, Chromium-release assay
Keywords adjuvant comparison
References Richards *et al.* 2004
- Mice were immunized with gp140 and an adjuvant that was an oil-in -water emulsion containing liposomes with lipid A with encapsulated antigen. Stable and unstable emulsions were found to have similar potencies of inducing antigen-specific T-cell proliferation and IgG antibodies, but stable emulsions also induced antigen-specific CTL responses. Stable emulsions had lowered IgG2a/IgG1 ratios than unstable.

HXB2 Location gp160 (309–317)
Author Location gp120 (310–318 SF2)
Epitope IYIGPGRAF
Epitope name Env310-9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Country Japan
References Ikeda-Moore *et al.* 1997
- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402.
- This peptide induced CTL in 1/4 HIV-1 + people tested.
- IYIGPGRAF bound to A*2402 strongly, the epitope can be processed in a vaccinia construct and presented – no specific CTL clones were obtained.

HXB2 Location gp160 (309–318)
Author Location gp120 (314–323 CM243 subtype CRF01)
Epitope ITVGPGQVFY
Epitope name E309-318
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords HIV exposed persistently seronegative (HEPS)
References Sriwanthana *et al.* 2001
- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was strongly reactive in HIV+ control study subject 184 who carried HLA-A11.

HXB2 Location gp160 (309–318)
Author Location gp120 (314–323 CM243 subtype CRF01)
Epitope ITVGPGQVFY
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords subtype comparisons
References Bond *et al.* 2001
- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.

CTL CD8+

- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This is one of the new A11 epitopes identified through the streamlined EpiMatrix method, and 2/8 tested FSWs recognized it.
- This epitope was not conserved in other subtypes, and exact matches were rare.

HXB2 Location gp160 (310–318)
Author Location
Epitope HIGPGRAFY
Epitope name Env-HY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Donor MHC A*3002, A*3201, B*4501, B*5301, Cw*0401, Cw*1202
Keywords HAART, ART
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- This epitope was newly defined in this study.
- Subject 00RCH33 was on HAART had a viral load of 2900 and CD4 count of 727 and also recognized the epitopes YPLTFGWCY, Nef(135-143), HLA B*5301; AETFYVDGA, RT(437-445), HLA B*4501; and RSLYNTVATLY, p17(76-86), HLA A*3002.
- Among HIV+ individuals who carried HLA A30, 3/16 (19%) recognized this epitope.

HXB2 Location gp160 (310–318)
Author Location gp120 (310–318)
Epitope HIGPGRAFY
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location gp160 (310–318)
Author Location
Epitope HIGPGRAFY
Epitope name Env-HY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A02, 6/29 (21%) recognized this epitope.

HXB2 Location gp160 (310–318)
Author Location gp120
Epitope HIGPGRAFY
Epitope name HY9(gp120)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A30)
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords non-susceptible form
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- The tested peptide sequence, ItlGPGRvwYTTGQII, contains a variant, tlGPGRvwY that differs by 4 substitutions from the previously described HLA-A30 epitope HIGPGRAFY. None of the 15 HLA-A30 carriers responded to the variant tlGPGRvwY.

HXB2 Location gp160 (310–318)
Author Location gp160 (313–321 WEAU)
Epitope TLGPGRVLY
Epitope name gp160 TY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*2902, B*0801, B*4403
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, immunodominance, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.
- This was one of five reasonably strong responses in early infection in the patient WEAU, and the epitope sequence did not vary during the first year of the infection.

HXB2 Location gp160 (310–323)

Author Location gp120 (315–328 MN)
Epitope HIGPGRAFYTTKNI
Epitope name p97
Immunogen vaccine
Vector/Type: canarypox prime with pseudovirion boost *Strain:* B clade IIIB, B clade MN *HIV component:* Gag, gp120, Protease
Species (MHC) mouse (H-2D^d)
References Arp *et al.* 1999

- The vaccine vCP205, canarypox vector, MN gp120 + Gag/Pro IIIB, with a HIV-1 pseudovirion boost was given to mice;)
- HIV-1 pseudovirion boost enhanced the CTL to this epitope in immunized BALB/ c mice as measured by CTL lysis and IFN gamma production.

HXB2 Location gp160 (311–318)
Author Location (MN)
Epitope IGPGRAFY
Immunogen vaccine
Vector/Type: B. abortus complex *Strain:* B clade MN *HIV component:* V3
Species (MHC) mouse (H-2D^d)
References Golding *et al.* 2002a

- Intranasal immunization of B. abortus conjugated to V3 peptides induces mucosal IFN-gamma producing T-cell responses in BALB/c mice.

HXB2 Location gp160 (311–319)
Author Location gp120 (311–320 IIIB)
Epitope RGPGRAFVT
Subtype B
Immunogen vaccine
Vector/Type: DNA, DNA with protein boost *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* IL-12
Species (MHC) mouse (A2)
Keywords vaccine-specific epitope characteristics
References Kiszka *et al.* 2002

- Transgenic mice expressing a HLA-A2/Kb chimeric protein were vaccinated with a full length gp160 or with gp160deltaV3, with the V3 loop deleted. Mice given gp160deltaV3 had a broader immune response than those given gp160, with increased responses to conserved HLA-A2 epitopes in the C1 region of gp120, KLTPLCVTL, and the C-term region of gp41, SLLNATAIAV.
- Greater resistance was conferred by the gp160deltaV3 than the gp160 vaccine to a challenge of vaccinia expressing heterologous gp160 from primary isolates (VI-06 and 89.6), and the resistance was conferred by CD8+ T-cells.
- The most intense CTL responses to the intact gp160 vaccine were directed at three V3 peptides.

HXB2 Location gp160 (311–319)
Author Location gp120 (312–320 H-2D^d)
Epitope IGPGRAFHT
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade SF2 *HIV component:* gp120
Species (MHC) mouse (D^d)
References Selby *et al.* 1997

- Murine CTL response to peptide observed after immunization with DNA plasmid containing HIV-1 (SF2) gp120 gene regulated by bacteriophage T7 promoter.
- CTL response required coadministration of rec vaccinia virus expressing T7 RNA polymerase or T7 RNA polymerase soluble protein.

HXB2 Location gp160 (311–319)
Author Location gp120 (SF2)
Epitope IGPGRAFHT
Immunogen vaccine
Vector/Type: DNA prime with gp120 boost *Strain:* B clade SF2 *HIV component:* gp120
Species (MHC) mouse (H-2D^d)
References Barnett *et al.* 1997

- CTL were induced by vaccine, and restimulated *in vitro* with V3 peptide.
- DNA vaccine with protein boost stimulated both CTL and antibodies.
- Strains SF2 (IGPGRAFHT), US4 (IGPGRAFYA), and CM235 (IGPGQVFYR) were tested.

HXB2 Location gp160 (311–319)
Author Location gp120 (312–320 SF2)
Epitope IGPGRAFHT
Subtype B
Immunogen vaccine
Vector/Type: DNA, vaccinia *Strain:* B clade SF2 *HIV component:* Gag, gp120
Species (MHC) mouse (H-2D^d)
Assay type Chromium-release assay
Keywords epitope processing, vaccine-induced epitopes
References Doe *et al.* 1996

- Spleen cells from mice with distinct MHC types were infused into HIV vaccinated scid mice, to study the antigen presenting cells used by CTL induced in intramuscular injections. Bone marrow derived cells are used for presenation, but DNA infection is not required for priming, rather APCs can present proteins synthesized in other host cells.

HXB2 Location gp160 (311–319)
Author Location
Epitope IFPFRAFYA
Subtype B
Immunogen vaccine
Vector/Type: modified vaccinia Ankara (MVA) *Strain:* B clade 89.6 *HIV component:* Env
Species (MHC) human
Assay type Intracellular cytokine staining, Chromium-release assay, Other
Keywords vaccine antigen design
References Wyatt *et al.* 2008a

CTL CD8+

- While propagating MVA encoding HIV 89.6 Env, excessively staining foci were studied and found to possess a single nucleotide deletion that conferred upon Env a 115 aa C-terminal truncation. Truncated Env was more highly expressed and so induced higher antibody and CTL responses without compromising its ability for CD4/co-receptor fusion. A similar truncation would be beneficial in MVA-based vaccines.
- To test for CTL response to Env epitopes, peptide P18-89.6A9, IFPFRAFYA , was used as stimulating peptide in Chromium release assays where wild type MVA/89.6 and truncated MVA/89.6T induced similar specific lytic activities. Intracellular staining also showed similar induction of IFN-gamma+; IFN-gamma+, TNF+; and IFN-gamma+, IL-2+ CTLs by both forms of the virus.

HXB2 Location gp160 (311–320)
Author Location Env (311–320)
Epitope RGPGRAFYTT
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

HXB2 Location gp160 (311–320)
Author Location gp160 (318–327 IIIB)
Epitope RGPGRAFVTI
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
References Alexander-Miller *et al.* 1996

- This epitope stimulates a CTL line derived from an HIV negative donor.
- This immunogenic peptide does not have the known binding motif for A2.1.
- The same optimal peptide for this human HLA-A2.1 epitope was observed for a murine H-2 D^d epitope.

HXB2 Location gp160 (311–320)
Author Location gp120 (311–320 IIIB)
Epitope RGPGRAFVTI
Immunogen
Species (MHC) human (A*0201)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*0201 epitope.

HXB2 Location gp160 (311–320)
Author Location gp160 (318–327 IIIB)
Epitope RGPGRAFVTI
Epitope name LR25
Subtype B
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade LAI *Adjuvant:* Incomplete Freund's Adjuvant (IFA), Montanide (ISA 720), P30, PLG
Species (MHC) mouse (A*0201)
Keywords binding affinity, vaccine-specific epitope characteristics, immunodominance
References Peter *et al.* 2001

- The stability of peptide binding to HLA-A2.1 was determined for six HLA-A2.1 peptides included in this vaccine study – ILKEPVHGV (RT), SLYNTVATL (p17), SLLNATDIAV (gp41) and LLWKGEGAV (RT) all bound with high affinity comparable to a influenza epitope reference (GILGFVFTL), while RGPGRAFVTI and VIYQYMDDL bound with a lower affinity (relative binding activity = 0.01).
- The four high-affinity peptides formed stable complexes with half-lives ranging between 8 and 32 hours, while the low affinity peptides had half lives of less than an hour.
- HLA-A2.1 transgenic mice were immunized with the six HIV-1 peptides and P30, as a universal T-helper epitope, with IFA or Montanide or microspheres as adjuvants.
- All peptides except VIYQYMDDL induced a stong CTL response in Cr-release assays - stronger responses were observed when peptides were delivered alone, indicating immunodominance when the combination was used.

HXB2 Location gp160 (311–320)
Author Location gp160 (318–327 IIIB)
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) human (A2)
References Achour *et al.* 1996

- Individual was immunized with rec vaccinia gp160 IIIB and boosted with purified gp160.
- Lysis only occurs with IIIB P18 peptide pulsed onto autologous targets; MN, RF, SIMI P18 peptides fail to stimulate CTL.
- Restimulating immune cells from gp160 IIIB vaccinees with MN, RF, or SIMI P18 did not enhance the MN, RF, or SIMI specific CTL response.

HXB2 Location gp160 (311–320)
Author Location gp160 (318–327 SIMI)
Epitope MGPKRAFYAT
Immunogen vaccine
Vector/Type: vaccinia prime with gp160 boost *Strain:* B clade SIMI *HIV component:* gp160

Species (MHC) human (A2)
References Achour *et al.* 1996

- Individual was immunized with rec vaccinia gp160 SIMI and boosted with purified recombinant gp160 SIMI.
- P18 MN and RF peptides were able to stimulate the HIV-specific CTL that arose in response to the SIMI vaccination, thus the P18 MN peptide (IGPGRAFYTT) and the P18 RF peptide (KGPGRVIYAT) could cross-react.
- The P18 IIIB peptide does not cross-react (RGPGRAFVTI in the epitope region)
- gp160 SIMI primed immune cells could generate a significantly broader specificity when stimulated with P18 MN or P18RF peptides, but not P18 IIIB.

HXB2 Location gp160 (311–320)
Author Location gp120 (311–320)
Epitope RGPGRAFVTI
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.

HXB2 Location gp160 (311–320)
Author Location gp160 (311–320)
Epitope RGPGRAFVTI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords acute/early infection, optimal epitope
References Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was recognized both in acute and chronic infection, but slightly more frequently in chronic infection.

HXB2 Location gp160 (311–320)
Author Location gp120
Epitope RGPGRAFVTI
Epitope name A2-RI10(gp120)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location gp160 (311–320)
Author Location gp160
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: vaccinia
Species (MHC) mouse (H-2^{d17})
References Hanke *et al.* 1998a

- MVA is an attenuated vaccinia that can not replicate in mammalian cells – strings of CTL epitopes were delivered and expressed in a MVA DNA vector.
- INFγ and CTL activity were induced after a single vaccination.
- An MVA boost enhanced the response.

HXB2 Location gp160 (311–320)
Author Location gp160
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: DNA, vaccinia *HIV component:* Env *Adjuvant:* IL-12
Species (MHC) mouse (H-2^{d})
References Gherardi *et al.* 2000

- Induction of HIV-1 specific CD8 gamma IFN secreting cells was enhanced when IL-12 and Env were given together in a prime, followed by a VV expressing Env boost.
- If IL-12 was also delivered as a boost from the viral vector, impairment of the IL-12 effects was noted, indicating that the vaccination schedule can be a critical parameter for success with DNA and vaccinia vectors used in combination with immunomodulators.
- The negative effect observed when IL-12 was delivered with the boost involved nitric oxide.

HXB2 Location gp160 (311–320)
Author Location Env
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* gp160, Rev *Adjuvant:* IL-12, IL-15, IL-2
Species (MHC) mouse (H-2^{d})
Keywords Th1
References Xin *et al.* 1999

CTL CD8+

- A study of the DNA vaccine pCMV160IIIB/REV with IL-15 and IL-2 or IL-12 expression plasmids.
- Intranasal immunization of BALB/c mice with HIV DNA and IL-15 plasmid induced increased Th1 and CTL responses.
- Co-administration of IL-15 with IL-12 or IL-2 plasmids did not alter the effect of IL-15.
- Both the CTL (peptide pulsed targets) and DTH response (injection of peptide into footpad) to this peptide was monitored.
- The Ab response to NNTRKSIRIQRGPGRAFVTIGKIGN was monitored, and IL-15 co-administration resulted in a decrease in the IgG1/IgG2a ratio.

HXB2 Location gp160 (311–320)
Author Location Env
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: vaccinia, Sindbis *HIV component:* V3
Species (MHC) mouse (H-2^d)
References Villacres & Bergmann 1999

- HIV-1 epitope p18 was expressed in two different vaccine vectors and the CTL response was compared in BALB/c mice.
- Class I tetramer staining showed that up to 13% of the CD8+ splenocytes were p18 specific in the acute response using vaccinia, only 4% using Sindbis.
- vp18 had more gamma IFN secreting splenocytes and activated CD4+ and CD8+ T cells.
- The overall decline in CD8+ T cells in the transition into memory was 2-3 fold for both vectors.
- Sindbis virus recombinants induced protective memory cytotoxic T cells, although reduced quantitatively, without vaccinia associated inflamation and replication.

HXB2 Location gp160 (311–320)
Author Location Env (318–327)
Epitope RGPGRAFVTI
Immunogen
Species (MHC) mouse (H-2^d)
Keywords epitope processing, immunodominance
References Lopez *et al.* 2000

- A series of protease and proteasome inhibitors was used to identify elements of the processing pathway of this epitope, called p18, both from within Env and from within a chimeric hepatitis B protein which allows proper processing.
- Lactacystin, a proteasome inhibitor, partially inhibits endogenous processing of p18 epitope suggesting both a proteasome pathway and an additional pathway can be used.
- Both TAP dependent and TAP-independent pathways can be used.
- 1,10-phenanthrolin (metallopeptidases inhibitor) blocks epitope presentation demonstrating metalloproteinase processing in the Tap-dependent pathway.
- The Tap-independent pathway does not involve processing by metalloproteinases.
- This epitope is immunodominant in mice, and is presented by multiple human HLA alleles – it as been suggested that the high processing efficiency of this epitope might result in poor presentation of co-expressed epitopes.

HXB2 Location gp160 (311–320)
Author Location gp120
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: vaccinia
Species (MHC) mouse (H-2^d)
References Hanke *et al.* 1998a; Hanke *et al.* 1998b

- This murine epitope was incorporated into a vaccine of CTL epitopes expressed together including 20 HIV epitopes recognized by humans from 12 HLA types, one murine HIV epitope and three macaque HIV epitopes, delivered in a vaccinia virus Ankara (VVA) construct.
- The murine vaccination was more effective at generating CTL when given i.v. rather than i.m.

HXB2 Location gp160 (311–320)
Author Location gp160 (318–327 IIIB)
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: peptide *HIV component:* CD4BS, HPG30, V3 *Adjuvant:* IL-12
Species (MHC) mouse (H-2^d)
References Hamajima *et al.* 1997

- B cell epitope HGP-30 also serves as a CTL epitope.
- Vaccine combined HGP-30, V3 loop peptide variants, and CD4 binding site peptide.
- IL-12 expression plasmid included with the vaccination enhanced the CTL response.

HXB2 Location gp160 (311–320)
Author Location gp160 (318–327 IIIB)
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^d)
Keywords Th1, Th2
References Arai *et al.* 2000

- Low-dosage 8 Br-cAMP given in combination with a DNA vaccine to BALB/c mice increased IgG and sIgA levels, and enhanced Th1, Th2 and CTL activity – the adjuvant activity may be mediated by activation of the CMV promotor in the DNA vaccine.

HXB2 Location gp160 (311–320)
Author Location gp120 (318–327 IIIB)
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: fusion protein with anthrax delivery domain *HIV component:* gp120
Species (MHC) mouse (H-2^d)
References Goletz *et al.* 1997

- Anthrax lethal toxin can deliver proteins to the cytosol of eukaryotic cells.
- A fusion protein linking the delivery domain of the anthrax protein to gp120 achieved cellular uptake, and gp120 was processed allowing presentation of this V3 epitope to CTL *in vitro*.

HXB2 Location gp160 (311–320)
Author Location gp160 (318–327 IIIB)

Epitope RGPGRAFVTI
Epitope name I-10
Immunogen in vitro stimulation or selection
Species (MHC) mouse (H-2^d)
References Takahashi *et al.* 2001

- Pre-incubation of HIV-1 (IIIB) gp160 specific CTL with peptide without APCs reduced cytolytic activity 3.5 fold and induced peptide concentration dependent IL-2 unresponsiveness that might be due to IL-2Rbeta down regulation.
- An enhanced cytolytic activity was observed by addition of anti-IFN-gamma, TNF-alpha or MIP-1beta to I-10 suppressed CTLs.

HXB2 Location gp160 (311–320)
Author Location gp160 (IIIB)
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^d)
Keywords Th1, Th2
References Shirai *et al.* 2001

- Helicobacter pylori induces Th1 responses early, but predominantly Th2 responses later in infection (at 6 weeks) – differentiation of HIV-1 gp160 CD4+ help and CD8+ CTL effector cells in response to HIV gp160-vaccinia vaccination is impaired in BALB/c mice infected with H. pylori.

HXB2 Location gp160 (311–320)
Author Location gp120 (V3) (IIIB)
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: influenza *Strain:* B clade IIIB *HIV component:* V3
Species (MHC) mouse (H-2^d)
Assay type Intracellular cytokine staining, Chromium-release assay
Keywords genital and mucosal immunity, memory cells, vaccine antigen design
References Garulli *et al.* 2004

- BALB/c mice were transiently infected vaginally with a recombinant influenza virus expressing an HIV CTL V3 epitope. Infection was promoted by prior progesterone treatment. This vaccination induced long-term cellular T-cell responses in mice. Responses were induced at both local mucosal and systemic sites against both influenza and V3 epitopes. Intranasal vaccination also resulted in T-cell responses in distant mucosal tissues.

HXB2 Location gp160 (311–320)
Author Location gp120 (318–327 IIIB)
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^d, H-2^p, H-2^u)
References Shirai *et al.* 1997

- Three class I MHC, H-$2^{d,p,u}$, that differ in sequence and serology, cross-present this peptide to T cells of each of the other haplotypes.
- The amino acids R, F, and I are each critical for strong CTL activity with all three MHC molecules.

HXB2 Location gp160 (311–320)
Author Location
Epitope RGPGRAFVTI
Subtype C
Immunogen vaccine
Vector/Type: DNA, DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* C clade Du422, C clade Du151 *HIV component:* Gag, gp160 deletions, Nef, RT, Tat
Species (MHC) mouse (H-2^{kd})
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, Th1
References Shephard *et al.* 2008

- A DNA (SAAVI DNA-C) and MVA (SAAVI MVA-C) vaccines vaccines were tested in BALB/c mice. Combining the vaccines in a DNA prime and MVA boost regimen increased the cumulative peptide response compared to the DNA vaccine alone 10-fold.
- Th1 cytokine IFN-γ and TNF-α levels from HIV-specific CD8 and CD4 T cells increased 20- and 8- fold respectively, with a SAAVI MVA-C boost.
- Effector and effector memory RT- and Env-epsific memory CD8 T cell subsets were boosted after MVA immunizations.
- CD8 epitope RGPGRAFVTI was used for detection of IFN-γ-secreting cells.

HXB2 Location gp160 (311–320)
Author Location Env (89.6)
Epitope IGPGRARYAR
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade 89.6 *HIV component:* gp160
Species (MHC) mouse (H-2D)
References Belyakov *et al.* 1998b

- Recombinant modified vaccinia virus Ankara (MVA), an attenuated vaccina which has lost the ability to replicate in mammalian cells, was used as the live vector for this vaccine study.
- A single intrarectal mucosal immunization resulted in long lasting mucosal CTL responses and production of proinflammatory cytokines in mucosal sites, indicating that MVA was as effective in inducing mucosal CTL as replicating recombinant vaccinia.

HXB2 Location gp160 (311–320)
Author Location Env (IIIB)
Epitope IGPGRARYAR
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* V3
Species (MHC) mouse (H-2D)
References Belyakov *et al.* 1998a

CTL CD8+

- HIV protection and mucosal CTL response was studied – an HIV peptide immunogen could protect against gp160 expressing vaccinia in a murine intrarectal challenge system in which neutralizing Abs did not play a role, demonstrating mucosal CTL at the site of exposure can be protective.

HXB2 Location gp160 (311–320)
Author Location gp120 (MN)
Epitope IGPGRAFYTT
Immunogen vaccine
Vector/Type: B. abortus complex
Species (MHC) mouse (H-2D^d)
References Lapham *et al.* 1996

- B. abortus-peptide conjugate induced a virus-specific CTL response in CD4+ lymphocyte depleted mice.

HXB2 Location gp160 (311–320)
Author Location gp160 (318–327 IIIB)
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* V3
Species (MHC) mouse (H-2D^d)
Keywords dendritic cells
References Takahashi *et al.* 1993

- Successful priming with vaccination of peptide pulsed splenic dendritic cells.

HXB2 Location gp160 (311–320)
Author Location gp160 (IIIB)
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: non-replicating adenovirus *Strain:* B clade IIIB *HIV component:* Env, Rev
Species (MHC) mouse (H-2D^d)
References Bruce *et al.* 1999

- A good HIV-1 Env immune response using non-replicating adenovirus vectors in BALB/c mice is dependent upon the presence of the stimulatory tat/rev 5'splice-donor site sequence and the presence of Rev.
- Administration of monocistronic RAd501 expressing env and RAd46 expressing rev resulted in a positive CTL response, but required two immunizations for a CTL response comparable to that induced by the bicistronic virus RAd142.
- Administration of RAd501 alone gave a low CTL response, but no humoral response, suggesting a lower level of antigen may be required to stimulate CTL.

HXB2 Location gp160 (311–320)
Author Location gp160 (318–327 IIIB)
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* V3
Species (MHC) mouse (H-2D^d)
References Takahashi *et al.* 1996

- Exposure of CD8+ CTL to free peptide corresponding to the epitope results in strong inhibition of the CTL response to targets presensitized with the same peptide.
- The authors propose this is due to a "self-veto", where the CTL is inactivated by a CD8+ cell carrying the appropriate peptide-MHC complex.

HXB2 Location gp160 (311–320)
Author Location gp120 (MN)
Epitope IGPGRAFYTT
Immunogen vaccine
Vector/Type: B. abortus complex
Species (MHC) mouse (H-2D^d)
References Lapham *et al.* 1996

- B. abortus-peptide conjugate induced a virus-specific CTL response in CD4+ lymphocyte depleted mice.

HXB2 Location gp160 (311–320)
Author Location gp160 (318–327 IIIB)
Epitope RGPGRAFVTI
Immunogen peptide-HLA interaction
Species (MHC) mouse (H-2D^d)
References Takeshita *et al.* 1995

- XGPXRXXXXI are critical for binding, consistent with H-2D^d motif XGPX(RKH)XXX(X)(LIF)

HXB2 Location gp160 (311–320)
Author Location Env
Epitope RGPGRAFTVTI
Immunogen vaccine
Vector/Type: DNA *HIV component:* V3
Species (MHC) mouse (H-2D^d)
References Hanke & McMichael 1999; Hanke *et al.* 1999

- Vaccinated mice elicited a CTL response to a gene gun-delivered multiepitope vaccine to two epitopes studied that are known to elicit CTL in mice: SYIPSAEKI from Plasmodium berghei and RGPGRAFTVTI from HIV-1 Env.
- Different vaccination protocols were tested and it was found that a gene gun mediated delivery followed by an MVA boost was as good as i. m. immunization followed by a MVA boost – this is advantageous as gene gun delivery requires far less DNA than i.m. DNA priming.
- CTL activity was high (60% - 70% specific lysis at effector target) when vaccinated with a single gene gun immunization and an MVA boost, and improved with two gene gun vaccinations.

HXB2 Location gp160 (311–320)
Author Location Env (IIIB)
Epitope RGPGRAFVTI
Epitope name I-10
Immunogen in vitro stimulation or selection
Species (MHC) mouse (H-2D^d)
Keywords epitope processing, immunodominance
References Nakagawa *et al.* 2000

- The CTL line LINE-IIIB was generated by repetitive restimulation of BALB/c spleen cells with vSC-25, IIIB gp160-expressing vaccinia.
- RGPGRAFVTI represents the active minimal epitope within the previously described immunodominant epitope P18IIIB (RIQRGPGRAFVTIGK, gp160(308-322)

- External processing of P18IIIB results in the removal of the 2 C-terminal residues (GK) of I-10 by ACE (angiotensin-1-converting-enzyme) in sera to produce I-10, and this processing is essential for target cell presentation of RIQRGPGRAFVTIGK.

HXB2 Location gp160 (311–320)
Author Location Env (IIIB)
Epitope RGPGRAFVTI
Epitope name p18-I10
Immunogen vaccine
Vector/Type: vaccinia, vesicular stomatitis virus (VSV) *Strain:* B clade HXB2, B clade IIIB *HIV component:* Env, Gag
Species (MHC) mouse (H-2D^d)
Keywords immunodominance
References Haglund *et al.* 2002a

- Different HIV strains were used for different regions: Env IIIB, Gag HXB2
- BALB/c mice were vaccinated with rec vesicular stomatitis virus (rVSV) expressing either HIV-1 Gag, Env, or both, and compared to using rec Env and Gag in vaccinia virus (rVVs). The primary response was determined by cell lysis, cytokine production and tetramer staining.
- Primary CTL responses to the immunodominant Env (RGPGRAFVTI) epitope peaked 5-7 days after intraperitoneal vaccination with Env-rVSV, 40% of the CD8+ cells were tetramer positive, and this response was 6-fold higher than the response to Env-rVV.
- Vaccinating with GagEnv-rVSV carrying both Gag and Env allowed recognition of both HIV-1 proteins, but at reduced levels compared to either Gag-rVSV or Env-rVSV alone.
- Intranasal immunization with Env-rVSV yielded CTL responses that were strong but reduced compared to an intraperitoneal route.

HXB2 Location gp160 (311–320)
Author Location Env (IIIB)
Epitope RGPGRAFVTI
Epitope name p18-I10
Subtype B
Immunogen vaccine
Vector/Type: vaccinia, vesicular stomatitis virus (VSV) *Strain:* B clade HXB2 *HIV component:* Env, Gag
Species (MHC) mouse (H-2D^d)
Keywords immunodominance
References Haglund *et al.* 2002b

- Different HIV strains were used for different regions: Env IIIB, Gag HXB2
- BALB/c mice were vaccinated with rec vesicular stomatitis virus (rVSV) expressing either HIV-1 Gag or Env, or both, and retention of memory responses and recall responses were studied by tetramer staining and IFN-gamma production.
- Seven months after vaccination with Env-rVSV, 6% of the CD8+ cells were tetramer positive for the immunodominant Env epitope; these cells had a memory phenotype, CD44-Hi positive.
- Env in rec vaccinia virus (Env-rVV) elicited a strong recall response, with up to 45% to the CD8+ T-cell population tetramer positive and activated (expressing CD62L-Lo), and capable of IFN-gamma production.
- A prime with Env-rVSV and heterologous boost of Env-rVV gave remarkably high levels of memory cells, with approximately 1/3 of the CD8+ splenocytes being Env specific memory cells 150 days after the boost.
- A Gag-rVSV or EnvGag-rVSV prime and with a heterologous Gag-rVV or EnvGag-rVV boost combination gave 40% tetramer positive CD8+ cells, but the fraction of IFN-gamma producing cells was only about 25%. Still the heterologous vector prime-boost combination showed a profound benefit.
- A HIV-1 protein rVSV prime, rVV boost was a more potent combination than a vector reversal of a rVV prime and rVSV boost.

HXB2 Location gp160 (311–320)
Author Location gp120 (V3) (IIIB)
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* V3 *Adjuvant:* Cholera toxin (CT), GM-CSF, IL-12, IL-18, IL-1α
Species (MHC) mouse (H-2D^d)
References Staats *et al.* 2001

- Cholera toxin (CT) is a potent adjuvant used in animal studies that is not safe in humans, so combinations of cytokins were used in nasal immunization of BALB/c mice V3 peptides to attempt to replace CT as a potent adjuvant.
- Peptide vaccine induced CTL activity was significantly increased by IL-1alpha , IL-18, and GMCSF given alone as adjuvant, but CT gave more potent CTL activity than any single cytokine.
- Combinations of cytokins could be more potent that CT as an adjuvant. The highest tetramer binding of H-2Dd peptide-specific PBMC after nasal immunization was observed with IL-1alpha plus IL-18 as adjuvant.
- Nasal immunization with HIV peptide in the presence of IL-1alpha, IL-12 and GM- CSF induced IFN-gamma-secreting cells in the cervical lymph node, the lung and the spleen, and was associated with upregulation of MHC class II and B7.1 on nonlymphocytes in NALT/nasal mucosal cells.
- Consistent results were obtained for the IIIB and the MN peptides.

HXB2 Location gp160 (311–320)
Author Location gp160 (318–327 IIIB)
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* beta-glucan lentinan, IL-2/Ig, liposome, PLG
Species (MHC) mouse (H-2D^d)
Keywords immunodominance
References Wierzbicki *et al.* 2002

- BALB/c mice were give an oral immunization with (PLG)-encapsulated plasmid DNA expressing gp160 and a boost of rec gp160 vaccinia vectors (rVV) with addition of murine IL-2/Ig plasmid or lentinan-associated liposomes. Lentinan increased CTL activity as measured by Cr-release assays against the immunodominant epitope RGPGRAFVTI, but didn't alter Ab responses. IL-2/Ig increased both type I and II activities, and increased Env specific CTL and Abs. Administration of liposomes and PLG microparticles with adjuvants facilitated gastrointestinal uptake.

HXB2 Location gp160 (311–320)
Author Location gp120 (LAI)
Epitope `RGPGRAFVTI`
Epitope name P18
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* Gag, gp120 *Adjuvant:* CpG immunostimulatory sequence (ISS)
Species (MHC) mouse (H-2D^{d})
References Horner *et al.* 2001

- Immunostimulatory sequences (ISS), also known as CpG motifs, stimulate innate immunity and enhance vaccine-specific immune responses.
- Intranasal immunization (i.n.) of BALB/c mice was more effective than intradermal (i.d.), and immunization with a gp120-ISS conjugate was more potent than immunizing with gp120 and separate ISS molecule – increased IgG1, IgG2a, IFN-gamma, MIP1-alpha and MIP1-beta production was observed, and only i.n. immunization gave IgA responses.
- The highest mucosal CTL activity in both the Lamina Propria and the Peyer's Patch was observed following intranasal delivery with the gp120/ISS conjugate.
- Cytokine, chemokine and CTL responses following gp120/ISS conjugate vaccination were CD4+ T-cell independent; gp120 specific antibodies were dependent on helper T cells.

HXB2 Location gp160 (311–320)
Author Location gp160 (V3) (IIIB)
Epitope `RGPGRAFVTI`
Epitope name I10
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2D^{d})
Keywords acute/early infection
References Takahashi *et al.* 2002

- During acute infection, high doses of virus result in "clonal exhaustion", a depletion of antigen specific T-cells.
- Recently stimulated CTL from BALB/c mice vaccinated with gp160-vaccinia showed a dose- and time-dependent induction of apoptosis when stimulated with antigenic peptide or H-2Dd/peptide tetramers.
- Restimulated CTL showed an upregulation of CD3-chain phosphorylation in comparison to cells stimulated with target cells, indicative of TCR-mediated apoptosis. Furthermore, apoptosis was inhibited by cyclosporin A and U0126, a mitogen activated kinase inhibitor specific for the ERK1/ERK2 MAPK kinase pathway, and a caspase 3 inhibitor.

HXB2 Location gp160 (311–320)
Author Location gp160 (V3) (MN)
Epitope `IGPGRAFYAT`
Epitope name MNT10
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2D^{d})
Keywords acute/early infection
References Takahashi *et al.* 2002

- During acute infection, high doses of virus result in "clonal exhaustion", a depletion of antigen specific T-cells.
- Recently stimulated CTL from BALB/c mice vaccinated with gp160-vaccinia showed a dose- and time-dependent induction of apoptosis when stimulated with antigenic peptide or H-2Dd/peptide tetramers.
- Restimulated CTL showed an upregulation of CD3-chain phosphorylation in comparison to cells stimulated with target cells, indicative of TCR-mediated apoptosis. Furthermore, apoptosis was inhibited by cyclosporin A and U0126, a mitogen activated kinase inhibitor specific for the ERK1/ERK2 MAPK kinase pathway, and a caspase 3 inhibitor.

HXB2 Location gp160 (311–320)
Author Location gp160 (V3) (HIV-IIIB)
Epitope `RGPGRAFVTI`
Epitope name P18-I10
Subtype B
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* IL-15, IL-2
Species (MHC) mouse (H-2D^{d})
Donor MHC H-2d
Assay type Cytokine production, Tetramer binding, Chromium-release assay
References Oh *et al.* 2003a

- IL-2 and IL-15 in vaccinia constructs were given with an HIV gp160 vaccinia vaccine to BALB/c mice. Both IL-2 and IL-15 induced strong and long-lasting antibody responses. Short-term CTL responses against HIV gp120 were enhanced by IL-2, but IL-15 enhanced both immediate CD8+ T cell responses and CD8+ T memory cells.

HXB2 Location gp160 (311–320)
Author Location gp160 (IIIB)
Epitope `RGPGRAFVTI`
Epitope name P18-I10
Subtype B
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* V3 *Adjuvant:* B7, ICAM, LFA-3
Species (MHC) mouse (H-2D^{d})
Donor MHC H-2d

Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding
References Oh *et al.* 2003b

- BALB/c mice were vaccinated with T-cell depleted splenocytes pulsed with peptides given in combination with immunostimulatory molecules B7, ICAM or LFA expressed in a recombinant pox virus. Increasing antigen gave an increased frequency of CD8+ T-cells, but the co-stimulatory molecules increased the avidity of the response.

HXB2 Location gp160 (311–320)
Author Location (89.6)
Epitope IGPGRAFYAR
Subtype B
Immunogen vaccine
Vector/Type: DNA *HIV component:* gp120 *Adjuvant:* Flex, a dendric cell growth factor
Species (MHC) mouse (H-2D^{d})
Donor MHC H-2d
Assay type Intracellular cytokine staining
Keywords dendritic cells
References Sailaja *et al.* 2003

- BALB/c mice were given a DNA vaccine that contained gp120 DNA covalently attached to the extracellular domain of the Fms-like tyrosine kinase receptor-3 ligand (FLex), a dendritic cell growth factor.
- Mice vaccinated i.m. with the FLex:gp120 chimeric gene gave a DC expansion similar to native Flex protein.
- gp120-specific stable CD8+ T-cell responses lasted 114 days after a prime/boost, and were observed in the presence and absence of Flex-DNA-induced dendritic cell (DC) expansion; strong Ab responses required DC expansion.

HXB2 Location gp160 (311–320)
Author Location gp120 (V3)
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: herpes simplex virus type-1 (HSV-1) amplicon *HIV component:* gp120
Species (MHC) mouse (H-2D^{d})
Donor MHC H-2d
Assay type Tetramer binding, JAM cytotoxicity assay
Keywords kinetics, memory cells
References Wang 2003

- Prime-boost combinations of gp120 combined with herpes simplex virus type-1 (HSV-1) amplicon particles, or gp120 in naked amplicon plasmid DNA, were compared in BLAB/c mice. Plasmid prime with particle boosts gave the strong primary (2 weeks) and memory responses (4 months).
- CD8+ T-cells reached their peak 8-28 days after the initial amplicon delivery.

HXB2 Location gp160 (311–320)
Author Location gp120 (V3)
Epitope RGPGRAFVTI
Epitope name P18-I10
Immunogen vaccine
Vector/Type: peptide, vaccinia *Strain:* B clade 89.6, B clade IIIB *HIV component:* gp160ΔV3 *Adjuvant:* Cholera toxin (CT), E. coli mutant heat labile enterotoxin (LT-R72), Incomplete Freund's Adjuvant (IFA), CpG immunostimulatory sequence (ISS)
Species (MHC) mouse (H-2D^{d})
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords dendritic cells, Th1, Th2, genital and mucosal immunity
References Belyakov *et al.* 2004

- Transcutaneous immunisation (TCI) of BALB/c mice induced adjuvant-dependent HIV-1 specific CTL responses in the spleen and the gut mucosa that resulted in protection against mucosal challenge against a recombinant vaccina virus carrying HIV-1 env. Activated DCs from skin were shown to migrate to immune-inductive sites in gut mucosa and to present antigen directly to resident lymphocytes.

HXB2 Location gp160 (311–320)
Author Location gp120 (V3)
Epitope RGPGRAFVTI
Subtype B
Immunogen vaccine
Vector/Type: herpes simplex virus type-1 (HSV-1) amplicon *Strain:* B clade LAI, B clade MN *HIV component:* gp120
Species (MHC) mouse (H-2D^{d})
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, JAM cytotoxicity assay
Keywords vaccine antigen design
References Hocknell *et al.* 2002

- BALB/c mice were immunized with HSV amplicons containing HIV-1 gp120. Helper virus free HSV-1 amplicon particles are capable of inducing potent cytoxic CD8+ T-cell and humoral immune responses to the HIV-1 antigen in mice. Previous infection with wild-type HSV-1 reduces amplicon-induced cellular immune responses to HIV gp120 modestly (40-60%), but severally reduced B-cell responses. The route of vaccination impacted the nature and level of the responses (i.m., i.d., and i. p.).

HXB2 Location gp160 (311–320)
Author Location gp120
Epitope RGPGRAFVTI
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* B clade MN *HIV component:* gp120, Protease, RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) humanized mouse (H-2D^{d})
Assay type CD8 T-cell Elispot - IFNγ
Keywords epitope processing, vaccine-specific epitope characteristics, immunodominance, immunotherapy
References Isaguliants *et al.* 2004

CTL CD8+

- Immunization of HLA-A*0201-transgenic mice with synthetic genes encoding clusters of human A*0201 CTL epitopes located at the sites of drug resistance mutations, induced RT-specific cellular responses indicating the immunogenicity of these constructs. This vaccine strategy may be a first step towards a therapeutic vaccine against drug-resistant strains. This epitope was included as a mouse marker for a CD8+ T-cell response.

HXB2 Location gp160 (311–320)
Author Location
Epitope RGPGRAFVTI
Epitope name R10I
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), polyepitope *HIV component:* Gag, p24 Gag, V3
Species (MHC) mouse (H-2D^d)
Assay type Cytokine production, Chromium-release assay
Keywords epitope processing, vaccine-specific epitope characteristics, immunodominance
References Wild *et al.* 2004

- A codon optimized gag DNA vaccine was compared to a myristylation defective gag and p24 alone, both of which lack signals for secretion from transfected cells. Gag-derived immunogens that were secreted as VLPs and those that remained intracellular (p24) each produced strong CTL responses, and neither the size of antigen nor cellular trafficking and localization significantly influenced the strength of humoral and cellular immune activation. The formation and release of VLPs was not essential for eliciting strong CTL. BALB/c mice were given the DNA vaccine by i.m. administration of plasmid DNA for the prime and boost.
- Linking the region encoding the V3 immunodominant epitope to the gag gene did not diminish the response to the Gag p24 epitope A9I, but did enable a response to the V3 epitope.
- Minigenes were made incorporating just 1 epitope, minitopes, carrying 1 of 3 murine class I epitopes linked to the Ad2-E3 protein-derived signal peptide to allow access of the epitope to the ER. Weak induction of cellular immune responses was observed, in contrast to the complex polyprotein.

HXB2 Location gp160 (311–320)
Author Location Env (318–327)
Epitope RGPGRAFVTI
Epitope name R10I
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2D^d)
Donor MHC H-2D
Assay type Intracellular cytokine staining
Keywords vaccine antigen design
References Samino *et al.* 2004

- The endogenous processing of the HIV-1 envelope glycoprotein generates several different natural peptidic species presented by the H-2D molecule in infected cells, the 9-, 10-, and 11-mer peptides, GPGRAFVTI, RGPGRAFVTI, and QRGPGRAFVTI. CTL with the same antigenicity could recognize all three forms. The complexity of the binding peptides suggests naturally processed proteins could provide more variety as antigens, stimualting more robust and diverse CTL responses.

HXB2 Location gp160 (311–320)
Author Location p18 (IIIB)
Epitope RGPGRAFVTI
Subtype B
Immunogen vaccine
Vector/Type: DNA with CMV promotor *Strain:* B clade IIIB *HIV component:* gp120 *Adjuvant:* IL-12
Species (MHC) mouse (H-2D^d)
Donor MHC H-2D
Assay type Cytokine production, proliferation, CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, memory cells, characterizing CD8+ T cells
References Seaman *et al.* 2004

- Delivery of plasmid IL-12 on day 10 after immunization of mice with an HIV-1 gp120 DNA vaccine resulted in expansion of gp120-specific CD8+ T-cells but had no effect on antigen-specific CD4+ T-cells and antibody responses. gp120-specific CD8+ T-cells were shown to primarly be effector memory and not central memory T-cells and did not expand following gp120 boost immunization.

HXB2 Location gp160 (311–320)
Author Location Env (gp160) (318–327 HIV-1 IIIB)
Epitope RGPGRAFVTI
Epitope name P18-I10
Immunogen peptide-HLA interaction
Species (MHC) mouse (H-2D^d)
Assay type Chromium-release assay, Other
Keywords binding affinity, structure
References Nakagawa *et al.* 2007

- To study the critical amino acids of both TCR and MHC that interact with peptide P18-I10 of HIV-1 IIIB, the authors used a series of mutant substituted peptides. Peptides substituted with Ala at various positions showed that positions 322R, 324F and 327I were essential for binding to H2-D^d. Residue 325V was critical for interacting with TCR. By employing D-amino acid derived peptides as mutants in order to avoid charge, size and molecular weight differences, they also show that 325V is necessary for CTL-induced cytotoxic activity. Using two distinct CTL clones and molecular modeling they determined that TCR sequences of CDR1 and not CDR3 critically interact with 325V.
- This 10-residue minimally active peptide lies within the immunodominant epitope, RIQRGPGRAFVTIGK, that belongs to gp160, the hypervariable region of Env. Substituted peptides used in this study were RGPGRAFiTI, RGPGRAFlTI, RGPGRAFaTI, RGPGRAFyTI, RGPGRAFfTI, RGPGRAFhTI, RGPGRAFtTI, RGPGRAFsTI, RGPGRAFeTI,RGPGRAFkTI, RGPGRAFrTI and RGPGRAFpTI. In addition, D-amino acid variants of the residues in parentheses were used - (r)GPGRAFVTI, RG(p)GRAFVTI, RGPG(r)AFVTI, RGPGR(a)FVTI,

RGPGRA(f)VTI, RGPGRAF(v)TI, RGPGRAFV(t)I, RGPGRAFVT(i), RGPGRAF(i)TI, RGPGRAF(l)TI, RGPGRAF(a)TI, RGPGRAF(y)TI, RGPGRAF(f)TI, RGPGRAF(h)TI and RGPGRAF(t)TI.

HXB2 Location gp160 (311–320)
Author Location gp120
Epitope RGPGRAFVTI
Epitope name H
Subtype A
Immunogen vaccine
Vector/Type: DNA with CMV promotor, modified vaccinia Ankara (MVA), DNA prime with modified vaccinia Ankara (MVA) boost, Other *Strain:* A clade, B clade, C clade Du422, Other *HIV component:* Gag, Nef, RT
Species (MHC) mouse (H-2D^d)
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords subtype comparisons, vaccine-induced epitopes, variant cross-recognition or cross-neutralization, antagonism
References Larke *et al.* 2007

- Cross-clade vaccine recognition was studied using either single-, multi or several anatomically separated single-clade vaccines. Limited cross-clade response was seen with single-clade administrations. Multi-clade vaccines gave immune interference (antagonism and original antigenic sin), reducing CTL response. Simultaneously administered but anatomically separated vaccines from clades A, B, C decreased antagonism and increased immune responses.
- No cross-reactivity was seen with epitope variants (iGPGqAFyat, fGPGqAFyTn, iGPGRAFyTt, iGPGqtFyat, iGlGqAlyTt, lGPGqAFyat, iGPGRAFyat, iGPGqvFyrt, mGPGRvFyTt) after immunization with Clade A containing index Epitope H, RGPGRAFVTI.

HXB2 Location gp160 (311–320)
Author Location gp120
Epitope RGPGRAFVTI
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB, SIV *HIV component:* gp120
Species (MHC) macaque, mouse (H-2Dd)
Assay type proliferation, Tetramer binding, CD4 T-cell Elispot - IFNγ, Chromium-release assay, Other
Keywords adjuvant comparison, vaccine antigen design, SIV
References Fuller *et al.* 2007

- HIV-epitope, RGPGRAFVTI, was fused to a Heptatis B core antigen (HBcAg) gene in order to improve immunogenicity of an epitope-based vaccine in mice. A vaccine containing hybrid HBcAg-epitope linked to an HIV-specific T helper epitope induced significantly higher responses than a hybrid HBcAG-epitope vaccine which perfomed better than epitope alone. The authors suggest that HBcAg could be a better carrier of foreign epitopes than even Hepatitis B surface antigen (HBsAg) - (previously studied).
- This work also deals with a multi-epitope SIV-based vaccine in non-human primates.

HXB2 Location gp160 (311–320)
Author Location gp160 (318–327 IIIB)
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* Env, Nef
Species (MHC) mouse (H-2L^d)
References Tobery & Siliciano 1997

- An HIV-1 Env vaccine was targeted for rapid cytoplasmic degradation.
- The rapidly degraded form rapidly stimulated CTL to this peptide, faster than the normal vaccinia-env.
- The rapidly degraded form also stimulated greater specific CTL lysis and higher CTLp frequencies than normal Env.
- Similar results were obtained for a Nef protein designed for rapid degradation.

HXB2 Location gp160 (311–320)
Author Location Env
Epitope RGPGRAFVTI
Subtype A, B
Immunogen vaccine
Vector/Type: DNA *Strain:* A clade, B clade *HIV component:* Env, Gag
Species (MHC) mouse (H-2d)
Country Finland
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Malm *et al.* 2007

- A novel mouse model was used to test the efficacy of 2 HIV DNA vaccines in protection against tumor challenge. Comparable immunogenicity between the single and multi-clade vaccines tested was seen in different mouse strains. CTL response to HIV-1-APCs was both in vivo and in vitro and this animal model was safe and not only evaluated vaccine immunogenicity but also confirmed the potency of GTU-multi-HIV vaccines.

HXB2 Location gp160 (311–320)
Author Location gp160 (318–327 IIIB)
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: DNA prime with peptide boost *Strain:* B clade IIIB *HIV component:* CD4BS, gp160, HPG30, V3
Species (MHC) macaque
References Okuda *et al.* 1997

- Murine BALB/c (H-2^d) and macaque both showed highest level of CTL vaccine response when a DNA vaccine was boosted with a peptide including four peptide subtypes of the V3 region, HPG-30 and a fragment of the CD4 binding region.

HXB2 Location gp160 (311–320)
Author Location gp120 (318–327)

CTL CD8+

Epitope RGPGRAFVTI
Immunogen HIV-1 infection
Species (MHC) human
References Kmieciak *et al.* 1998b

- Increased CTL response to cells expressing a VV construct ΔV3 mutant compared with a full-length env gene product.
- This epitope doesn't have A2 anchors, but has features that confer promiscuous A2 binding, which may relate to the inhibitory effect seen in this paper.

HXB2 Location gp160 (311–320)
Author Location gp160 (318–327 IIIB)
Epitope RGPGRAFVTI
Epitope name R10I
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* V3
Species (MHC) mouse
Keywords optimal epitope
References Nehete *et al.* 1995

- RGPGRAFVTI was defined as the optimal peptide for vaccination, out of RIQRGPGRAFVTIGK.
- This peptide, in a carrier-free form in Freund's adjuvant, could stimulate Env specific CTL in BALB/c mice.

HXB2 Location gp160 (311–320)
Author Location Env (IIIB)
Epitope RGPGRAFVTI
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* gp160, Rev *Adjuvant:* MIP-1α
Species (MHC) mouse
References Lu *et al.* 1999

- MIP-1alpha co-inoculation increased IgG1/IgG2a ratio T-helper type 1 response.
- A MIP-1 alpha expression plasmid increased the CTL response to this DNA vaccine, as well as the T help response, presumably by the MIP-1 alpha interacting with T lymphocytes and macrophages.

HXB2 Location gp160 (311–320)
Author Location
Epitope RGPGRAFVTI
Epitope name P18
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade BH10 *HIV component:* gp120 *Adjuvant:* GM-CSF
Species (MHC) mouse
References Barouch *et al.* 2002

- gp120 encoding DNA co-injected with a plasmid carrying GMCSF gave meager CD4+ T-cell responses in BALB/c mice relative to the enhanced response to bicistronic gp120 and GMCSF cloned into the same vector and expressed from the same promoter.
- Both mono and bicistronic DNA vaccines induced similar CTL responses directed against the H-2Dd restricted P18 peptide RGPGRAFTVTI in murine splenocytes despite the greatly enhanced proliferative responses.

HXB2 Location gp160 (311–320)
Author Location gp120 (313–322 BRU)
Epitope RGPGRAFVTI
Epitope name Pep 09
Subtype B, C
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade BRU *HIV component:* gp160, Rev, Tat
Species (MHC) mouse
Keywords subtype comparisons, Th1
References Arora & Seth 2001

- Plasmid DNA encoding gp160, tat, rev was given i.m. to immunize BALB/c mice.
- Vaccine-induced CTL activity produced a low degree of cell lysis of V3-peptide pulsed target cells, using a B (RGPGRAFVTI) or C (RIGGPGQTFYATG) clade V3 peptides. Th1 proliferative T-cell responses were observed, and weak Ab responses.

HXB2 Location gp160 (311–320)
Author Location Env (IIIB)
Epitope RGPGRAFVTI
Epitope name 10 Env
Subtype B
Immunogen vaccine
Vector/Type: influenza prime with vaccinia boost *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) mouse
Donor MHC H-2d
Assay type Cytokine production, proliferation, CD8 T-cell Elispot - IFNγ
Keywords Th1, Th2, genital and mucosal immunity
References Gherardi *et al.* 2003

- Mice were intranasally primed with a recombinant influenza virus A vector that carries HIV-1 Env inserted into its hemagglutinin protein. Boosting was performed intranasally with either influenza-Env or intraperitoneally with two vaccinia virus recombinants expressing the Env protein, VVenv and MVAenv.
- Peritoneal heterologous immunization with VVenv induced a 60-fold higher CD8+ IFN-gamma T cell responses than homologous influenza prime-boost. The intraperitoneal MVAenv boost response was greater than the VVenv boost in the spleen and genital lymph nodes, while the VVenv response gave the highest boost with the intranasal route.
- Mice with increased CD8+-T-cell responses also had a higher Th1/Th2 ratio, indicated by the cytokine secretion profile and the IgG2a/IgG1 ratio.

HXB2 Location gp160 (311–320)
Author Location gp160
Epitope RGPGRAFVTI
Epitope name P18-I10
Subtype B

CTL CD8+

Immunogen vaccine
Vector/Type: vaccinia with H1 influenza HA gene cassette *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) mouse
Assay type Chromium-release assay
Keywords genital and mucosal immunity
References Kuribayashi *et al.* 2004

- The intraepithelial compartment of the intestinal mucosa is shown to be a major site for preventing virus spread by thymus-derived CD8alphaß-positive Ag specific CTLs and CD8alpha,alpha+gamma,delta cells, which regulate virus spread in a P18-I10 vaccinia vector mouse infection model.

HXB2 Location gp160 (311–320)
Author Location Env
Epitope RGPGRAFVTI
Subtype B
Immunogen vaccine
Vector/Type: vesicular stomatitis virus (VSV) *Strain:* B clade *HIV component:* Env
Species (MHC) human
Country United States
Assay type Tetramer binding, Other
Keywords memory cells
References Ramsburg *et al.* 2007

- The requirement for CD4 T cell help in primary versus memory CTL responses was examined. Since a VSV vector encoding HIV Env was used as vaccine, responses specific to HIV-1 Env epitope RGPGRAFVTI as well as VSV epitope N were tested. Both primary and memory responses to the Env epitope did not require Th help. However, primary CTL responses to Env were 2-3 fold higher in the presence of CD4 T cells, while memory responses were tested until 3 months post-priming. Thus memory CTL maintenance dependency on CD4 T cell help is epitope-dependent.

HXB2 Location gp160 (311–320)
Author Location gp120
Epitope RGPGRAFVTI
Subtype C
Immunogen vaccine
Vector/Type: modified vaccinia Ankara (MVA) *Strain:* C clade Du422 *HIV component:* Env, Gag, Nef, RT, Tat
Species (MHC) human, mouse
Country United States, South Africa
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine antigen design
References Burgers *et al.* 2008

- 5 genes from southern African HIV subtype C vaccine strains Du151 and Du422 were developed into a recombinant MVA polygene and were characterized in mice. A double recombinant, SAAVI MVA-C, was used to overcome genetic instability of env by inserting Grttn (gag, reverse transcriptase, tat and nef) and gp150 at 2 sites. Env infectivity as well as murine T-cell-immune response that was boosted by second inoculation were shown .
- Peptides used to test for mouse CTL responses were H-2K(d)-restricted Gag AMQMLKDTI, H-2K(d)-restricted RT VYY-DPSKDLIA and H-2D(d)-restricted Env RGPGRAFVTI.
- Epitope RGPGRAFVTI from HIV gp120 was inserted at the 3'end of the gene to generate gp150CT in order to facilitate mouse anti-HIV immune assays.

HXB2 Location gp160 (311–320)
Author Location
Epitope IGPGRAFYAR
Subtype B
Immunogen vaccine
Vector/Type: modified vaccinia Ankara (MVA) *Strain:* B clade 89.6 *HIV component:* Env
Species (MHC) human
Assay type Intracellular cytokine staining, Chromium-release assay, Other
Keywords vaccine antigen design, co-receptor
References Wyatt *et al.* 2008a

- While propagating MVA encoding HIV 89.6 Env, excessively staining foci were studied and found to possess a single nucleotide deletion that conferred upon Env a 115 aa C-terminal truncation. Truncated Env was more highly expressed and so induced higher antibody and CTL responses without compromising its ability for CD4/co-receptor fusion. A similar truncation would be beneficial in MVA-based vaccines.
- To test for CTL response to Env epitopes, peptide P18-89.6R10, IGPGRAFYAR, was used as stimulating peptide in Chromium release assays where wild type MVA/89.6 and truncated MVA/89.6T induced similar specific lytic activities. Intracellular staining also showed similar induction of IFN-gamma+; IFN-gamma+, TNF+; and IFN-gamma+, IL-2+ CTLs by both forms of the virus.

HXB2 Location gp160 (311–320)
Author Location gp120
Epitope LGPGRVWYTT
Epitope name RI10(gp120)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.

CTL CD8+

- Author defined epitope LGPGRVWYTT elicited an immune response in Chinese HIV-1 positive subjects as part of peptide ITlGPGRvwyTtGQII. This epitope differs from the previously described HLA-A2-restricted epitope sequence, RGPGRAFVTI, at 5 residues, lGPGRvwyTt.
- 1 of the 55 HLA-A2 carriers responded to an lGPGRvwyTt-containing peptide with a magnitude of CTL response of 55 SFC/million PBMC (author communication and Fig.1).

HXB2 Location gp160 (311–324)
Author Location Env (307–321)
Epitope `IGPGKAFYATGDIIG`
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized by mice co-immunized with Env and Tat, but not by mice immunized with Env alone.

HXB2 Location gp160 (312–320)
Author Location gp120 (V3) (IIIB)
Epitope `GPGRAFVTI`
Subtype B
Immunogen vaccine
Vector/Type: fowlpoxvirus *Strain:* B clade BRVA, B clade IIIB, B clade JY1, B clade LR150, B clade MN, B clade RF *HIV component:* V3
Species (MHC) mouse (H-2^d)
Keywords vaccine-specific epitope characteristics, immunodominance
References Vázquez Blomquist *et al.* 2002

- BALB/c mice were vaccinated with a polyepitope V3 vaccine in a fowlpoxvirus carrying concatonated 15 mer sections of the V3 loops of HIV-1 isolates LR150, JY1, RF , MN, BRVA and IIIB with 5-aa linkers between, fused to the N-term of p64K protein from Neisseria meningitidis.
- Intraperitoneal immunization elicited the strongest V3-specific IFN-gamma response in splenocytes, compared to intravenous and subcutaneous immunization. Intraperitoneal immunization conferred protection in a recombinant vaccinia virus challenge model.
- The immunodominant response was directed against the IIIB peptide (the IIIB immunizing peptide was SIRIQRGPGRAFVTI, the peptide used to probe the response by Elispot was GPGRAFVTI).
- Low CTL responses were also detected to the LR150 (SRGIRIGPGRAILAT) and RF (RKRITMGPGRVYYTT) peptides, no responses were detected to the JY1 (RQSTPIGLGQALYTT), BRVA (RKSITKGPGRVIYAT), or MN (RKRIHIGPGRAFYTT) peptides.

HXB2 Location gp160 (312–320)
Author Location gp120 (V3)
Epitope `GPGRAFVTI`
Subtype B
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost, polyepitope, DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade BRVA, B clade IIIB, B clade JY1, B clade LR150, B clade MN, B clade RF *HIV component:* V3 *Adjuvant:* IFNγ
Species (MHC) mouse (H-2^d)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ
Keywords Th1
References Gómez *et al.* 2004

- Priming of mice with DNA-TAB vector, a polyepitope string carrying 8 different V3 loop sequences, followed by a booster with VV-TAB or MVA-TAB, induced humoral responses, as well as a CD8+ T-cell response against V3 epitopes from three different subtype B HIV isolates. The highest values of specific CD8+ T-cell response were achieved when priming with DNA-TAB and a DNA vector expressing IFN-gamma, followed by a MVA-TAB boost. The T-cell response was Th1.
- The eight V3 loops were linked with an A-G-G-G-A sequence. The three peptides that elicited a response were LR150, SRGIRIGPGRAIL; MN, RKRIHIGPGRAFY; and IIIB, SIRIQRGPGRAFVTI. These peptides were located at the beginning, middle and end of the polyepitope, indicating all parts were able to be processed. It is not known if there is an H-2d epitope in the other five V3 loop variants that did not elicit a response.

HXB2 Location gp160 (314–322)
Author Location gp120 (312–320)
Epitope `GRAFVTIGK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*2705)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords Th1, characterizing CD8+ T cells
References Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- One of seven patients responded to this peptide with GzB producing cells and with IFN-gamma producing cells.

HXB2 Location gp160 (314–322)
Author Location gp120 (314–322)
Epitope GRAFVTIGK
Immunogen peptide-HLA interaction
Species (MHC) human (B27)
References Jardetzky *et al.* 1991

- Study of peptide binding to HLA-B27.

HXB2 Location gp160 (321–330)
Author Location gp160
Epitope EIIGDIRQAY
Epitope name EY10
Immunogen HIV-1 infection
Species (MHC) human (A*2501)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a A*2501 epitope.

HXB2 Location gp160 (321–330)
Author Location gp120 (322–330 HIV-MN)
Epitope EIIGDIRQAY
Epitope name EY10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2501)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Positions 1, 5 and 10 (last)in the epitope had potentially experienced positive selection. qIIGDIRQAY, dIIGDIRQAh, EIIGnIRQAh and EIIGDIRQAh escape variants were found.

HXB2 Location gp160 (322–336)
Author Location Env
Epitope IIGDIRQAHCNISRE
Subtype A, B, C, D
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost, protein *Strain:* B clade 1007, B clade 1035 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse
Country United States
Assay type Cytokine production
Keywords subtype comparisons, immunodominance
References Brown *et al.* 2006

- A vaccine study with B clade Envs in mice was unertaken to assess a subtype-specificity of responses. Four T-cell hybridomas responsive to subtype B envelope proteins were tested against 20 different subtype B envelope proteins and a protein each from subtypes A, C and D. IL-2 production was measured.
- No consistent correlation was found between T cell specificity towards epitopes from a certain (B) subtype or lack of specificity towards other (A, C, D) subtype.
- Not only did T-cell specificity not vary with subtype, but pairwise sequence comparisons of gp120 envelope sequences showed that some US-derived sequences were more similar to sequences from distant countries than to each other.
- Changes in core epitopes, flanking and distant regions, all affected responsiveness of the hybridomas to different subtype Env epitopes, showing that it is not only core changes that can eliminate T cell reactivity to an epitope.
- The above findings were substantiated by database analyses showing that epitope distributions are not necessarily dictated by subtype.
- This paper lists several variants of the epitope above,IIGDIRQAHCNISRE.

HXB2 Location gp160 (326–340)
Author Location Env (323–337)
Epitope IRQAHCNISGEKWNN
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.

CTL CD8+

- This epitope was recognized by mice co-immunized with Env and Tat, but not by mice immunized with Env alone.

HXB2 Location gp160 (334–342)
Author Location Env
Epitope SRAKWNNTL
Epitope name SL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- SL9, SRAKWNNTL, is a novel HLA-B27-restricted epitope that elicits a CTL IFN-gamma response in the same range as Los Alamos database peptides.

HXB2 Location gp160 (337–361)
Author Location gp120 (337–368 LAI)
Epitope KWNNTLKQIDSKLREQFGNNKTIIF
Subtype B
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* gp160
Species (MHC) human
Keywords CD4+ CTL
References Johnson *et al.* 1994a

- CD4+ CTL clones were obtained from an HIV-1 vaccinia-env vaccinee.

HXB2 Location gp160 (339–354)
Author Location gp120 (339–361 LAI)
Epitope NNTLKQIDSKLREQFG
Subtype B
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* gp160
Species (MHC) human
Keywords CD4+ CTL
References Johnson *et al.* 1994b

- CD4+ CTL isolated from LAI IIIB gp160 vaccinees.

HXB2 Location gp160 (340–348)
Author Location gp120 (346–354 CM243 subtype CRF01)
Epitope RVLKQVTEK
Epitope name E340-348
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords HIV exposed persistently seronegative (HEPS)
References Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was weakly reactive in HIV+ control study subject 053 who carried HLA-A11.

HXB2 Location gp160 (340–348)
Author Location gp120 (346–354 CM243 subtype CRF01)
Epitope RVLKQVTEK
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords subtype comparisons
References Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This is one of the new A11 epitopes identified through the streamlined EpiMatrix method, and 2/8 tested FSWs recognized it.
- This epitope was not conserved in other subtypes, and exact matches were rare.

HXB2 Location gp160 (340–349)
Author Location gp120 (W6.ID)
Epitope NTLKQIVIKL
Immunogen vaccine
Vector/Type: protein *Strain:* B clade W61D *HIV component:* gp120
Species (MHC) chimpanzee (Patr-B*14)
Keywords immunodominance
References Balla-Jhagjhoorsingh *et al.* 1999a

- An HIV-1 rgp120 vaccine induced strong humoral and cellular immune response in sibling chimpanzees, but only one of the two made a detectable CTL response to this Patr-B*14 restricted immunodominant epitope.

HXB2 Location gp160 (341–349)
Author Location gp120 (341–349 HIV-MN)
Epitope TLSQIVTKL
Epitope name TL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203

Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Position 4 in the epitope had potentially experienced positive selection. TLSkIVTKL escape variant was found.

HXB2 Location gp160 (342–356)
Author Location Env (339–353)
Epitope LKQIVTKLQAQFENK
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized both by mice co-immunized with Env and Tat, and by mice immunized with Env alone.

HXB2 Location gp160 (344–361)
Author Location gp160 (348–366 WEAU)
Epitope QIVEKLREIKQFKNKTIVF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*2902, B*0801, B*4403
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, immunodominance, escape, kinetics, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.
- WEAU had a reaction to an eptiope within this peptide, and there was very rapid accumulation of substitutions; variation continued through the last sample collected.

HXB2 Location gp160 (346–361)
Author Location Env (343–357)
Epitope VTKLQAQFENKTIVF
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized by mice co-immunized with Env and Tat, but not by mice immunized with Env alone.

HXB2 Location gp160 (349–364)
Author Location Env (346–360)
Epitope LQAQFENKTIVFKQS
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse

CTL CD8+

Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized by mice co-immunized with Env and Tat, but not by mice immunized with Env alone.

HXB2 Location gp160 (363–376)
Author Location (C consensus)
Epitope `PSSGGDLEITTHSF`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*18)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location gp160 (369–375)
Author Location gp120 (374–380 BRU)
Epitope `PEIVTHS`
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Dadaglio *et al.* 1991

- Defined through blocking CTL activity, and Env deletions.

HXB2 Location gp160 (374–382)
Author Location Env
Epitope `HSFNCGGEF`
Epitope name 1325
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A02, A03, B08, B51, Cw01, Cw07
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for HSFNCGGEF: 76%

HXB2 Location gp160 (375–383)
Author Location gp120 (379–387 LAI)
Epitope `SFNCGGEFF`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1516)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*1516 epitope.

HXB2 Location gp160 (375–383)
Author Location Env
Epitope `SFNCGGEFF`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1516)
Donor MHC A*0202, A*0301, B*0702, B*1516
Country United States
Keywords escape, acute/early infection
References Bernardin *et al.* 2005

- Full HIV genomes from nine individuals were analyzed for mutations prior to seroconversion and 7 to 28 days later. It was found that the influence of the host's HLA type was reflected within weeks of infection; a statistically significant number of early nonsynonymous mutations were observed within previously reported CTL epitopes.
- E to G mutation was observed in position 7.

HXB2 Location gp160 (375–383)
Author Location
Epitope `SFNCGGEFF`
Immunogen HIV-1 infection
Species (MHC) human (B*1516, Cw04)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.

- Epitope SFNCGGEFF when restricted by HLA-B1516, elicited a magnitude of response of 765 SFC with a functional avidity of 0.5nM. When restricted by HLA-Cw04, it elicited a magnitude of response of 640 SFC with a functional avidity of 0.5nM.

HXB2 Location gp160 (375–383)
Author Location gp120 (375–383 IIIB)
Epitope SFTCGGEFF
Immunogen HIV-1 infection
Species (MHC) human (B15)
Keywords responses in children, mother-to-infant transmission, escape
References Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- An additional variant that gave a positive, though reduced, CTL response: SSTCGGEFF and SFTCGGGFF.
- SFTCGGGVF was an escape mutant.

HXB2 Location gp160 (375–383)
Author Location gp120 (375–383 SF2)
Epitope SFNCGGEFF
Immunogen HIV-1 infection
Species (MHC) human (B15)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with preseroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B15+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 1/1 group 2, and 0/1 group 3.

HXB2 Location gp160 (375–383)
Author Location gp120 (375–383)
Epitope SFNCGGEFF
Immunogen HIV-1 infection
Species (MHC) human (B15)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 5 epitopes from this individual that varied over time where the internal mutations became fixed; a dramatic decrease in CTL activity against the wild type epitope was observed as the mutation arose. The sfncRgeff variant residue found at 20 and 47 months postseroconversion.

HXB2 Location gp160 (375–383)
Author Location gp120
Epitope SFNCGGEFF
Epitope name SF9(gp120)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B15)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B15-restricted epitope SFNCGGEFF elicited an immune response in Chinese HIV-1 positive subjects as peptide GDPEIVMHSFNCGGEFFY but not as peptide SFNCGGEFFYCNTTQLF.
- 2 of the 21 HLA-B15 carriers responded to FLGKIWPShK-containing peptide with average magnitude of CTL response of 495 SFC/million PBMC.

HXB2 Location gp160 (375–383)
Author Location Env (375–383)
Epitope SFNCGGEFF
Immunogen HIV-1 infection
Species (MHC) human (B15, Cw*0401, Cw*0407, Cw4)
Country Philippines, Taiwan
Keywords escape
References Liang *et al.* 2008

- 1100 unique full-length Env sequences were analyzed and the positive selection (PS) pressure determined. The QUASI method was used across Clades A, B, C and D, to find PS sites dispersed across Env.
- Frequency of PS sites is stable over time.
- 25% to 61% PS sites are shared between subtypes A, B, C and D, so it is inferred that immune responses are targeted against the same general regions.
- Significant correlations between PS sites and neutralizing antibody response, helper response, antibody plus CTL response are found. This suggests that the NAb response might be the driving force behind HIV-1 Env evolution.

- PS-free sites that are targeted greatly by NAb and CTL were found. Functional reasons for the lack of positive selection in such regions must exist.
- PS-site-rare regions (conserved regions of Env) were examined for PS, and epitopes located in such regions. Epitope SFNCGGEFF, restricted by HLA-B15, -Cw4, -Cw*0401, -C*0407, is on a region free from positive selection. It is found in Filipino and Taiwanese populations and has no known association with progression to AIDS.

HXB2 Location gp160 (375–383)
Author Location gp120 (375–383)
Epitope `SFNCGGEFF`
Immunogen
Species (MHC) human (B*1516, B15, B63)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 121/200 Brazilian HIV sequences; common variants are tFNCGGEFF and SFNCrGEFF.

HXB2 Location gp160 (375–383)
Author Location gp120
Epitope `SFNCGGEFF`
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B63)
Assay type CD8 T-cell Elispot - IFNγ
Keywords cross-presentation by different HLA, optimal epitope
References Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This is a putative HLA-B63/57/58 epitope containing the B58 supertype binding motif. Borderline significantly more often recognized in subjects who carry B63, but not B57/B58.

HXB2 Location gp160 (375–383)
Author Location gp120 (375–383 IIIB)
Epitope `SFNCGGEFF`
Immunogen HIV-1 infection
Species (MHC) human (B15, B63)
References Wilson *et al.* 1997a

- This is the optimal peptide for two CTL clones that recognize this epitope in the context of two different HLA molecules, Cw4 and B15.
- Predominant form in proviral DNA of the individual with B15 restricted CTL was SFTCGGEFF and this was recognized.
- Recognition of a minor autologous variant (SFNCRGEFF) from the B15 donor was greatly reduced.

HXB2 Location gp160 (375–383)
Author Location gp120 (376–383 PV22)
Epitope `SFNCGGEFF`
Immunogen HIV-1 infection
Species (MHC) human (Cw*0401)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a C*0401 epitope.

HXB2 Location gp160 (375–383)
Author Location gp120
Epitope `SFNCGGEFF`
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (Cw*0401, Cw*0407)
Keywords HIV exposed persistently seronegative (HEPS), cross-presentation by different HLA
References Bird *et al.* 2002

- 4/123 (2 HIV-1 positive, 2 HEPS) Kenyan female sex workers carried the novel allele HLA Cw*0407.
- HLA Cw*0407 did not differ from Cw*0401 in the region associated with the binding pocket, and Cw*0407 was shown to cross-present a previously defined Cw*0401 epitope, SFNCGGEFF (gp120).

HXB2 Location gp160 (375–383)
Author Location gp120 (376–383 PV22)
Epitope `SFNCGGEFF`
Immunogen HIV-1 infection
Species (MHC) human (Cw4)
References Johnson *et al.* 1993

- Conserved epitope.

HXB2 Location gp160 (375–383)
Author Location gp120 (376–383 PV22)
Epitope `SFNCGGEFF`
Immunogen HIV-1 infection
Species (MHC) human (Cw4)
References Wolinsky *et al.* 1996

- Longitudinal study of epitope variation *in vivo*.

HXB2 Location gp160 (375–383)
Author Location gp120 (376–383)
Epitope `SFNCGGEFF`
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (Cw4)
Keywords HIV exposed persistently seronegative (HEPS), immunodominance
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.

- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-Cw4 women, 1/2 HEPS and 10/11 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in 6 of the 10/11 responsive HIV-1 infected women, and not in the HEPS case.

HXB2 Location gp160 (375–383)
Author Location
Epitope SFNCGGEFF
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* Other *HIV component:* gp160
Species (MHC) human
Donor MHC A3, A33; B15 (63), B27
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location gp160 (375–383)
Author Location Env
Epitope SFNCGGEFF
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101, B*1567, B*8101, Cw*1402, Cw*1801
Country Kenya
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2008

- To evaluate the use of IFN-gamma ELISpot and proliferation assays, the two were compared in a cohort of HIV-1-infected Kenyan sex-workers. ELISpot does not always correlate with viral load and replication or disease progression. The exclusive use of these assays makes definition of CTL response in disease incomplete, especially for memory T cells.
- Despite assaying for 24 INF-gamma and 41 proliferative responses, only 5 of these responses overlapped in the same subject. 18 peptide-epitopes including 10 epitopes and their variants were used in this study.
- SFNCGGEFF did not elicit proliferation, but elicited an ELISpot response in 1 subject.

HXB2 Location gp160 (375–384)
Author Location (C consensus)
Epitope SFNCRGEFFY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*29)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- SFNCRGEFFY is an optimal epitope.

HXB2 Location gp160 (375–384)
Author Location (B consensus)
Epitope SFNCGGEFFY
Epitope name SY10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A29)
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location gp160 (375–384)
Author Location
Epitope SFNCGGEFFY
Immunogen HIV-1 infection
Species (MHC) human (A29)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.

- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope SFNCGGEFFY elicited a magnitude of response of 855 SFC with a functional avidity of 0.0001nM.

HXB2 Location gp160 (375–384)
Author Location gp120 (375–384)
Epitope SFNCGGEFFY
Immunogen
Species (MHC) human (A29)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 120/200 Brazilian HIV sequences; common variants are tFNCGGEFFY and SFNCrGEFFY.

HXB2 Location gp160 (375–384)
Author Location Env (375–384)
Epitope SFNCGGEFFY
Immunogen HIV-1 infection
Species (MHC) human (A29)
Country Zimbabwe
Keywords escape, optimal epitope
References Liang *et al.* 2008

- 1100 unique full-length Env sequences were analyzed and the positive selection (PS) pressure determined. The QUASI method was used across Clades A, B, C and D, to find PS sites dispersed across Env.
- Frequency of PS sites is stable over time.
- 25% to 61% PS sites are shared between subtypes A, B, C and D, so it is inferred that immune responses are targeted against the same general regions.
- Significant correlations between PS sites and neutralizing antibody response, helper response, antibody plus CTL response are found. This suggests that the NAb response might be the driving force behind HIV-1 Env evolution.
- PS-free sites that are targeted greatly by NAb and CTL were found. Functional reasons for the lack of positive selection in such regions must exist.
- PS-site-rare regions (conserved regions of Env) were examined for PS, and epitopes located in such regions. Epitope SFNCGGEFFY, restricted by HLA-A29 is on a region free from positive selection. It is found in Zimbabwean populations and has no known association with progression to AIDS.

HXB2 Location gp160 (375–384)
Author Location gp120
Epitope SFNCGGEFFY
Epitope name SY10(gp120)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A29)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A29-restricted epitope SFNCGGEFFY elicited an immune response in Chinese HIV-1 positive subjects as part of peptide GDPEIVMHSFNCGGEFFY.

HXB2 Location gp160 (376–383)
Author Location gp120
Epitope FNCGGEFF
Immunogen
Species (MHC) human (Cw4)
References Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive,
- HIV-2 sequence: TNCRGEFL – no cross-reactivity Johnson *et al.* [1993]

HXB2 Location gp160 (376–383)
Author Location gp120 (376–383)
Epitope FNCGGEFF
Immunogen
Species (MHC) human (Cw4)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 147/200 Brazilian HIV sequences; a common variant is FNCrGEFF.

HXB2 Location gp160 (376–384)
Author Location gp120 (376–384 IIIB)
Epitope FNCGGEFFY
Immunogen HIV-1 infection
Species (MHC) human (A29)
References Wilson *et al.* 1997a

- This is the optimal peptide for two CTL clones derived from two different donors.
- FNCRGEFFY and FNCRGGFFY are major and minor autologous variants in one of the donors, and showed reduced or no stimulatory activity for CTL from the host.
- The IIIB form and the form FNCAGEFFY were present in the other donor, and the CTL line had reduced activity with the FNCAGEFFY form relative to the index peptide.

HXB2 Location gp160 (376–384)
Author Location gp120 (376–384 IIIB)

Epitope PNCGGEFFY
Immunogen HIV-1 infection
Species (MHC) human (A29)
Keywords responses in children, mother-to-infant transmission, escape
References Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- PNCRGEFFY was an escape variant.

HXB2 Location gp160 (376–384)
Author Location gp120 (376–384 LAI)
Epitope FNCGGEFFY
Epitope name E2
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A29)
Keywords HAART, ART
References Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNgamma production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

HXB2 Location gp160 (376–384)
Author Location gp120
Epitope FNCGGEFFY
Immunogen HIV-1 infection
Species (MHC) human (A29)
Assay type Intracellular cytokine staining
Keywords immunodominance, genital and mucosal immunity
References Kaul *et al.* 2003

- Predefined immunodominant peptide responses were used to compare CD8+ T cells responses in the blood and cervix of 16 HIV+ Kenyan sex workers. Cervical responses were detected in 8/10 women from whom adequate samples could be obtained. The frequency of the CD8+ T cell response in the genital tract was comparable to the blood, with a trend toward being slightly higher.
- The immunodominant response was to this epitope in the PBMC of 1/16 patients (Kaul *et al.* 2001, AIDS, 107:1303).

HXB2 Location gp160 (376–384)
Author Location
Epitope FNCGGEFFY
Immunogen HIV-1 infection
Species (MHC) human (A29)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope FNCGGEFFY elicited a magnitude of response of 80 SFC with a functional avidity of 0.1nM.

HXB2 Location gp160 (376–384)
Author Location gp120 (376–384)
Epitope FNCGGEFFY
Immunogen
Species (MHC) human (A29)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 145/200 Brazilian HIV sequences; a common variant is FNCrGEFFY.

HXB2 Location gp160 (376–384)
Author Location gp120 (376–384)
Epitope FNCGGEFFY
Epitope name FNC
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART, supervised treatment interruptions (STI), immunodominance, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- One of the 7/8 study subjects that were HLA B8 recognized this CTL epitope.
- Patient SC19(HLA A11/12, B8/44, Cw06/0701, DR3/7, DR52/53, DQ 2/8) had a CTL response to epitopes FLKEKGGL, GEIYKRWII, ACQGVGGPGHK, AVDLSHFLK, and FNCGGEFFY that declined during therapy initiated at day 197.

HXB2 Location gp160 (376–384)
Author Location gp160

CTL CD8+

Epitope FNCGGEFFY
Epitope name FNC
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART, supervised treatment interruptions (STI)
References Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFNgamma Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

HXB2 Location gp160 (376–387)
Author Location gp120 (381–392 BRU)
Epitope KNCGGEFFYCNS
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Dadaglio *et al.* 1991

- Defined through blocking CTL activity, and Env deletions.

HXB2 Location gp160 (376–387)
Author Location Env (379–)
Epitope KNCGGEFFYCNS
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A*0202, A*0301, B*0702, B*1516
Country United States
Keywords escape, acute/early infection
References Bernardin *et al.* 2005

- Full HIV genomes from nine individuals were analyzed for mutations prior to seroconversion and 7 to 28 days later. It was found that the influence of the host's HLA type was reflected within weeks of infection; a statistically significant number of early nonsynonymous mutations were observed within previously reported CTL epitopes.
- E to G mutation was observed in position 6.

HXB2 Location gp160 (377–386)
Author Location gp160 (374–383 SUMA)
Epitope NCGGEFFYCN
Epitope name gp160 NN10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*1103, A*2402, B*1402, B*1501, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, acute/early infection, characterizing CD8+ T cells
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape muations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

HXB2 Location gp160 (377–386)
Author Location gp120 (377–386)
Epitope NCGGEFFYCN
Immunogen
Species (MHC) human
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 135/200 Brazilian HIV sequences; a common variant is NCrGEFFYCN in subtypes C and BF.

HXB2 Location gp160 (377–387)
Author Location gp120 (377–387)
Epitope NSGGEFFYSNS
Immunogen
Species (MHC) human (A2)
References Hickling *et al.* 1990

- Peptides recognized by class I restricted CTL can bind to class II.

HXB2 Location gp160 (383–391)
Author Location gp120 (385–393)
Epitope FYCNTTQLF
Epitope name Env385-9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Country Japan
References Ikeda-Moore *et al.* 1997

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402.
- This peptide induced CTL in 1/4 HIV-1 + people tested.

- FYCNTTQLF bound to A*2402 strongly, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

HXB2 Location gp160 (383–391)
Author Location gp160 (380–389 SUMA)
Epitope FYCNTTQLF
Epitope name GP160 FF9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Donor MHC A*1103, A*2402, B*1402, B*1501, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, acute/early infection, characterizing CD8+ T cells
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape muations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

HXB2 Location gp160 (383–391)
Author Location gp120
Epitope FYCNTTQLF
Epitope name FF9(gp120)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A24)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A24-restricted epitope FYCNTTQLF elicited an immune response in Chinese HIV-1 positive subjects as part of peptide SFNCGGEFFYCNTTQLF.
- 2 of the 30 HLA-A24 carriers responded to FYCNTTQLF-containing peptide with average magnitude of CTL response of 120 SFC/million PBMC.

HXB2 Location gp160 (393–400)
Author Location Env
Epitope STWNVNGTW
Epitope name SW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- SW9, STWNVNGTW, is a novel HLA-B27-restricted epitope that elicits a CTL IFN-gamma response in the same range as Los Alamos database peptides.

HXB2 Location gp160 (404–420)
Author Location gp120
Epitope GSNNTVGNPIILPCRI
Subtype A, B, C, D
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost, protein *Strain:* B clade 1007, B clade 1035
Species (MHC) human
Assay type Cytokine production
Keywords subtype comparisons, immunodominance
References Brown *et al.* 2006

- A vaccine study with B clade Envs in mice was unertaken to assess a subtype-specificity of responses. Four T-cell hybridomas responsive to subtype B envelope proteins were tested against 20 different subtype B envelope proteins and a protein each from subtypes A, C and D. IL-2 production was measured.
- No consistent correlation was found between T cell specificity towards epitopes from a certain (B) subtype or lack of specificity towards other (A, C, D) subtype.
- Not only did T-cell specificity not vary with subtype, but pairwise sequence comparisons of gp120 envelope sequences showed that some US-derived sequences were more similar to sequences from distant countries than to each other.

- Changes in core epitopes, flanking and distant regions, all affected responsiveness of the hybridomas to different subtype Env epitopes, showing that it is not only core changes that can eliminate T cell reactivity to an epitope.
- The above findings were substantiated by database analyses showing that epitope distributions are not necessarily dictated by subtype.
- This paper lists several variants of the epitope above, GSNNTVGNPIILPCRI.

HXB2 Location gp160 (410–429)
Author Location gp120 (410–429 PV22)
Epitope GSDTITLPCRIKQFINMWQE
Immunogen in vitro stimulation or selection
Species (MHC) human (DRA)
Keywords CD4+ CTL
References Bouhdoud *et al.* 2000

- CTL were studied through PBMC stimulation *in vitro* by gp120 pulsed autologous monocytes.
- Human CD4+ CTL clone (Een217) is an MHC class II HLA-DRA restricted CTL clone that can lyse antigen presenting HLA-DRA-transfected murine L cells – natural variants of the epitope resulted in an anergic response.
- Low concentrations of the HXB2-derived variant (GSDTITLPCRIKQIINMWQK) induced T cell anergy – higher concentrations could induce proliferation and cytotoxic activity.
- CDC42 (TGDIITLPCRIKQII-NRWQV), Eli (TNTNITLQCRIKQIIKMVAG) and Z3 (CTGNITLPCRIKQIIMNWQE) variants did not induce proliferation, cytotoxic or anergic responses.

HXB2 Location gp160 (416–424)
Author Location Env (413–421 SF2)
Epitope LPCRIKQII
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Keywords subtype comparisons, rate of progression
References Tomiyama *et al.* 1999

- HLA-B27, -B51, and -B57 are associated with slow progression to AIDS, while HLA-B35, -B8, -B24 are associated with a rapid progression to AIDS (Nat. Med. 2:405, 1996;Lancet 22:1187, 1986;Hum Immunol 22:73, 1988;Hum Immunol 44:156, 1995)
- 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%
- Of the 172 HIV-1 peptides with HLA-B*5101 anchor residues, 33 bound to HLA-B*5101, seven of these peptides were reactive with CTL from 3 B*5101 positive individuals, and six were properly processed.
- Four of the six epitopes were highly conserved among B subtype sequences, LPCRIKQII is not conserved.

HXB2 Location gp160 (416–424)
Author Location gp160 (416–424 LAI)
Epitope LPCRIKQII
Subtype B
Immunogen
Species (MHC) human (B*5101)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*5101 epitope.

HXB2 Location gp160 (416–424)
Author Location gp120 (378–385)
Epitope LPCRIKQII
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B51)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location gp160 (416–424)
Author Location gp160 (416–429)
Epitope LPCRIKQII
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epitopes, but this increased over time.

HXB2 Location gp160 (416–424)
Author Location gp160 (416–424)
Epitope LPCRIKQII
Epitope name gp160 LI9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.

- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-B51-restricted autologous epitope LPCRIKQII elicited CTL responses at the limit of detection for ELISpots at the last 2 time points. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location gp160 (416–424)
Author Location gp120
Epitope `LPCRIKWII`
Epitope name LI9(gp120)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide sequence (LVEICTEMEKEGKISKI) contains the exact sequence of a previously described HLA-B51 optimal epitope, EKEGKISKI, none of the 15 HLA-B51 carriers responded to it (author communication and Fig.1).

HXB2 Location gp160 (416–429)
Author Location gp120 (410–429 H3DCG)
Epitope `LPCRIKQFINMWQE`
Immunogen HIV-1 infection
Species (MHC) human (DR4)
Keywords CD4+ CTL
References Siliciano *et al.* 1988

- CD4+ CTL restricted by class II HLA-DR4, targets primed by CD4 mediated uptake of gp120.

HXB2 Location gp160 (416–435)
Author Location gp120 (421–440 LAI)
Epitope `LPCRIKQFINMWQEVGKAMY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Dadaglio *et al.* 1991

- Defined through blocking CTL activity, and Env deletions.

HXB2 Location gp160 (419–427)
Author Location gp120 (424–432 HXB2)
Epitope `RIKQIINMW`
Subtype B
Immunogen
Species (MHC) human (A*3201)
References Harrer *et al.* 1996b

- C. Brander notes that this is an A*3201 epitope in the 1999 database.

HXB2 Location gp160 (419–427)
Author Location gp120 (419–427 HXB2)
Epitope `RIKQIINMW`
Subtype B
Immunogen
Species (MHC) human (A*3201)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*3201 epitope.

HXB2 Location gp160 (419–427)
Author Location
Epitope `RIKQIINMW`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*3201)
Donor MHC A*3204, A*7412, B*0702, B*4403, Cw*0210, Cw*0702
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- Known epitope RIKQIINMW is HLA-A*3201-restricted. Response to a peptide containing this epitope was detected in an HLA-A*3204 positive rapid progressor, 12 weeks post-infection.

HXB2 Location gp160 (419–427)
Author Location gp120 (419–427)
Epitope `RIKQIINMW?`
Immunogen HIV-1 infection
Species (MHC) human (A29, A32)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the A2+ individuals was A29 and responded to RIKQIINMW, and another responder was A32 and these are thought to be presenting molecules.
- The sequence is unclear – Betts calls both peptide 30 and peptide 32 gp120 419–427 and the peptide sequences are not provided.

CTL CD8+

HXB2 Location gp160 (419–427)
Author Location gp120 (424–432 LAI)
Epitope RIKQFINMW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A32)
References Ray *et al.* 1998

- Autologous virus was used to detect CTL in two individuals, and in both cases strain-specific autologous CTL were found.
- The autologous epitope sequence was RIKQIINMW, MN and RF were KIKQFINMW and RIKQFVNMW respectively, and all were reactive with CTL clones.

HXB2 Location gp160 (419–427)
Author Location gp120 (420–428)
Epitope RIKQIINMW
Immunogen HIV-1 infection
Species (MHC) human (A32)
References Ferris *et al.* 1999

- This epitope is processed by a TAP1/2 dependent mechanism.

HXB2 Location gp160 (419–427)
Author Location gp120
Epitope RIKQIINMW
Epitope name A32-RW10(gp120)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A32)
Donor MHC A32, B44; A30, A32, B18, B27
Keywords HAART, ART, supervised treatment interruptions (STI)
References Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient B displayed the greatest response to epitope B44-AW11(p24) and also responded to A32-PW10(RT) in both PB and LN samples, while a third response against epitope A32-RW10(gp120) was only detected in the LN sample. Patient D displayed the greatest response to B27-KK10 (p24), and also responded to A30-RY11(p17), A32-PW10(RT), A30-KY11(RT), A32-RW10(gp120), and B18-YY9(Nef).

HXB2 Location gp160 (419–427)
Author Location Env (424–432 BRU)
Epitope RIKQIINMW
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (A32)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 0/9 CRF02_AG-infected Ivorians, and 3/9 B-infected French subjects.

HXB2 Location gp160 (419–427)
Author Location gp120
Epitope RIKQIINMW
Epitope name RW9(gp120)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A32)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Prewviously described HLA-A32-restricted epitope RIKQIINMW elicited an immune response in Chinese HIV-1 positive subjects as part of peptides ENITLPCRIKQIINMW and CRIKQIINMWQEVGKAMY.

HXB2 Location gp160 (419–427)
Author Location gp120
Epitope RIKQFINMW
Epitope name RW9(gp120)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A32)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.

- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A32-restricted epitope RIKQFINMW elicited an immune response in Chinese HIV-1 positive subjects.

HXB2 Location gp160 (421–435)
Author Location gp120 (421–440 LAI)
Epitope KQFINMWQEVGKAMY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Dadaglio *et al.* 1991
- Defined through blocking CTL activity, and Env deletions.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Clerici *et al.* 1991a
- Helper and cytotoxic T cells can be stimulated by this peptide (T1)

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Cease *et al.* 1987
- Helper and cytotoxic T cells can be stimulated by this peptide (T1)

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^a, H-2^b, H-2^f)
References Shirai *et al.* 1992
- In a murine system multiple class I molecules can present to CTL.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Immunogen HIV-1 exposed seronegative
Species (MHC) human
References Pinto *et al.* 1995
- CTL and T helper cell reactivity in healthcare workers exposed to HIV.

HXB2 Location gp160 (421–436)
Author Location gp120 (MN)
Epitope KQIINMWQEVGKAMYA
Immunogen HIV-1 infection
Species (MHC) chimpanzee
References Lubeck *et al.* 1997
- Epitope-specific CTL detected in chimpanzees immunized with adenovirus-HIV-1 MN gp160 recombinant.
- CTL response may account for protection against subsequent HIV-1 SF2 challenge in a chimpanzee lacking neutralizing antibodies.
- Helper and cytotoxic T cells can be stimulated by this peptide (T1)

HXB2 Location gp160 (425–434)
Author Location Env
Epitope NMWQEVGKAM
Epitope name 1257
Subtype multiple
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A02, A30, B39; A02, A03, B44, Cw05, Cw07
Country United States
Assay type T-cell Elispot
Keywords binding affinity, computational epitope prediction
References De Groot *et al.* 2003
- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for NMWQEVGKAM: 50%

HXB2 Location gp160 (432–451)
Author Location gp120 (439–458 IIIB)
Epitope KAMYAPPISGQIRCSSNITG
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *HIV component:* CD4BS, Gag, gp120, V3
Species (MHC) macaque
References Wagner *et al.* 1998b
- A VLP is a non-infectious virus-like particle self-assembled from HIV Pr55 gag – macaques were immunized with VLPs bound to either gp120 or V3+CD4 linear domains Gag and Env specific CTL were stimulated in each case, and Ab response to gag and gp120 was elicited, but the gp120 neutralizing response occurred only with whole gp120, not V3+CD4 – despite the CTL and Ab response, immunized macaques were infected by intervenous challenge with SHIV chimeric challenge stock.
- CTL specific for this epitope could be found both before and after SHIV challenge.

HXB2 Location gp160 (434–443)
Author Location gp120 (431–440)
Epitope MYAPPIGGQI
Immunogen vaccine
Vector/Type: peptide
Species (MHC) mouse (H-2K^d)
References Duarte *et al.* 1996

CTL CD8+

- Tolerization of CTL response with continued administration of soluble peptide.

HXB2 Location gp160 (434–448)
Author Location
Epitope MYAPPIRGQIRCSSN
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* gp140
Species (MHC) mouse
Assay type proliferation, T-cell Elispot
References Kumar *et al.* 2006c

- A recombinant plasmid DNA construct expressing env gp140 from B clade isolate 6101 was developed.
- The construct was highly immunogenic in mice and cross-reacted with clade C peptides. 3 immunodominant peptides were mapped out. Proliferation was observed in CD4+, CD8+ and CCR+ memory T cells.
- Immunodominant peptide MYAPPIRGQIRCSSN overlapped with the SYFPEITHI database predicted epitope MYAPPISGQ for the Balb/C mouse H2-Kd loci.

HXB2 Location gp160 (435–443)
Author Location
Epitope YAPPISGQI
Immunogen SHIV infection
Species (MHC) macaque (Mamu-A*01)
References Egan *et al.* 1999

- SHIV-infected rhesus macaques have high frequencies of response to the SIVmac epitope gag p11C,C-M (CTPYDINQM) but only a fraction of A*01 monkeys tested have responses to SIVmac pol epitope STPPLVRLV and HIV-1 env epitope YAPPISGQI.

HXB2 Location gp160 (435–443)
Author Location gp41 (89.6)
Epitope YAPPISGQI
Epitope name p41A
Immunogen SHIV infection, vaccine
Vector/Type: DNA, modified vaccinia Ankara (MVA) *Strain:* B clade 89.6, B clade HXBc2 *HIV component:* Env, Gag *Adjuvant:* IL-2/Ig
Species (MHC) macaque (Mamu-A*01)
Keywords immunodominance
References Barouch *et al.* 2001a

- Mamu-A*01+ rhesus monkeys infected with SHIV-89.6 and SHIV-HXBc2 make immunodominant responses to SIV Gag p11C epitope (CTPYDINQM) and a subdominant response to HIV-1 Env p41A epitope (YAPPISGQI)
- The binding affinities are the same for the two Mamu A*01 epitopes, so that is not what dictates the dominance.
- Monkeys vaccinated with MVA vectors carrying SIV gag/pol and HIV-1 env showed the same p11C epitope dominance and p41A epitope subdominance, but co-dominance was observed and the response to p41A increased when DNA vaccination was done using the SIV and HIV genes under CMV promotor control with IL2-IG adjuvant.

HXB2 Location gp160 (435–443)
Author Location Env
Epitope YAPPISGQI
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade 89.6P, SIV *HIV component:* Env, Gag
Species (MHC) macaque (Mamu-A*01)
Assay type Flow cytometric T-cell cytokine assay
Keywords vaccine-specific epitope characteristics, rate of progression, kinetics, memory cells, characterizing CD8+ T cells
References Davenport *et al.* 2004

- Activation and expansion of antigen-specific CD8+ T-cells shows a delay following infection that allows early viral replication. Until day 10, the kinetics of CD8+ T-cell expansion was the same in vaccinated and control macaques. An increase in virus-specific CD8+ T-cell numbers around day 10 in vaccinated macaques coincides with a slowing in viral replication. This indicates that while cytotoxic T-lyphocyte-inducing vaccines may have a long-term benefit in controling viral replication and preventing disease progression, they cannot prevent infection.

HXB2 Location gp160 (435–443)
Author Location Env (89.6)
Epitope YAPPISGQI
Epitope name p41A
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade 89.6, SIV *HIV component:* Env, Gag *Adjuvant:* IL-2/Ig
Species (MHC) macaque
References Barouch *et al.* 2000; Shen & Siliciano 2000

- Different HIV strains were used for different regions: SIVmac239 Gag and HIV-1 89.6P Env
- Monkeys that received the DNA vaccines augmented with IL-2/Ig were infected when challenged with pathogenic SHIV-89.6P, but had potent CTL responses, stable CD4+ T-cell counts, preserved virus-specific CD4+ T-cell responses, low to undetectable viral loads, and no evidence of disease or mortality by day 140 after challenge – monkeys that got a sham vaccine had high viral load, progressed to disease, and were half were dead by day 140.
- IL2/Ig consisting of interleukin-2 (IL-2) for immune stimulation, and the Fc portion of immunoglobulin G (IgG) for stability, was delivered either as protein or as DNA – both enhance the CTL response to vaccination, DNA IL2/Ig giving the most intense response.
- Responses to a dominant Mamu A*01 gag epitope SIV Gag p11C (CTPYDINQM) and a subdominant epitope HIV-1 Env p41A (YAPPISGQI) were tracked and had good durability prior to challenge, and the higher the prechallenge peak p11C CTL response, the lower the post-challenge viral load.
- No NAb responses were detected in the vaccinated monkeys prior to challenge, and comparable peak NAb titers developed in vaccinated monkeys and control monkeys with preserved CD4+ T-cells.
- Shen *et al.* 2000 is an accompanying commentary.

HXB2 Location gp160 (435–443)

Author Location Env (89.6)
Epitope YAPPISGQI
Epitope name p41A
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade 89.6, SIV *HIV component:* Env, Gag-Pol *Adjuvant:* IL-2/Ig
Species (MHC) macaque
Keywords immunodominance
References Barouch *et al.* 2001b

- Different HIV strains were used for different regions: SIVmac239 Gag/Pol and HIV-1 89.6P Env
- Four monkeys were vaccinated with a modified vaccinia Ankara (MVA) vaccine that elicited strong CTL to the immunodominant SIV gag epitope in 4/4 animals, and 1/4 made a response to the HIV Env epitope YAPPISGQI, as determined by tetramer staining and chromium release assays.
- The animals were infected when challenged with pathogenic SHIV-89.6P, but had potent CTL responses, secondary NAb responses upon challenge, partial preservation of CD4+ T-cell counts, lower viral loads, and no evidence of disease or mortality by day 168 after challenge – monkeys that got a sham vaccine had high viral load, progressed to disease, and 2/4 were dead by day 168.

HXB2 Location gp160 (444–453)
Author Location Env
Epitope RCSSNITGLL
Immunogen
Species (MHC) human (B56)
References De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conservered regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 of the predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFNγ production in an ELISPOT assay.
- RCSSNITGLL was newly defined as an epitope in this study, and was shown to stimulate an ELISPOT response, despite not detectably binding to HLA-B7.

HXB2 Location gp160 (466–475)
Author Location Env (464–473)
Epitope EVFRPGGGDM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2601)
Country Japan
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay, Other, HLA binding
Keywords immunodominance, optimal epitope
References Satoh *et al.* 2005

- Reverse immunogenetics was used to identify HIV-1 epitopes presented by HLA-A*2601. 110 peptides were predicted to bind to HLA-A*2601. 24 of these were demonstrated to bind through a HLA-A*2601 stabilization assay. Four of these, including this one, were shown to be epitopes endogenously presented by this allele, that can induce peptide-specific CD8 T-cells.HLA-A*2601 is common in Asia.
- This epitope was recognized in only 1/7 HLA-A*2601 HIV infected individuals.

HXB2 Location gp160 (466–480)
Author Location Env (457–471)
Epitope EIFRPGGGDMRDNWR
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Specifically, mice immunized with Gag and Tat, responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specificaly drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were no significantly affected by co-immunization with Env.
- This epitope was recognized by mice co-immunized with Env and Tat, but not by mice immunized with Env alone.

HXB2 Location gp160 (478–486)
Author Location Env (469–477)
Epitope NWRSELYKY
Subtype B
Immunogen HIV-1 infection, peptide-HLA interaction
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance
References Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, NWRSELYKY, is similar to human protein peroxysomal acylcoA thioestherase, sequence hNWRSELY.

CTL CD8+

HXB2 Location gp160 (486–494)
Author Location gp160 (485–493 SUMA)
Epitope YKVVKIEPL
Epitope name GP160 YL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*1103, A*2402, B*1402, B*1501, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, acute/early infection, characterizing CD8+ T cells
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape muations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

HXB2 Location gp160 (489–508)
Author Location gp120 (494–513 BRU)
Epitope VKIEPLGVAPTKAKRRVVQR
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Dadaglio *et al.* 1991

- Defined through blocking CTL activity, and Env deletions.

HXB2 Location gp160 (489–508)
Author Location Env (501–)
Epitope VKIEPLGVAPTKAKRRVVQR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A*0202, A*0301, B*0702, B*1516
Country United States
Keywords escape, acute/early infection
References Bernardin *et al.* 2005

- Full HIV genomes from nine individuals were analyzed for mutations prior to seroconversion and 7 to 28 days later. It was found that the influence of the host's HLA type was reflected within weeks of infection; a statistically significant number of early nonsynonymous mutations were observed within previously reported CTL epitopes.
- K to R mutation was observed in position 16.

HXB2 Location gp160 (489–508)
Author Location Env (496–506 BH10, LAI)
Epitope VKIEPLGVAPTKAKRRVVQR
Immunogen HIV-1 infection
Species (MHC) human
References Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is VAPTKAKRRVV) has similarity with the mast/stem cell growth factor receptor precursor fragment VVPTKADKRRSV.

HXB2 Location gp160 (489–508)
Author Location Env (497–512 BH10, LAI)
Epitope VKIEPLGVAPTKAKRRVVQR
Immunogen HIV-1 infection
Species (MHC) human
References Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is APTKAKRRVVQREKRA) has similarity with the human interferon-related IFRD2 (PC4-B) protein fragment ARTKARSRVRDKRA.

HXB2 Location gp160 (490–504)
Author Location Env
Epitope EIKPLGVAPTTTKRR
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CTL Env epitope, not previously described, and found within peptide EIKPLGVAPTTTKRR elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (494–508)
Author Location Env
Epitope LGVAPTTTKRRWER
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CTL Env epitope, not previously described, and found within peptide LGVAPTTTKRRWER elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (511–523)
Author Location Env
Epitope RAVGMGALIFEFL
Subtype CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide RAVGMGALIFEFL from subtype CRF02_AG.

HXB2 Location gp160 (511–526)
Author Location (C consensus)
Epitope RAVGIGAVFLGFLGAA
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location gp160 (519–543)
Author Location gp41 (519–543)
Epitope FLGFLGAAGSTMGAASLTLTVQARC
Immunogen HIV-1 infection
Species (MHC) human (Cw7)
References Nehete *et al.* 1998a

- Three long-term non-progressors and one asymptomatic HIV+ individual were studied and found to have HLA class I C-restricted CD8+ Env-specific CTLs – Cw7 specific CTL were found against three peptides, including this one.
- HLA-C antigens are expressed on lymphoid cells to a lesser extent, 10% of either HLA-A or HLA-B.
- HLA-C confers protection against lysis by natural killer cells and by non-MHC-restricted effector T cells and Cw7 directly governs this resistance to lysis – the authors hypothesize that pathogens that inhibit antigen expression and class I expression may particularly down regulate Cw7, thus triggering non-MHC restricted killing.

HXB2 Location gp160 (529–537)
Author Location Env (529–)
Epitope TMGAASITL
Epitope name Env529
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* gp160 *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was an intermediate A2 binder that did not induce CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 5/17 HIV+ HLA-A2 subjects.

HXB2 Location gp160 (529–537)
Author Location gp41 (529–537)
Epitope TMGAASITL
Immunogen
Species (MHC) human (A2)
Keywords subtype comparisons, viral fitness and reversion

CTL CD8+

References de Queiroz *et al.* 2007
- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 37/50 Brazilian HIV sequences.

HXB2 Location gp160 (529–537)
Author Location
Epitope TMGAASITL
Epitope name Env 529
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords variant cross-recognition or cross-neutralization
References Thorn *et al.* 2007
- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Env 529 TMGAASITL epitope was found in 3 patients and 5 of them had a CTL immune response to it.
- The epitope TMGAASITL is one of the most frequently targeted and sequence variation was seen in TCR interacting residues.

HXB2 Location gp160 (529–537)
Author Location Env (529–)
Epitope TMGAASITL
Epitope name Env529
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, acute/early infection
References Fomsgaard *et al.* 2008
- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.
- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Env control epitope TMGAASITL, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients.

HXB2 Location gp160 (548–565)
Author Location Env
Epitope IVQQQSNLLRAIEAQQHL
Epitope name ENV-75
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007
- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, IVQQQSNLLRAIEAQQHL differs from the consensus C sequence IVQQQSNLLRAIEAQQHL at 0 amino acid positions, i.e. the two clades' peptides are identical.

HXB2 Location gp160 (552–571)
Author Location Env (552–571)
Epitope QSNLLRAIEAQQHMLQLTVW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002
- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location gp160 (555–565)
Author Location gp41

Epitope LLRAIEAQQHL
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A11.1)
Country Thailand
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords optimal epitope
References Kantakamalakul *et al.* 2006

- T cell responses in CRF01_AE infected individuals from Thailand were studied.
- Based on two overlapping peptide sequences that were both reactive, as well as conserved anchor residues, this peptide is suggested to contain a previously defined epitope, RAIEAQQHL, that is reported to be restricted by HLA-B51, -Cw*0304 and -Cw*0801.

HXB2 Location gp160 (557–564)
Author Location (C consensus)
Epitope RAIEAQQM
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- RAIEAQQM is an optimal epitope.

HXB2 Location gp160 (557–565)
Author Location gp41 (46–54)
Epitope RAIEAQQHL
Immunogen HIV-1 infection
Species (MHC) human (B*1501, B*5101, Cw*0304)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope RAIEAQQHL was predicted to be restricted by HLA B*1501, B*1517, B*5101 and C*0304.

HXB2 Location gp160 (557–565)
Author Location gp41 (557–565)
Epitope RAIEAQQHL
Epitope name RL9
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (B*51, Cw*03)
Country Kenya
Assay type Cytokine production, proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2007

- The authors suggest that epitope variation has different effects on the HIV- specific immune responses of effector memory T cells (Tem) and central memory T cells (Tcm). They show a lack of correlation between IFN-gamma ELISPOT (Tem typical) and proliferation (Tcm typical) assays for specific epitopes in subjects. Since proliferating CTL also correlate with high intracellular IFN-gamma levels, they surmise that proliferating Tcm differentiate to express Tem functions.
- They also show that proliferating CTL numbers correlate with higher CD4 cell counts.
- Several patients responded strongly to epitope variants that were not part of their autologous HIV-1 sequences. Thus they suggest more comprehensive functional characterizations than the usual overnight IFN-gamma ELISPOTs as well as assessments of Tem versus Tcm specific responses rather than general CTL immune responses.
- 5 variants of this index epitope RAIEAQQHL, RL9, were tested - RAIEAQQHm, RAIEAQQqm, RAIEvQQHL, RAIEgQQHL, RAIEtQQHL. The index peptide RAIEAQQHL and variant RAIEAQQHm while being most prevalent, are commonly recognized in ELISPOT but do not elicit proliferation. Conversely, the relatively rare variant RAIEvQQHL had proliferative responses more often than it was recognized by ELIspot.
- RL9 has previously published restriction to HLA-Cw*03 and -B*51.

HXB2 Location gp160 (557–565)
Author Location gp41 (557–665)
Epitope RAIEAQQWQ
Epitope name E3
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Keywords HAART, ART, escape
References Samri *et al.* 2000

- The epitope was recognized by patient 246#1 in a study of the effects of therapy escape mutations on CTL recognition.

HXB2 Location gp160 (557–565)
Author Location gp41 (46–54 HIV-MN)
Epitope RAIEAQQHL
Epitope name RL9
Subtype B
Immunogen HIV-1 infection

Species (MHC) human (B*5101)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.

HXB2 Location gp160 (557–565)
Author Location gp160 (557–565)
Epitope RAIEAQQHL
Immunogen HIV-1 infection
Species (MHC) human (B15, B51)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these eptiopes, but this increased over time.

HXB2 Location gp160 (557–565)
Author Location gp41 (557–565 IIIB)
Epitope RAIEAQQHL
Immunogen HIV-1 infection
Species (MHC) human (B51)
References Sipsas *et al.* 1997

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB.
- KAIEAQQHL, a variant found in HIV-1 NY5CG, was also recognized.
- RAIEAQQHM, a variant found in HIV-1 JRCSF, was also recognized.
- RAIDAQQHL, a variant found in HIV-1 ETR, was also recognized.
- RAIKAQQHL, a variant found in HIV-1 CDC42, was also recognized.

HXB2 Location gp160 (557–565)
Author Location gp41 (557–565)
Epitope RAIEAQQHL
Immunogen HIV-1 infection
Species (MHC) human (B51)
References Ferris *et al.* 1999

- This epitope can be processed by a TAP1/2 dependent mechanism.

HXB2 Location gp160 (557–565)
Author Location gp41 (557–565)
Epitope RAIEAQQWQ
Epitope name RAI
Immunogen HIV-1 infection
Species (MHC) human (B51)
Keywords HAART, ART, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- None of the 8 study subjects recognized this epitope but none were HLA B51+

HXB2 Location gp160 (557–565)
Author Location gp41 (47–55)
Epitope RAIEAQQHL
Immunogen HIV-1 infection
Species (MHC) human (B51)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location gp160 (557–565)
Author Location gp41 (557–565 LAI)
Epitope RAIEAQQHL
Epitope name E3
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
Keywords HAART, ART
References Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNgamma production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

HXB2 Location gp160 (557–565)

Author Location gp41
Epitope RAIEAQQHL
Epitope name B51-RL9(qp41)
Immunogen HIV-1 infection
Species (MHC) human (B51)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location gp160 (557–565)
Author Location gp41
Epitope RAIEAQQHL
Epitope name RL9(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide sequences (IVQQQSNLL-RAIEAQQHL and LRAIEAQQHLLQLTVWGI) contain the exact sequence of a previously described HLA-B51 epitope, RAIEAQQHL, none of the 15 HLA-B51 carriers responded to it (author communication and Fig.1).

HXB2 Location gp160 (557–565)
Author Location gp41
Epitope RAIEAQQHL
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B57, B58, B63)
Assay type CD8 T-cell Elispot - IFNγ
Keywords cross-presentation by different HLA, optimal epitope
References Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This is a putative HLA-B63/57/58 epitope containing the B58 supertype binding motif. Significantly more often recognized by B63+ and B57/58+ subjects than by negative subjects.

HXB2 Location gp160 (557–565)
Author Location Env (gp160) (557–565)
Epitope RAIEAQQHL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*0304)
Keywords subtype comparisons
References Currier *et al.* 2002a

- Cross-reactive responses were found in PBMC isolated from individuals infected with either B or CRF01_AE clade viruses, as determined by Elispot assays of target cells expressing recombinant vaccinia viruses expressing HIV-1 gag, env, nef and pol from many clades.
- CTL from subject US101, infected with a clade B virus, displayed broad cross-reactivity to HIV-1 clade A, B, C, D, CRF01_AE, F G, recognized this epitope. Clade B and C had a L->M change in the C-term position that was tolerated. The H clade Env was not cross-reactive, and had the sequence RA-IAARQHM.

HXB2 Location gp160 (557–565)
Author Location gp41 (46–54)
Epitope RAIEAQQHL
Immunogen
Species (MHC) human (Cw*0304)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location gp160 (557–565)
Author Location (C consensus)
Epitope RAIEAQQHM
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords cross-presentation by different HLA, characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.

CTL CD8+

- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location gp160 (557–565)
Author Location gp160 (557–565)
Epitope RAIEAQQHL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*12)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, RAIEAQQHL, was detected within overlapping peptides IVQQQNNLLRAIEAQQHL and LRAIEAQQHLQLTVWGI.

HXB2 Location gp160 (557–565)
Author Location gp41 (46–54)
Epitope RAIEAQQHL
Immunogen
Species (MHC) human (Cw*15)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location gp160 (557–565)
Author Location
Epitope RAIEAQQHL
Immunogen HIV-1 infection
Species (MHC) human (Cw03, Cw15)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- Based on a prediction of the minimum number of HLA alleles needed to cover the HLA representation in all responders to this epitope, a minimum set of 6 alleles was found: 2 alleles previously known to be associated (Cw03, Cw15) and 4 additional alleles (A02, A30, B58, Cw04).

HXB2 Location gp160 (557–565)
Author Location gp41 (46–54)
Epitope RAIEAQQHL
Epitope name RL9
Immunogen HIV-1 infection
Species (MHC) human (Cw15, Cw3)
Assay type CTL suppression of replication
Keywords class I down-regulation by Nef
References Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Env epitope RAIEAQQHL-recognizing HLA-C restricted CTLs were unaffected by Nef.

HXB2 Location gp160 (557–565)
Author Location
Epitope RAIEAQQHM
Epitope name RM9
Immunogen
Species (MHC) human (Cw8)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a Cw08 epitope.

HXB2 Location gp160 (557–565)
Author Location gp41 (557–565 IIIB)
Epitope RAIEAQQHL
Immunogen HIV-1 infection
Species (MHC) human
Keywords responses in children, mother-to-infant transmission
References Wilson *et al.* 1996

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.
- RAIDAQQHL and RVIEAQQHL, naturally occurring variants, were found in mother and are recognized.

HXB2 Location gp160 (557–565)
Author Location gp41 (557–565)
Epitope RAIEAQQHL
Immunogen HIV-1 infection
Species (MHC) human
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.

- 1/11 of the A2+ individuals was HLA A*0201, A32, B60, B78, and responded to RAIEAQQHL, previously noted to be B51.

HXB2 Location gp160 (557–565)
Author Location gp41 (557–565 IIIB)
Epitope RAIEAQQHL
Immunogen HIV-1 infection
Species (MHC) human
Keywords mother-to-infant transmission, escape
References Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- This epitope was invariant in both the mother and her infant.

HXB2 Location gp160 (557–565)
Author Location Env (555–567 BH10, LAI)
Epitope RAIEAQQHL
Immunogen HIV-1 infection
Species (MHC) human
References Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is LLRAIEAQQHLL) has similarity with human MHC class II regulatory factor RFX1 fragment LLRLMEDQQHMA.

HXB2 Location gp160 (557–565)
Author Location gp160
Epitope RAIEAQQHL
Subtype A, B, C, D
Immunogen HIV-1 infection, vaccine
Vector/Type: vaccinia *Strain:* A clade, B clade, D clade NDK, C clade consensus *HIV component:* Env
Species (MHC) human
Donor MHC A*3201, A*3601, B*5301, B*8101, Cw*0401, Cw*0804
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References McKinnon *et al.* 2005

- Interclade cross-reactivity of clades A, B, C, and D was tested using recombinant vaccinia-based IFN-gamma Elispot assay. 47/74 women had a positive Elispot response to at least one clade, and cross-clade responses were frequent. Clade A responses were most frequent, as expected, as clade A dominates the Kenyan epidemic (85% of the 47 women responded to clade A Env, 74% to B, 62% to C, and 43% to D). Cross-clade CD8 T-cell responses were common and directed at conserved epitopes.
- There was a greater magnitude of response to A clade peptides in individuals who responded to more than one clade; a 2-fold higher response was observed in clade A in 36% (9/25) of these individuals, and the response to A peptides was never lower. VTEEFNMWK responses were detected in 2 women that had Env responses to all 4 clades, and clade A gave the highest responses; a VnEEFNMWK variant was in clade B and D, and the clade C Env carried VnEEFNMWe. One woman also reacted with RAIEAQQHL, the other with KNCSFNMTT. RAIEAQQHL was identical in clades A, B, and D, while C carried RAIEAQQHm.

HXB2 Location gp160 (557–565)
Author Location Env
Epitope RAIEAQQHL
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101, B*1567, B*8101, Cw*1402, Cw*1801; A*0201, A*2901, B*0801, B*4805, Cw*0304, Cw*1505; A*6802, A*7401, B*1510, B*4901, Cw*0304, Cw*0701
Country Kenya
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2008

- To evaluate the use of IFN-gamma ELISpot and proliferation assays, the two were compared in a cohort of HIV-1-infected Kenyan sex-workers. ELISpot does not always correlate with viral load and replication or disease progression. The exclusive use of these assays makes definition of CTL response in disease incomplete, especially for memory T cells.
- Despite assaying for 24 INF-gamma and 41 proliferative responses, only 5 of these responses overlapped in the same subject. 18 peptide-epitopes including 10 epitopes and their variants were used in this study.
- RAIEAQQHL did not elicit proliferation alone in any subject; but elicited ELISpot response in 3 subjects; and both responses in 1 subject.

HXB2 Location gp160 (557–565)
Author Location Env
Epitope RAIEVQQHL
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101, B*3701, B*8101, Cw*0602, Cw*1801; A*6802, A*7401, B*1510, B*4901, Cw*0304, Cw*0701
Country Kenya
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2008

- To evaluate the use of IFN-gamma ELISpot and proliferation assays, the two were compared in a cohort of HIV-1-infected Kenyan sex-workers. ELISpot does not always correlate with viral load and replication or disease progression. The exclusive use of these assays makes definition of CTL response in disease incomplete, especially for memory T cells.

CTL CD8+

- Despite assaying for 24 INF-gamma and 41 proliferative responses, only 5 of these responses overlapped in the same subject. 18 peptide-epitopes including 10 epitopes and their variants were used in this study.
- RAIEVQQHL elicited proliferation response in 1 subject; and ELISpot response in 1 subject.

HXB2 Location gp160 (557–566)
Author Location Env (557–566)
Epitope RAIEAQQHML
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef. 3
- of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope RAIEAQQHML had >50% conservation across clades B and non-Indian C, but showed no conservation to subtype A. It is predicted to be restricted by HLA-A*69 or -B*40

HXB2 Location gp160 (565–573)
Author Location Env (565–)
Epitope LLQLTVWGI
Epitope name Env565
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* Env *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced CD8+ T-cell IFN gamma responses in mice. Responses to the peptide were not detected in 17 HIV+ HLA-A2 subjects.

HXB2 Location gp160 (565–573)
Author Location gp41 (565–573)
Epitope LLQLTVWGI
Immunogen
Species (MHC) human (A2)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 26/50 Brazilian HIV sequences; a common variant is mLQLTVWGI in subtypes C and BF.

HXB2 Location gp160 (565–573)
Author Location
Epitope LLQLTVWGI
Epitope name Env 565
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Previously defined Env 565 LLQLTVWGI epitope was found in 6 patients but none had CTL immune responses to it.

HXB2 Location gp160 (565–573)
Author Location Env (731–739)
Epitope LLQLTVWGI
Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind four of the five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802).

HXB2 Location gp160 (570–589)

Author Location gp41 (571–590 LAI)
Epitope VWGIKQLQARILAVERYLKD
Subtype B
Immunogen vaccine
Vector/Type: vaccinia prime with gp160 boost *Strain:* B clade LAI *HIV component:* gp160
Species (MHC) human (DR1)
Keywords CD4+ CTL
References Kent *et al.* 1997a

- VWGIKQLQARILAVERYLKD, present in HIV-1 LAI, was the immunizing strain.
- VWGIKQLQARVLAVERYLKD, present in HIV-1 MN, was also recognized.
- VWGIKQPQARVLAVERYLRD was the form carried by the autologous strain that infected the vaccinee.
- Lysis of the target cells by CD4+ CTL was inhibited with the addition of the peptide representing the autologous strain.
- The infecting virus epitope also antagonized the proliferative functions of the CD4+ CTL clone.
- The behavior of the autologous strain presents a possible mechanism for vaccine failure since the infecting virus not only escapes CTL activity, but inhibits the ability of CTL to recognize other variants.

HXB2 Location gp160 (572–590)
Author Location gp41 (572–590 BRU)
Epitope GIKQLQARILAVERYLKDQ
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU *HIV component:* gp160
Species (MHC) human (DPw4.2)
References Hammond *et al.* 1991

- CD4+ CTL.

HXB2 Location gp160 (575–599)
Author Location gp41 (575–599 IIIB)
Epitope QLQARILAVERYLKDQQLLGIWGCS
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Jassoy *et al.* 1992

- Epitope recognized by CTL clone derived from CSF.

HXB2 Location gp160 (577–587)
Author Location gp41 (6558–6568)
Epitope QTRVLAIERYL
Epitope name QL11
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B*5802)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HLA associated polymorphism
References Ngumbela *et al.* 2008

- HLA-B*5801 and -B*5802 differ by 3 aa, but B*5801 is associated with effective HIV-1 viral load control and B*5802 with rapid disease progression. By studying n=1074 HIV-C positive subjects with chronic infection, it was shown that HLA-B*5802 is ineffectual in immune control of AIDS.
- Env epitope Q11, QTRVLAIERYL, is the optimal one targeted by HLA-B*5802 and all its variants showed broad CTL cross-recognition, indicating lack of escape. Q11 variants include QaRVLAIERYL, QTRVLAmERYL, QTRVLAlERYL, QTRVLAvERYL and QaRVLAmERYL.

HXB2 Location gp160 (577–587)
Author Location (C consensus)
Epitope QTRVLAIERYL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5802)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- QTRVLAIERYL is an optimal epitope.

HXB2 Location gp160 (578–586)
Author Location Env
Epitope ARVLAVERY
Epitope name AY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- AY9, ARVLAVERY, is a novel HLA-B27-restricted epitope that elicits a CTL IFN-gamma response in the same range as Los Alamos database peptides.

HXB2 Location gp160 (580–592)
Author Location Env
Epitope VLALERYLKDQQL
Subtype CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

CTL CD8+

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide VLALERYLKDQQL from subtype CRF02_AG.

HXB2 Location gp160 (583–592)
Author Location gp41 (583–592 PV22)
Epitope VERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Jassoy *et al.* 1993

- HIV-1 specific CTLs release γ-IFN, and α- and β-TNF.

HXB2 Location gp160 (583–592)
Author Location Env
Epitope VERYLKDQQL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Donor MHC A1, A19, B*3501, B44, Cw16, Cw7; A*0201, A19, B14, B44, Cw16, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
References Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-B14 restricted epitope, VERYLKDQQL was mutated to VERYLrDQQL in the daughter D2 isolate.

HXB2 Location gp160 (584–592)
Author Location gp41 (584–592)
Epitope ERYLKDQQL
Epitope name EL9
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (A*32, B*14)
Country Kenya
Assay type Cytokine production, proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2007

- The authors suggest that epitope variation has different effects on the HIV- specific immune responses of effector memory T cells (Tem) and central memory T cells (Tcm). They show a lack of correlation between IFN-gamma ELISPOT (Tem typical) and proliferation (Tcm typical) assays for specific epitopes in subjects. Since proliferating CTL also correlate with high intracellular IFN-gamma levels, they surmise that proliferating Tcm differentiate to express Tem functions.
- They also show that proliferating CTL numbers correlate with higher CD4 cell counts.
- Several patients responded strongly to epitope variants that were not part of their autologous HIV-1 sequences. Thus they suggest more comprehensive functional characterizations than the usual overnight IFN-gamma ELISPOTs as well as assessments of Tem versus Tcm specific responses rather than general CTL immune responses.
- 6 variants of this index epitope ERYLKDQQL, EL9, were tested - ERYLqDQQL, EsYLqDQQL, EsYLKDQQL, ERYLrDQQL, ERYLtDQQL, ERYLsDQQL. EL9 has previously published restrictions to HLA-B*14 and -A*32.

HXB2 Location gp160 (584–592)
Author Location gp41
Epitope ERYLKDQQL
Epitope name EL9(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A32)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A32-restricted epitope ERYLKDQQL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide RVLAVERYLKDQQLLGIW.

HXB2 Location gp160 (584–592)
Author Location gp41 (584–592 HXB2)
Epitope ERYLKDQQL
Epitope name E4
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A32, B14)

CTL CD8+

Keywords HAART, ART
References Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNgamma production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

HXB2 Location gp160 (584–592)
Author Location gp41 (584–592)
Epitope `ERYLKDQQL`
Immunogen
Species (MHC) human (A32, B14)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 35/50 Brazilian HIV sequences; all variants detected (ERYrKDQQL, ERYgKDQQL, and ERYqKDQQL) involved the same residue.

HXB2 Location gp160 (584–592)
Author Location gp41
Epitope `ERYLRDQQL`
Immunogen HIV-1 infection
Species (MHC) human (B*14)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2002

- Neisseria gonorrhea cervititis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
- Ghonorrhea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

HXB2 Location gp160 (584–592)
Author Location (C consensus)
Epitope `ERYLKDQQL`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*14)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location gp160 (584–592)
Author Location Env (584–592)
Epitope `ERYLKDQQL`
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human (B*14)
Assay type Other
Keywords kinetics
References Wick *et al.* 2005

- Experimental and mathematical models were used to estimate the number of HIV-infected cells that can be killed by CD8+ T-cells. On average, CTLs can kill from 0.7 to 3.0 cells/day.
- CTL clones LWC8 and 115M21 recognize epitope ERYLKDQQL and were used to study the inhibition of HIV-1 replication in acutely infected cells in vitro.

HXB2 Location gp160 (584–592)
Author Location (C consensus)
Epitope `ERYLKDQQL`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1401)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- ERYLKDQQL is an optimal epitope.

HXB2 Location gp160 (584–592)
Author Location gp41 (584–592 PV22)
Epitope `ERYLKDQQL`
Immunogen HIV-1 infection
Species (MHC) human (B*1402)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*1402 epitope.

HXB2 Location gp160 (584–592)
Author Location gp160 (598–597 BORI, SUMA)
Epitope `ERYLKDQQL`
Epitope name gp160 EL9
Subtype B

Immunogen HIV-1 infection
Species (MHC) human (B*1402)
Donor MHC A*2902, B*1402, Cw*0802; A*1103, A*2402, B*1402, B*1501, Cw*0802
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, immunodominance, escape, acute/early infection, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient BORI had high viral loads and rapid CD4 decline. BORI mounted 8 detected responses. BORI did not control viral replication well, and escape mutations occurred early and in most epitopes, 6/7 that were precisely identified.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Eleven variants in the ERYLKDQQL epitope were found in the patient BORI. ERYLKeQQp came up first at day 17 from onset of symptoms, but wasn't tested for escape properties. ERYLrDQQL came up next, by day 31, but didn't confer escape in a Cr release assay. By day 218, three variants were found, all of which gave a diminished response: ERYLtDQQL, ERYLqDQQL, and ERYLsDQQL. By day 556 a complex mixture was present, also including the ERYLmDQQL variant that gave a further reduction in the response, and many double mutants: ERYLmDQrL, ERYLmDrQL, ERYLmDQlL, ERYLtDQrL and ERYrtDQrL.
- In SUMA, the only variation found in the 24 epitopes was in three overlapping epitopes in Tat, and in this gp160 epitope; variation accumulated early in infection in the Tat epitopes, but this epitope was stable until a sample 736 days post-infection, when only the ERYLqDQQL variant was detected. This variant was not tested with CTL from SUMA, but gave a diminished response in BORI.

HXB2 Location gp160 (584–592)
Author Location Env
Epitope `ERYLKDQQL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1402, B14)
Donor MHC A1, A19, B*3501, B44, Cw16, Cw7; A*0201, A19, B14, B44, Cw16, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
References Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-B14/B*1402 restricted epitope, ERYLKDQQL was mutated to ERYLrDQQL in the daughter D2 isolate.

HXB2 Location gp160 (584–592)
Author Location gp41
Epitope `ERYLKDQQL`
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Wagner *et al.* 1998a

- CTL specific for HIV epitopes were used to show that the mediators of both the cytolytic (granzyme A was used as the marker) and non-cytolytic (HIV-1 inhibitory chemokines MIP-1 α and RANTES were used as markers) anti-viral responses are localized within the CTL's cytotoxic granules.

HXB2 Location gp160 (584–592)
Author Location gp41 (584–592)
Epitope `ERYLKDQQL`
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords HAART, ART
References Kalams *et al.* 1999b

- Two patients were followed before and after HAART – reduced plasma HIV-1 RNA levels resulted in a decline in HIV *in vivo* activated specific CTL such that by day 260 CTL activities were undetectable.
- ERYLKDQQL was the dominant response in one of the individuals, SLYNTVATL subdominant.
- Sporadic breakthrough in viremia resulted in increases in CTLp.
- Peptide-tetramer staining demonstrated that declining levels of *in vivo*-activated CTL were associated with a decrease in expression of CD38.
- Memory CTL frequency directed against Vac-Gag, Vac-RT, Vac-Env, and Vac-Nef initially increased with HAART and then decreased with the decline of the viral load.

HXB2 Location gp160 (584–592)
Author Location gp41 (591–599 SF2)
Epitope ERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-A3, -A32, -B7, -B14.

HXB2 Location gp160 (584–592)
Author Location gp41 (591–599 SF2)
Epitope ERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords subtype comparisons
References Cao *et al.* 1997a

- The consensus sequence for clades B, C, and D is ERYLKDQQL.
- The consensus sequence for clade A is ERYLRDQQL and it is equally reactive.
- The consensus sequence for clade E is ERYLKDQKF and it is not reactive.

HXB2 Location gp160 (584–592)
Author Location gp41
Epitope ERYLKDQQL
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B14)
Keywords subtype comparisons, HIV exposed persistently seronegative (HEPS)
References Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A and D subtype consensus are identical to the B clade epitope, ERyLkDQQL.

HXB2 Location gp160 (584–592)
Author Location gp41 (584–592)
Epitope ERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Sipsas *et al.* 1997

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB.

HXB2 Location gp160 (584–592)
Author Location gp41 (584–592)
Epitope ERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Yang *et al.* 1996

- CD4+ cell lines acutely infected with HIV were studied to determine their susceptibility to lysis by CTL.
- Clones specific for RT lysed HIV-1 infected cells at lower levels than Env or Gag specific clones.
- The distinction was thought to be due to lower expression of RT relative to Env and Gag.
- CTL can lyse infected cells early after infection, possibly prior to viral production.

HXB2 Location gp160 (584–592)
Author Location gp41 (584–592)
Epitope ERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human (B14)
Assay type CTL suppression of replication
References Yang *et al.* 1997a

- CTL inhibit HIV-1 replication at effector cell concentrations comparable to those found *in vivo*.
- CTL produced HIV-1-suppressive soluble factors – MIP-1α, MIP-1β, RANTES, after antigen-specific activation.
- CTL suppress HIV replication more efficiently in HLA-matched cells.

HXB2 Location gp160 (584–592)
Author Location gp41 (584–592 PV22)
Epitope ERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Johnson *et al.* 1992

- Two overlapping CTL epitopes were mapped with different HLA restriction (also see YLKDQQLL HLA-B8)

HXB2 Location gp160 (584–592)
Author Location gp41 (584–592 PV22)
Epitope ERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Jassoy *et al.* 1993

- HIV-1 specific CTLs release γ-IFN, and α- and β-TNF.

HXB2 Location gp160 (584–592)
Author Location gp41 (584–592 HXB2)
Epitope ERYLKDQQL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Kalams *et al.* 1994; Kalams *et al.* 1996

- Longitudinal study of T cell receptor usage in a single individual.
- Persistence of oligoclonal response to this epitope for over 5 years.

HXB2 Location gp160 (584–592)
Author Location gp41 (584–592)
Epitope ERYLKDQQL
Immunogen peptide-HLA interaction
Species (MHC) human (B14)
References DiBrino *et al.* 1994a

- Epitope studied in the context of HLA-B14 binding.

HXB2 Location gp160 (584–592)

Author Location gp41 (584–592)
Epitope ERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Hammond *et al.* 1995

- This peptide can be processed for HLA-B14 presentation in a TAP-1/2 independent pathway.

HXB2 Location gp160 (584–592)
Author Location gp41 (584–592)
Epitope ERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Kalams *et al.* 1996

- CTL response to this epitope was studied in 5 HLA-B14 positive persons.
- CTL responses were detected in all five, and CTL clones were isolated from 4/5.
- A diverse repertoire of TCRs recognized this epitope, with similar fine specificities.
- 3/5 subjects showed no variation in viral sequence, 2/5 had a dominant variant that resulted in poor recognition, ERYLQDQQL.
- A minor CTL response specific for the ERYLQDQQL could be detected by two individuals, but the major CTL response was to the ERYLKDQQL form even when it was the minority form.
- Some single amino acid substitutions were well tolerated by most of the CTL clones tested, but others, particularly in the center three amino acid positions, abrogated peptide stimulatory activity.

HXB2 Location gp160 (584–592)
Author Location gp120 (584–592)
Epitope ERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Ferris *et al.* 1999; Hammond *et al.* 1995

- This epitope is processed by both TAP1/2 dependent and independent mechanisms.

HXB2 Location gp160 (584–592)
Author Location gp41
Epitope ERYLKDQQL
Immunogen
Species (MHC) human (B14)
References Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective.
- HIV-2 sequence: EKYLQDQAR – no cross-reactivity Johnson *et al.* [1992]

HXB2 Location gp160 (584–592)
Author Location gp41 (SF2)
Epitope ERYLKDQQL
Epitope name EL9
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords acute/early infection
References Goulder *et al.* 2001a

- Data from patient AC13 suggest a role for this epitope in initial control of viremia in acute infection, as it is one of several subdominant CTL epitopes recognized during the initial decline in viremia.
- A CTL response to SL9, SLYNTVATL, was not evident until 18 months post-presentation.
- Recognized by two A*0201-positive chronically infected subjects.

HXB2 Location gp160 (584–592)
Author Location gp41 (584–592)
Epitope ERYLKDQQL
Epitope name 588K
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords HAART, ART, TCR usage
References Islam *et al.* 2001

- Transcript frequencies of four CTL clones from patient 115, with a chronic and stable HIV-1 infection, were tracked in a longitudinal study of samples collected 6-11 years post infection: clone M21 and E15 recognize ERYLKDQQL,and clone D87 recognizes variant ERYLQDQQL, and clone p175b recognizes the A2 epitope SLYNTVATL.
- CTL clone M21 uses the Vβ 4, CDR3 VKDGA, Jβ 1.2 TCR beta gene, and clone E15 uses the Vβ 4, CDR3 VEDWGGAS Jβ 2.1 TCR beta gene, and D87 uses Vβ8, ALNRVD, Jβ2.1.
- Responses were stable even through HAART with undetectable viral loads but frequencies varied over time by 100-fold, ranging from 0.012% of the total population for SLYNTVATL at its lowest point to 3.78% for M21, with the relative frequencies of clones shifting over time.

HXB2 Location gp160 (584–592)
Author Location gp41 (589–597 SF2)
Epitope ERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with preseroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B14+ individuals that had a CTL response to this epitope broken down by group: 3/3 group 1, 1/2 group 2, and 0/0 group 3.

HXB2 Location gp160 (584–592)
Author Location gp41 (589–597)
Epitope ERYLRDQQL
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B14)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location gp160 (584–592)
Author Location gp41 (JRCSF)
Epitope ERYLKDQQL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Severino *et al.* 2000

- Primary HLA-B14+ CD4+ CD3+ and HLA-mismatched lymphocytes from uninfected donors were infected with JRCSF after isolation then cocultured with the B14-restricted CTL clone 15160/D75 specific for ERYLKDQQL, and viral inhibition was MHC-restricted.
- Primary monocytes and monocyte-derived DC were generated from the same donors, replication of HIV-1 in these cell types was less efficient than in lymphocytes and could also be inhibited by MHC-restricted CTL.
- DC-lymphocyte cluster cultures allowed vigorous viral replication and MHC-restricted CTL viral inhibition was blunted or lost depending on the ratio of DC to CD4+ lymphocyte in the culture.

HXB2 Location gp160 (584–592)
Author Location gp41 (SF2)
Epitope ERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human (B14)
References Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.

HXB2 Location gp160 (584–592)
Author Location Env (589–597)
Epitope ERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords early-expressed proteins, kinetics
References Guillon *et al.* 2002b

- An early-expressed Nef protein was modified to contain Env and Pol epitopes to enable the study the effect of expression kinetics on CTL mediated suppression of replication. The "EpiNef" construct was inserted into a recombinant vaccinia virus which was used to infect a target cell line; the target cells were lysed by CTL clones specific for the Env and Pol epitopes indicating that they were properly processed.

HXB2 Location gp160 (584–592)
Author Location gp41 (584–592)
Epitope ERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human (B14)
Keywords class I down-regulation by Nef
References Yang *et al.* 2002

- Nef down-modulates class I protein expression, and this study demonstrates directly that Nef-deleted HIV-1 NL-43 can be more effectively killed *in vitro* than NL-43 with an intact Nef. The effect was shown to be specific for class I presentation of epitopes, and unlike Nef, deleting Vpr did not alter CTL susceptibility of NL43 infected cells. The CTL clone 15160D75, specific for the class I B14 presented epitope ERYLKDQQL, was one of four used in this study.

HXB2 Location gp160 (584–592)
Author Location gp41
Epitope ERYLKDQQL
Epitope name B14-EL9(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Donor MHC A32, B14, B7
Keywords HAART, ART, supervised treatment interruptions (STI)
References Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (`http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html`) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient A displayed the greatest response to epitope B14-EL9(gp41), a strong response to B7-TL9(p24), and responses to B7-TM9(Nef) and A32-PW10(RT).

HXB2 Location gp160 (584–592)
Author Location gp41
Epitope ERYLKDQQL
Subtype A, B, C, D
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag

CTL CD8+

Species (MHC) human (B14)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location gp160 (584–592)
Author Location gp41 (73–81)
Epitope ERYLKDQQL
Epitope name Env EL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Assay type Chromium-release assay
Keywords binding affinity, TCR usage, characterizing CD8+ T cells
References Yang *et al.* 2003b

- Killing efficiency of CTLs and their ability to suppress viral replication is shown to depend more on epitope specificity than to antigenic avidity. Different clones recognizing the same epitope had similar killing efficiency despite their variation in avidity. Nef specific CTL clones tended to be most inhibitory, followed by Gag, then by RT specific clones, regardless of avidity.
- 4/14 CTL T-cell clones tested were specific for Env EL9. Under conditions of excess peptide (100ug/ml), there was no difference in their lytic potential; all possessed similar effector capacity. Avidity was measured as the sensitizing dose of peptide required for 50% of maximal killing (SD50), which varied from 20 pg/ml to 100 ng/ml, over four orders of magnitude for all 14 epitopes. The SD50 range for Env EL9 was 5,000 - 60,000 pg/ml.

HXB2 Location gp160 (584–592)
Author Location (B consensus)
Epitope ERYLKDQQL
Epitope name EL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Donor MHC A28, A29, B14, B44, Cw8; A25, A32, B08, B14, Cw7, Cw8
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 2/9 individuals recognized this epitope, presented by HLA-B14.

HXB2 Location gp160 (584–592)
Author Location Env (584–592)
Epitope ERYLKDQQL
Epitope name EL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B14)
Donor MHC A*02, A*68, B*14, B*52, Cw*08, Cw*12
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords escape, characterizing CD8+ T cells, optimal epitope
References Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- The variant ERYLqDQQL was the only form of the epitope detected over a 6-year period in this person. Elispot reactions were reduced to the autologous form relative to the B clade consensus form, ERYLKDQQL.

HXB2 Location gp160 (584–592)
Author Location gp41
Epitope ERYLKDQQL
Epitope name EL9
Immunogen
Species (MHC) (B14)
Keywords review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion
References Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

HXB2 Location gp160 (584–592)
Author Location gp41
Epitope ERYLKDQQL
Epitope name B14-EL9(gp41)
Immunogen HIV-1 infection
Species (MHC) human (B14)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location gp160 (584–592)
Author Location
Epitope ERYLKDQQL
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (B14)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location gp160 (584–592)
Author Location gp41 (subtype B)
Epitope ERYLKDQQL
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B*1402, B14)
Keywords subtype comparisons
References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among B and D clade viruses.
- The Clade A version of the epitope is ERYLRDQQL.

HXB2 Location gp160 (584–592)
Author Location gp41 (584–592)
Epitope ERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human
References Price *et al.* 1995

- Study of cytokines released by HIV-1 specific activated CTL.

HXB2 Location gp160 (584–592)
Author Location gp41 (584–592)
Epitope ERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human
References Borrow *et al.* 1994

- Three out of five patients with HIV-1 symptomatic infection controlled their viral infection well and mounted an early, strong HIV-1 specific MHC restricted CTL response.
- One of the three, study subject BORI, specifically recognized this peptide.

HXB2 Location gp160 (584–592)
Author Location gp160
Epitope ERYLRDQQL
Subtype A, B, C, D
Immunogen HIV-1 infection, vaccine
Vector/Type: vaccinia *Strain:* A clade, B clade, D clade NDK, C clade consensus *HIV component:* Env
Species (MHC) human
Donor MHC A*0202, A*7401, B*1503, B*5802, Cw*0202, Cw*0602; A*0201, A*3009, B*4501, B*5802, Cw*0202, Cw*1601
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References McKinnon *et al.* 2005

- Interclade cross-reactivity of clades A, B, C, and D was tested using recombinant vaccinia-based IFN-gamma Elispot assay. 47/74 women had a positive Elispot response to at least one clade, and cross-clade responses were frequent. Clade A responses were most frequent, as expected, as clade A dominates the Kenyan epidemic (85% of the 47 women responded

CTL CD8+

to clade A Env, 74% to B, 62% to C, and 43% to D). Cross-clade CD8 T-cell responses were common and directed at conserved epitopes.

- There was a greater magnitude of response to A clade peptides in individuals who responded to more than 1 clade; a 2-fold higher response was observed in clade A in 36% (9/25) of these individuals, and the response to A peptides was never lower. ERYLRDQQL responses were detected in 2 women who had Env responses to all 4 clades, and clade A gave the highest responses; a ERYLkDQQL variant was in clade B and C, and the clade D Env carried ERsLkDQQL. The epitope VSGFLALAW was also recognized by 1 of the women.
- HLA-B*5802 was the only HLA common to both women who reacted with ERYLRDQQL, so may be the presenting allele.

HXB2 Location gp160 (584–592)
Author Location
Epitope ERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101; B*0801, B*1401
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- ERYLKDQQL was recognized by a placebo patient after infection.

HXB2 Location gp160 (584–592)
Author Location Env
Epitope ERYLKDQQL
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*6802, A*7401, B*1510, B*4901, Cw*0304, Cw*0701; A*2902, A*3601, B*1510, B*4201, Cw*0304, Cw*1701
Country Kenya
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2008

- To evaluate the use of IFN-gamma ELISpot and proliferation assays, the two were compared in a cohort of HIV-1-infected Kenyan sex-workers. ELISpot does not always correlate with viral load and replication or disease progression. The exclusive use of these assays makes definition of CTL response in disease incomplete, especially for memory T cells.
- Despite assaying for 24 INF-gamma and 41 proliferative responses, only 5 of these responses overlapped in the same subject. 18 peptide-epitopes including 10 epitopes and their variants were used in this study.
- ERYLKDQQL elicited proliferation alone in 3 subjects; and no ELISpot response.

HXB2 Location gp160 (584–594)
Author Location gp41 (584–594)
Epitope ERYLKDQQLLG
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A1A1, B14, B8, Cw7, Cw8
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

HXB2 Location gp160 (584–594)
Author Location gp41 (584–594)
Epitope ERYLKDQQLLG
Immunogen
Species (MHC) human
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 35/50 Brazilian HIV sequences; all variants detected (ERYrKDQQLLG, ERYgKDQQLLG, and ERYqKDQQLLG) involved the same residue.

HXB2 Location gp160 (585–592)
Author Location gp41 (584–591 SF2)
Epitope RYLRDQQL
Epitope name Env584-8
Subtype B
Immunogen HIV-1 infection

Species (MHC) human (A*2402)
Country Japan
References Ikeda-Moore *et al.* 1997

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402.
- This peptide induced CTL in 2/4 HIV-1 + people tested.
- RYLRDQQL bound to A*2402 weakly, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

HXB2 Location gp160 (585–592)
Author Location gp41 (590–597 LAI)
Epitope `RYLKDQQL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Shankar *et al.* 1996

HXB2 Location gp160 (585–592)
Author Location Env
Epitope `RYLKDQQL`
Epitope name RL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- RL8, RYLKDQQL, is a known HLA-B27-restricted epitope used as a positive control for eliciting CTL IFN-gamma response.

HXB2 Location gp160 (585–593)
Author Location gp41 (585–593)
Epitope `RYLKDQQLL`
Immunogen
Species (MHC) human (A*23, A24)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 35/50 Brazilian HIV sequences; all variants detected (RYrKDQQLL, RYgKDQQLL, and RYqKDQQLL) involved the same residue.

HXB2 Location gp160 (585–593)
Author Location gp41 (585–593)
Epitope `RYLKDQQLL`
Immunogen HIV-1 infection
Species (MHC) human (A*2301)
Donor MHC A*2301, B*1503, B*3501, Cw2, Cw7
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

HXB2 Location gp160 (585–593)
Author Location Env
Epitope `RYLKDQQLL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2301)
Donor MHC A*2301, A*6801, B*5801, B*5802
Country United States
Keywords escape, acute/early infection
References Bernardin *et al.* 2005

- Full HIV genomes from nine individuals were analyzed for mutations prior to seroconversion and 7 to 28 days later. It was found that the influence of the host's HLA type was reflected within weeks of infection; a statistically significant number of early nonsynonymous mutations were observed within previously reported CTL epitopes.
- K to E mutation was observed in position 4.

HXB2 Location gp160 (585–593)
Author Location
Epitope `RYLKDQQLL`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2301, A*2402)
Donor MHC A*2301, A*6802, B*1510, B*5802, Cw*0511, Cw*0611
Country South Africa

CTL CD8+

Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- Known epitope RYLKDQQLL is HLA-A*2301 and -A*2402-restricted. Response to a peptide containing this epitope was detected in a rapid progressor 12 weeks post-infection.

HXB2 Location gp160 (585–593)
Author Location gp41 (584–591 SF2)
Epitope `RYLRDQQLL`
Epitope name Env584-9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Country Japan
References Ikeda-Moore *et al.* 1997

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402.
- This peptide induced CTL in 4/4 HIV-1 + people tested.
- RYLRDQQLL bound to A*2402 strongly, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

HXB2 Location gp160 (585–593)
Author Location gp41 (591–598 LAI)
Epitope `RYLKDQQLL`
Subtype B
Immunogen
Species (MHC) human (A*2402)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*2402 epitope.

HXB2 Location gp160 (585–593)
Author Location (C consensus)
Epitope `RYLKDQQLL`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location gp160 (585–593)
Author Location Nef
Epitope `RYLKDQQLL`
Epitope name RL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords HAART, ART, responses in children, dendritic cells
References Zhang *et al.* 2006b

- Immune responses in HIV-1 infected children either undregoing HAART or not were analysed. HIV-specific CTLs were lower in children responding to HAART than in non-responders and HAART-naive children. CTL frequency was correlated with myeloid DC frequency in treatment-naive patients, and inversely correlated with duration of virus supression following treatment.
- 11 of the 22 children had significant responses to SL9. USE INA's NOTES

HXB2 Location gp160 (585–593)
Author Location gp41 (74–82)
Epitope `RYLKDQQLL`
Immunogen HIV-1 infection
Species (MHC) human (A23)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location gp160 (585–593)
Author Location gp41
Epitope `RYLKDQQLL`
Epitope name A24-RL9(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A24)
Donor MHC A24, B27, B7
Keywords HAART, ART, supervised treatment interruptions (STI)
References Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (`http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html`) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.

- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient C displayed the greatest response to B27-KK10(p24), and in decreasing order also responded to A24-RW8(Nef), B7-IL9(gp41), A24-RL9(gp41), A24-YL8(gp41), and B7-TM9(Nef).

HXB2 Location gp160 (585–593)
Author Location Env
Epitope RYLKDQQLL
Epitope name RW8
Immunogen HIV-1 infection
Species (MHC) human (A24)
Donor MHC A2, A24, B38, B60, Cw12, Cw2
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, early treatment
References Montefiori *et al.* 2003

- HIV-1 + patient AC10 underwent early HAART treatment, which was discontinued 1.5 years later. At this timepoint potent NAb responses against autologous virus were detected. Treatment interruption initially induced weak CD8+ responses directed against 5 epitopes. By days 873d and 923d the CTL response had broadened to target 22 epitopes; of these six were fully characterized. Eventually the virus escaped the NAb response, but escape was not accompanied by a rise in viral load, and the authors suggest the virus was contained by the CTL response.

HXB2 Location gp160 (585–593)
Author Location gp41
Epitope RYLKDQQLL
Epitope name A24-RL9(gp41)
Immunogen HIV-1 infection
Species (MHC) human (A24)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location gp160 (585–593)
Author Location
Epitope RYLKDQQLL
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (A24)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location gp160 (585–593)
Author Location
Epitope RYLKDQQLL
Immunogen HIV-1 infection
Species (MHC) human (A24)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope RYLKDQQLL elicited a magnitude of response of 80 SFC with a functional avidity of 5nM.

HXB2 Location gp160 (585–593)
Author Location
Epitope RYLKDQQLL
Immunogen HIV-1 infection
Species (MHC) human (A24)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

CTL CD8+

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (A24), an additional HLA (A23) was statistically predicted to be associated with this epitope.

HXB2 Location gp160 (585–593)
Author Location gp41
Epitope RYLKDQQLL
Epitope name RL9(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A24)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A24-restricted epitope RYLKDQQLL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide RVLAVERYLKDQQLL-GIW.
- 7 of the 30 HLA-A24 carriers responded to RYLKDQQLL-containing peptide with average magnitude of CTL response of 551 SFC/million PBMC (author communication and Fig.1).

HXB2 Location gp160 (585–595)
Author Location gp41 (584–591 SF2)
Epitope RYLRDQQLLGI
Epitope name Env584-11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Country Japan
References Ikeda-Moore *et al.* 1997

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402.
- This peptide induced CTL in 4/4 HIV-1 + people tested.
- RYLRDQQLLGI bound to A*2402 with medium strength, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

HXB2 Location gp160 (585–595)
Author Location Env (584–594)
Epitope RYLRDQQLLGI
Epitope name Env584-11
Immunogen vaccine
Vector/Type: Sendai virus vector system (SeV)
Species (MHC) human (A*2402)
References Kawana-Tachikawa *et al.* 2002

- A Sendai virus vector system (SeV) was developd that expressed HLA-A*2402-restricted class I/peptide complexes; this system could be used to detect responses and has the potential to elicit immune responses.
- MHC class I/peptide tetramers could be made using this system that bound to epitope-specific CTLs in PBMCs.
- Cells transfection with SeV modified to express A*2402-HIV epitope complexes induced CTL mediated specific cell lysis.

HXB2 Location gp160 (586–593)
Author Location gp41 (584–591 NL43)
Epitope YLKDQQLL
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
References Dai *et al.* 1992

- The lysine (K) is critical for eliciting a HLA-A24 CTL response.
- C. Brander notes that this is an A*2402 epitope in the 1999 database, and suggested that the epitope is RYLKQQLL.

HXB2 Location gp160 (586–593)
Author Location gp41 (591–598)
Epitope YLRDQQLL
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A24)
Keywords subtype comparisons, HIV exposed persistently seronegative (HEPS), immunodominance
References Kaul *et al.* 2001a

- Variants (R)YL(R/K)DQQLL are specific for the A/B clade.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-A24 women, 3/4 HEPS and 10/10 HIV-1 infected women recognized this epitope, and (R)YL(R/K)DQQLL tended to be reactive in HEPS and infected women, RDYVDRFFKTL in infected women only.
- The dominant response to this HLA allele was to this epitope in all 3/4 HEPS cases but in only 4 of the 10/10 HIV-1 infected women.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.

HXB2 Location gp160 (586–593)
Author Location gp41 (580–587 CM243 subtype CRF01)
Epitope YLKDQQLL
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A24)
Keywords subtype comparisons
References Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- The only HLA-A24 FSW tested did not recognized the E clade version of this epitope RYLKDQKLL, which differs from the previously defined B clade version by one amino acid, YLKDQQLL, with an additional amino acid added on.

HXB2 Location gp160 (586–593)
Author Location gp41 (591–598)
Epitope YLKDQQLL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A24)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords Th1, characterizing CD8+ T cells
References Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- One of seven patients responded to this peptide with GzB producing cells, and a different patient responded with IFN-gamma producing cells.

HXB2 Location gp160 (586–593)
Author Location gp41
Epitope YLKDQQLL
Epitope name A24-YL8(gp41)
Immunogen HIV-1 infection
Species (MHC) human (A24)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location gp160 (586–593)
Author Location
Epitope YLKDQQLL
Immunogen HIV-1 infection
Species (MHC) human (A24)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope YLKDQQLL elicited a magnitude of response of 170 SFC with a functional avidity of 0.005nM.

HXB2 Location gp160 (586–593)
Author Location gp41
Epitope YLKDQQLL
Epitope name RL9(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A24)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A24-restricted epitope YLKDQQLL elicited an immune response in Chinese HIV-1 positive subjects RVLAVERYLKDQQLLGIW.
- 7 of the 30 HLA-A24 carriers responded to YLKDQQLL-containing peptide with average magnitude of CTL response of 551 SFC/million PBMC (author communication and Fig.1).

HXB2 Location gp160 (586–593)
Author Location gp41 (586–593 LAI)
Epitope YLKDQQLL

Epitope name E1
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A24, B8)
Keywords HAART, ART
References Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNgamma production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

HXB2 Location gp160 (586–593)
Author Location gp41 (subtype A)
Epitope YLKDQQLL
Subtype A
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human, macaque (A24, B8)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location gp160 (586–593)
Author Location gp160 (586–593)
Epitope YLKDQQLL
Epitope name YL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*08)
Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-B*08-restricted autologous epitope YLKDQQLL elicited CTL responses at the earliest time point, with a reduction in response frequency just before disease progression at the second time point. Viral sequencing showed the emergence of an escape variant K3R, YLrDQQLL, between the first 2 ELISpot samplings. By the third time point, neither YL8 sequence was able to elicit an immune response. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location gp160 (586–593)
Author Location gp41 (586–593)
Epitope YLKDQQLL
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*0801 epitope.

HXB2 Location gp160 (586–593)
Author Location gp41
Epitope YLKDQQLL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Donor MHC A*0101, A*0301, B*0801, B*5101; A*0101, B*0801
Country United Kingdom
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords escape, acute/early infection, variant cross-recognition or cross-neutralization
References Milicic *et al.* 2005

- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of

an overlapping epitope of distinct restriction in the recipient. In an early acute infection of the donor, the precise timing of transmission determines the viral variants transmitted.
- The second donor in the study shares A*0101 and B*0801 with his partner. Escape variant ylQdqqll was transmitted, and it reduces binding to B*0801 by 92% relative to YLKDQQLL.

HXB2 Location gp160 (586–593)
Author Location gp41 (586–593)
Epitope YLKDQQLL
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Johnson *et al.* 1992
- Two overlapping CTL epitopes were mapped with different HLA restriction (also see ERYLKDQQL HLA-B14)

HXB2 Location gp160 (586–593)
Author Location gp41 (586–593)
Epitope YLKDQQLL
Immunogen peptide-HLA interaction
Species (MHC) human (B8)
References Sutton *et al.* 1993
- Predicted epitope based on B8-binding motifs, from larger peptide QLQARILAVERYLKDQQLLGIWGCS.

HXB2 Location gp160 (586–593)
Author Location gp41 (76–83)
Epitope YLKDQQLL
Immunogen
Species (MHC) human (B8)
References Goulder *et al.* 1997g
- Included in a study of the B8 binding motif.

HXB2 Location gp160 (586–593)
Author Location gp41
Epitope YLKDQQLL
Immunogen
Species (MHC) human (B8)
References Rowland-Jones *et al.* 1999
- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive.
- HIV-2 sequence: YLQDQARL – no cross-reactivity Johnson *et al.* [1992]

HXB2 Location gp160 (586–593)
Author Location gp41 (586–593)
Epitope YLKDQQLL
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B8)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location gp160 (586–593)
Author Location gp41 (586–593)
Epitope YLKDQQLL
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Day *et al.* 2001
- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual.

HXB2 Location gp160 (586–593)
Author Location Env (586–593)
Epitope YLKDQQLL
Epitope name YL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A*01, A*11, B*08, B*15, Cw*04, Cw*07
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords escape, characterizing CD8+ T cells, optimal epitope
References Koibuchi *et al.* 2005
- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- The autologous form of the epitope, YLKDQQLL, matched the B consensus throughout the 5-year period of study, except for 1 rare variant at the first time point, YLrDQQLL, and 1 at year 5, YLKgQQLL.

HXB2 Location gp160 (586–593)
Author Location
Epitope YLKDQQLL
Immunogen
Species (MHC) (B8)
Keywords review, immunodominance, escape, vaccine antigen design
References Altfeld & Allen 2006
- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection.

HXB2 Location gp160 (586–593)
Author Location gp160
Epitope YLRDQQLL
Immunogen HIV-1 infection
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 1/22 HEPS sex worker controls, ML887.

HXB2 Location gp160 (586–598)
Author Location gp41 (586–598)
Epitope `YLRDQQLLGIWGC`
Immunogen HIV-1 infection
Species (MHC) human (Cw7)
References Nehete *et al.* 1998a

- Three long-term non-progressors and one asymptomatic HIV+ individual were studied and found to have HLA class I C-restricted CD8+ Env-specific CTLs – Cw7 specific CTL were found against three peptides, including this one.
- HLA-C antigens are expressed on lymphoid cells to a lesser extent, 10% of either HLA-A or HLA-B.
- HLA-C confers protection against lysis by natural killer cells and by non-MHC-restricted effector T cells and Cw7 directly governs this resistance to lysis – the authors hypothesize that pathogens that inhibit antigen expression and class I expression may particularly down regulate Cw7, thus triggering non-MHC restricted killing.

HXB2 Location gp160 (594–608)
Author Location gp41
Epitope `GIWGCSGKLICTTAV`
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Jin *et al.* 1998b

- Progressive HIV-1 infection and CD4 decline was associated decreased the IL-2-expandable HIV-1 CTL response in 10 asymptomatic HIV-infected patients – this observation may be partially due to a reduction and impaired function of T helper cells, CTL exhaustion and APC dysfunction.
- Continued presence of HIV-1 specific memory cells (CTLp) was observed in three patients, one to GIWGCSGKLICTTAV, one to ALIWEDLRSLCLFSY, and one to PIPIHYCAPAGFAILKCNNK.

HXB2 Location gp160 (594–608)
Author Location gp41 (SF2)
Epitope `GIWGCSGKLICTTAV`
Epitope name Peptide2
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type Chromium-release assay
References Carmichael *et al.* 1996

- Cross-reactivity of Env-specific CTL clones from 14 seropositive HIV-1 infected patients was tested using peptides based on 3 B clade variants (MN, IIIB, and RF). The proportion of CTL clones that cross-recognized conserved variants was low. Most CTL clones recognized only one peptide variant, indicating most Env responses are not cross-reactive within the B clade.
- This HLA B17(57) epitope was newly identified within gp41 of HIV-1 SF2. SF2 and IIIB have identical sequences within this peptide, but the T-cell clone that recognizes this peptide does not recognize the MN (gFwgcsgklicttTv) or RF (giwgcsgklicttTv) variants of this peptide.

HXB2 Location gp160 (606–614)
Author Location gp41 (605–615 LAI)
Epitope `TAVPWNASW`
Subtype B
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* gp160
Species (MHC) human (B*3501)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*3501 epitope.

HXB2 Location gp160 (606–614)
Author Location gp41 (606–614 HXB2)
Epitope `TAVPWNASW`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Keywords epitope processing
References Ferris *et al.* 1996

- Natural form of this peptide is not glycosylated, suggesting initial Class I processing may occur in the cytosol.

HXB2 Location gp160 (606–614)
Author Location gp41 (605–615 LAI)
Epitope `TAVPWNASW`
Subtype B
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* gp160
Species (MHC) human (B35)
References Johnson *et al.* 1994b

- Epitope for vaccine induced CD8+ clone.

HXB2 Location gp160 (606–614)
Author Location gp41 (606–614 LAI)
Epitope `TAVPWNASW`
Subtype B
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* gp160
Species (MHC) human (B35)
References Johnson *et al.* 1994a

- HLA restricted CTL response to epitope in HIV-1 vaccinia-env vaccinees.

HXB2 Location gp160 (606–614)

Author Location gp41 (606–614 LAI)
Epitope TAVPWNASW
Subtype B
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* gp160
Species (MHC) human (B35)
References Hammond *et al.* 1995

- Peptide only processed by a TAP-1/2-dependent pathway.

HXB2 Location gp160 (606–614)
Author Location gp41 (606–614)
Epitope TAVPWNASW
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Ferris *et al.* 1999

- This epitope is processed by a TAP1/2 dependent mechanism.

HXB2 Location gp160 (606–614)
Author Location gp41 (subtype B)
Epitope TAVPWNASW
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B35)
Keywords subtype comparisons
References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among A, B and D clade viruses.

HXB2 Location gp160 (606–614)
Author Location gp41 (606–614)
Epitope TAVPWNASW
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B35)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location gp160 (606–614)
Author Location gp41 (606–614)
Epitope TAVPWNASW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC A3, A33, B14, B35, Cw*0401, Cw*0802
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

HXB2 Location gp160 (606–614)
Author Location Env (96–104)
Epitope TAVPWNASW
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 5/9 patients recognized this epitope.

HXB2 Location gp160 (606–614)
Author Location gp41
Epitope TAVPWNASW
Epitope name TW9(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.

- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B35-restricted epitope TAVPWNASW elicited an immune response in Chinese HIV-1 positive subjects as part of peptide KLICTTAVPWNASWSNK.
- 1 of the 12 HLA-B35 carriers responded to a TAVPWNASW-containing peptide with average magnitude of CTL response of 800 SFC/million PBMC (author communication and Fig.1).

HXB2 Location gp160 (614–631)
Author Location (C consensus)
Epitope WSNKSQEEIWDNMTWMQW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location gp160 (614–631)
Author Location (C consensus)
Epitope WSNKSQEEIWDNMTWMQW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0401)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location gp160 (634–648)
Author Location gp41 (641–655 SF2)
Epitope EIDNYTNTIYTLLEE
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-A1, A2, B51, and B57.

HXB2 Location gp160 (678–686)
Author Location Env (679–687 subtype B)
Epitope WLWYIKIFI
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN *HIV component:* gp160
Species (MHC) human (A*0201)
Keywords binding affinity
References Kundu *et al.* 1998a

- Ten HIV-1 + HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period.
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity.
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual.
- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses.

HXB2 Location gp160 (678–686)
Author Location gp41 (678–686)
Epitope WLWYIKIFI
Immunogen
Species (MHC) human (A2)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 45/50 Brazilian HIV sequences.

HXB2 Location gp160 (678–686)
Author Location Env
Epitope WLWYIKIFI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2.1)
Donor MHC A1, A19, B*3501, B44, Cw16, Cw7; A*0201, A19, B14, B44, Cw16, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
References Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.

- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-A2.1 restricted epitope, WLWYIKIFI was the only one mutated, to WLWYIrIFI in the mother M2 isolate.

HXB2 Location gp160 (680–688)
Author Location gp41 (679–687 SF2)
Epitope WYIKIFIMI
Epitope name Env679-9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Country Japan
References Ikeda-Moore *et al.* 1997

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402.
- This peptide induced CTL in 1/4 HIV-1 + people tested.
- WYIKIFIFMI bound to A*2402 strongly, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

HXB2 Location gp160 (680–688)
Author Location gp41 (680–688)
Epitope WYIKIFIMI
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope WYIKIFIMI was predicted to be restricted by HLA A*0203, A*0206, A*2402.

HXB2 Location gp160 (680–688)
Author Location gp41 (680–688)
Epitope WYIKIFIMI
Immunogen
Species (MHC) human (A*2402)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 41/50 Brazilian HIV sequences.

HXB2 Location gp160 (680–688)
Author Location Env
Epitope WYIKIFIII
Subtype B, C, AE
Immunogen HIV-1 infection
Species (MHC) human
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- This infrequently found reference epitope, WYIKIFIII, was cross-recognized by patients infected with several HIV subtypes but in less than half the responders. The predicted HLA restriction was to supertype A24.

HXB2 Location gp160 (681–689)
Author Location Env (681–)
Epitope YIKIFIMIV
Epitope name Env681
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* Env *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

CTL CD8+

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 2/17 HIV+ HLA-A2 subjects.

HXB2 Location gp160 (681–689)
Author Location gp41 (681–689)
Epitope YIKIFIMIV
Immunogen
Species (MHC) human (A2)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 41/50 Brazilian HIV sequences.

HXB2 Location gp160 (681–689)
Author Location
Epitope YIKIFIMIV
Epitope name Env 681
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Env 681 YIKIFIMIV epitope was one of the most conserved in Env, and was found in 7 patients but only 2 had a CTL immune response to it.

HXB2 Location gp160 (685–693)
Author Location Env (686–694 subtype B)
Epitope FIMIVGGLV
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN *HIV component:* gp160
Species (MHC) human (A*0201)
Keywords binding affinity
References Kundu *et al.* 1998a

- Ten HIV-1 + HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period.
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity.
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual.
- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses.
- ALTERNATIVE EPITOPE: IMIVGGLVGL – no CTL response was shown to the peptides FIMIVGGLV or IMIVGGLVGL.

HXB2 Location gp160 (698–707)
Author Location Env (696–706)
Epitope VFAVLSIVNR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*3303)
References Hossain *et al.* 2001; Takiguchi *et al.* 2000

- HLA-A33 a very common allele in Asian, with HLA-A*3303 the most common among the Japanese. New A*3303 epitopes were defined to better characterize the immune response in this population.
- The anchor motif for HLA*3303 (A, I, L, V, F, Y in position 2 (F and Y bind most strongly), and R (K is also tolerated) in the C-terminal position) was used to define 82 potentially reactive peptides in Env; 37/82 peptides bound to A*3303; 3/37 peptides could induce peptide-specific CTL in bulk PBMC cultures from 1/3 HLA A*3303 positive individuals tested.
- CTL clones were isolated that killed target cells in a concentration dependent manner after pulsing with the VFAVLSIVNR peptide, that could also kill cells transfected with env expressed from a vaccinia vector. Bulk cultures were tested from six additional people, and only 1/6 reacted with this peptide, but the peptide is in a highly variable region.

HXB2 Location gp160 (698–707)
Author Location gp41 (187–196)
Epitope VFAVLSIVNR
Immunogen HIV-1 infection
Species (MHC) human (A*3303)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location gp160 (698–707)
Author Location gp41
Epitope VFAVLSIVNR
Epitope name VR10(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B7-restricted epitope VFAVLSIVNR elicited no immune response in Chinese HIV-1 positive subjects as part of peptide LVGLRIVFAVLSIVNRVR.
- Although the tested peptide sequence (LVGLRIVFAVLSIVNRVR) contains the exact sequence of a previously described HLA-B7 optimal epitope, VFAVLSIVNR, none of the 9 HLA-B7 carriers responded to it (author communication and Fig.1).

HXB2 Location gp160 (700–708)
Author Location gp41 (705–714)
Epitope AVLSVVNRV
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Ferris *et al.* 1999
- This epitope is processed by a TAP1/2 dependent mechanism.

HXB2 Location gp160 (700–708)
Author Location Env (695–705 BH10, LAI)
Epitope AVLSVVNRV
Immunogen HIV-1 infection
Species (MHC) human
References Maksiutov *et al.* 2002
- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is LRIVFAVLSVV) has similarity with the human chemokine-factor 3 fragment LRLVFALVTAV .

HXB2 Location gp160 (701–719)
Author Location Env (691–710)
Epitope VLSIVNQVRRQGYSPLSFQT
Immunogen HIV-1 infection
Species (MHC) human (B15)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape
References Geels *et al.* 2003
- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 5 epitopes from this individual that varied over time where the internal mutations became fixed; a dramatic decrease in CTL activity against the wild type epitope was observed as the mutation arose. The vlsivnKvrrqgysplsfqt variant found at 20 and 47 months postseroconversion.

HXB2 Location gp160 (701–720)
Author Location gp41 (701–720 BH10)
Epitope VLSIVNRVRQGYSPLSFQTH
Immunogen HIV-1 infection
Species (MHC) human (A32)
References Safrit *et al.* 1994a
- Recognized by CTL derived from acute seroconverter.

HXB2 Location gp160 (702–721)
Author Location Env (702–721)
Epitope LSIVNRVRQGYSPLSFQTLT
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002
- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location gp160 (704–712)
Author Location gp160 (704–712 LAI)
Epitope IVNRNRQGY
Subtype B
Immunogen
Species (MHC) human (A*3002)
Keywords optimal epitope
References Goulder *et al.* 2001a; Llano *et al.* 2009
- C. Brander notes this is an A*3002 epitope.

HXB2 Location gp160 (704–712)
Author Location gp41
Epitope IVNRVRQGY
Epitope name IY9 (gp41)
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
References Goulder *et al.* 2001a
- HLA-A*3002 is very common in African populations, 50% of Zimbabweans express HLA-A30, 44% in African Zulu, so five new HIV epitopes were characterized that are presented by this HLA molecule.
- A rapid method was developed combining ELISPOT with intracellular IFN-γ staining of PBMCs to map optimal epitopes, then HLA presenting molecules were defined – this method was completed within 48 to 72 hours of receipt of blood.
- Two individuals were studied: Subject 199 (HLA A*0201/*3002 B*4402/51 Cw2/5), a Caucasian, and Subject 6007 (HLA A*3002/ B53/*5801 Cw4/7) an African-Caribbean.
- In both HLA-A*3002 individuals the response to RSLYNTVATLY was dominant.
- In subject 199 four additional A*3002 epitopes were identified.
- Three quantitative assays, ELISPOT, precursor frequency and chromium release, confirmed a hierarchy of response: RY11 (p17) > KY9 (gp41) > KY9 (RT-53) > IY9 (gp41)

CTL CD8+

HXB2 Location gp160 (704–712)
Author Location Env
Epitope IVNRNRQGY
Epitope name A30-IY9(env)
Immunogen HIV-1 infection
Species (MHC) human (A30)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location gp160 (704–712)
Author Location gp41
Epitope IVNRNRQGY
Epitope name IY9(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A30)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide AVLSIVNRNRQGYSPLSF contains the exact sequence of a previously described HLA-A30 epitope, IVNRNRQGY, none of the 9 HLA-A30 carriers responded to it (author communication and Fig.1).

HXB2 Location gp160 (704–712)
Author Location Env
Epitope VINRVRQGY
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0201, A*0205, B*1502, B*5801, Cw*0401, Cw*0701; A*3001, A*6802, B*1801, B*4201, Cw*0304, Cw*1701; A*6802, A*7401, B*1510, B*4901, Cw*0304, Cw*0701
Country Kenya
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2008

- To evaluate the use of IFN-gamma ELISpot and proliferation assays, the two were compared in a cohort of HIV-1-infected Kenyan sex-workers. ELISpot does not always correlate with viral load and replication or disease progression. The exclusive use of these assays makes definition of CTL response in disease incomplete, especially for memory T cells.
- Despite assaying for 24 INF-gamma and 41 proliferative responses, only 5 of these responses overlapped in the same subject. 18 peptide-epitopes including 10 epitopes and their variants were used in this study.
- VINRVRQGY elicited proliferation alone in 3 subjects; and ELISpot response in 1 separate subject.

HXB2 Location gp160 (704–714)
Author Location gp41 (704–714)
Epitope IVNRVRQGYSP
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008

- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.
- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.
- CTL immune response to consensus sequence IVNRVRQ-GYSP was elicited in subject 00016.

HXB2 Location gp160 (712–720)
Author Location Env
Epitope YSPLSLQTL
Epitope name YL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*01)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords binding affinity
References Cao *et al.* 2008

- For the first time, viral immune evasion is reported via an insertion mutation, in an ART-naive patient. A 3 aa repeat, SPT inserted within p6<sup>Pol<sup> epitope NL8 is reported. This insertion is associated often with ART drug resistance to NRTI drugs. Thus immune pressure and drug resistance may cause HIV-1 to select the same variation.
- A concomitant insertion mutation APP, is seen in p6<sup>Gag<sup>, permitting viral budding.
- Epitope YSPLSLQTL bound its MHC I less strongly than NL8 (NSPTRREL) did its MHC I molecule.

HXB2 Location gp160 (712–720)
Author Location gp41 (201–209)
Epitope YSPLSLQTL
Epitope name YL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*0102)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Last position (9)in the epitope had potentially experienced positive selection. YSPLSLQTr escape variant was found.

HXB2 Location gp160 (713–721)
Author Location Env
Epitope SPLSFQTRL
Epitope name Env1131
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Novel Env epitope SPLSFQTRL elicits IFN-gamma ELISpot responses in 1/7 subjects; and bound HLA-B7 with high affinities in soluble and cell-based assays.

HXB2 Location gp160 (742–761)
Author Location Env (742–761)
Epitope RDRSIRLVSGFLALAWDDLR
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location gp160 (744–753)
Author Location Env
Epitope RSIRLVSGFL
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*6802, A*7401, B*1510, B*4901, Cw*0304, Cw*0701; A*0101, A*2301, B*0702, B*4501, Cw*0702, Cw*1601
Country Kenya
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2008

- To evaluate the use of IFN-gamma ELISpot and proliferation assays, the two were compared in a cohort of HIV-1-infected Kenyan sex-workers. ELISpot does not always correlate with viral load and replication or disease progression. The exclusive use of these assays makes definition of CTL response in disease incomplete, especially for memory T cells.
- Despite assaying for 24 INF-gamma and 41 proliferative responses, only 5 of these responses overlapped in the same subject. 18 peptide-epitopes including 10 epitopes and their variants were used in this study.
- RSIRLVSGFL elicited proliferation in 2 subjects; ELISpot responses in none.

HXB2 Location gp160 (747–755)
Author Location gp41 (747–755)
Epitope RLVNGSLAL
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Parker *et al.* 1992

- Studied in the context of HLA-A2 peptide binding.

HXB2 Location gp160 (747–755)
Author Location gp41 (741–749 CM243 subtype CRF01)
Epitope RLVSGFLAL
Epitope name E747-755
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HIV exposed persistently seronegative (HEPS)
References Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.

- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was reactive in HIV+ control study subject 144 who carried HLA-A2.

HXB2 Location gp160 (747–755)
Author Location gp41 (741–749 CM243 subtype CRF01)
Epitope RLVSGFLAL
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords subtype comparisons
References Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- 2/4 tested FSWs recognized the E clade version of this epitope, which differs from the previously defined B clade version by two amino acids, RLVNGSLAL.
- This epitope was somewhat conserved 4/8 subtypes: CRF01 (E), B, C, and G.

HXB2 Location gp160 (747–763)
Author Location (C consensus)
Epitope RLVSGFLALAWDDLRSL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0202)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location gp160 (749–757)
Author Location gp160
Epitope VSGFLALAW
Subtype A, B, C, D
Immunogen HIV-1 infection, vaccine
Vector/Type: vaccinia *Strain:* A clade, B clade, D clade NDK, C clade consensus *HIV component:* Env
Species (MHC) human
Donor MHC A*0202, A*7401, B*1503, B*5802, Cw*0202, Cw*0602
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References McKinnon *et al.* 2005

- Interclade cross-reactivity of clades A, B, C, and D was tested using recombinant vaccinia-based IFN-gamma Elispot assay. 47/74 women had a positive Elispot response to at least one clade, and cross-clade responses were frequent. Clade A responses were most frequent, as expected, as clade A dominates the Kenyan epidemic (85% of the 47 women responded to clade A Env, 74% to B, 62% to C, and 43% to D). Cross-clade CD8 T-cell responses were common and directed at conserved epitopes.
- There was a greater magnitude of response to A clade peptides in individuals who responded to more than 1 clade; a 2-fold higher response was observed in clade A in 36% (9/25) of these individuals, and the response to A peptides was never lower. ERYLRDQQL responses were detected in 2 women who had Env responses to all 4 clades, and clade A gave the highest responses; an ERYLkDQQL variant was in clade B and C, and the clade D Env carried ERsLkDQQL. The epitope VSGFLALAW was also recognized by 1 of the women; A and C clade were identical, while clade B carried VnGsLiLAW, clade D VnGlsAiAW.

HXB2 Location gp160 (749–757)
Author Location Env
Epitope VSGFLALAW
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0201, A*0205, B*1503, B*5801, Cw*0401, Cw*0701; A*6802, A*7401, B*1510, B*4901, Cw*0304, Cw*0701; A*0101, B*3701, B*8101, Cw*0602, Cw*1801; A*0103, A*0201, B*4901, B*5702, Cw*0708, Cw*1801
Country Kenya
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2008

- To evaluate the use of IFN-gamma ELISpot and proliferation assays, the two were compared in a cohort of HIV-1-infected Kenyan sex-workers. ELISpot does not always correlate with viral load and replication or disease progression. The exclusive use of these assays makes definition of CTL response in disease incomplete, especially for memory T cells.
- Despite assaying for 24 INF-gamma and 41 proliferative responses, only 5 of these responses overlapped in the same subject. 18 peptide-epitopes including 10 epitopes and their variants were used in this study.
- VSGFLALAW elicited proliferation alone in 4 subjects; and ELISpot response in none.

HXB2 Location gp160 (749–757)
Author Location Env
Epitope VNGFLALAW
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*2902, A*3601, B*1510, B*4201, Cw*0304, Cw*1701; A*0101, A*2301, B*0702, B*4501, Cw*0702, Cw*1601; A*0101, B*3701, B*8101, Cw*0602, Cw*1801
Country Kenya

Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2008

- To evaluate the use of IFN-gamma ELISpot and proliferation assays, the two were compared in a cohort of HIV-1-infected Kenyan sex-workers. ELISpot does not always correlate with viral load and replication or disease progression. The exclusive use of these assays makes definition of CTL response in disease incomplete, especially for memory T cells.
- Despite assaying for 24 INF-gamma and 41 proliferative responses, only 5 of these responses overlapped in the same subject. 18 peptide-epitopes including 10 epitopes and their variants were used in this study.
- VNGFLALAW elicited proliferation alone in 3 subjects; and ELISpot response in 1 subject.

HXB2 Location gp160 (754–768)
Author Location gp41
Epitope `ALIWEDLRSLCLFSY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B55)
References Jin *et al.* 1998b

- Progressive HIV-1 infection and CD4 decline was associated decreased the IL-2-expandable HIV-1 CTL response in 10 asymptomatic HIV-infected patients – this observation may be partially due to a reduction and impaired function of T helper cells, CTL exhaustion and APC dysfunction.
- Continued presence of HIV-1 specific memory cells (CTLp) was observed in three patients, one to GIWGCSGKLICTTAV, one to ALIWEDLRSLCLFSY, and one to PIPIHYCAPAGFAILKCNNK.

HXB2 Location gp160 (754–768)
Author Location gp41 (SF2)
Epitope `ALIWERDLRSLCLFSY`
Epitope name Peptide78
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B55)
Assay type Chromium-release assay
References Carmichael *et al.* 1996

- Cross-reactivity of Env-specific CTL clones from 14 seropositive HIV-1 infected patients was tested using peptides based on 3 B clade variants (MN, IIIB, and RF). The proportion of CTL clones that cross-recognized conserved variants was low. Most CTL clones recognized only one peptide variant, indicating most Env responses are not cross-reactive within the B clade.
- This HLA B22(55) epitope was defined using SF2 peptides. The CTL clone that recognized it did not cross-recognize the MN, IIIB, or RF variants of this peptide.

HXB2 Location gp160 (754–768)
Author Location gp41 (761–775)
Epitope `ALIWEDLRSLCLFSY`
Epitope name Peptide 701.78
Immunogen HIV-1 infection
Species (MHC) human (B55)
Donor MHC A11, A24, B44, B55
Country United Kingdom
Assay type Flow cytometric T-cell cytokine assay, Other
Keywords HAART, ART, immunodominance, TCR usage, memory cells
References Weekes *et al.* 2006

- The effect of HAART on the population size, phenotype and function of HIV- and HCMV-specific CTL clones was analyzed. It was determined that the clonal composition of gag and env HIV-specific CD8 T-cells did not change after HAART. Following HAART, the size of immunodominant HIV-specific CD8 T-cell clones was found to diminish even with the relative preservation of functional memory responses. Maintainance of such strong functional responses implied the preferential loss of HIV-specific cells that have reduced cloning efficiency in vitro. HCMV-specific CTL clones had different kinetics and phenotypes than HIV-specific CTL clones in the same subject.

HXB2 Location gp160 (760–767)
Author Location gp41 (760–767)
Epitope `LRSLFLFS`
Immunogen HIV-1 infection
Species (MHC) human (A*2301)
Donor MHC A*2301, B*1503, B*3501, Cw2, Cw7
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

HXB2 Location gp160 (767–775)
Author Location gp41 (766–774 SF2)
Epitope `SYRRLRDLL`
Epitope name Env766-9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Country Japan
References Ikeda-Moore *et al.* 1997

CTL CD8+

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402.
- This peptide induced CTL in 1/4 HIV-1 + people tested.
- SYRRLRDLL bound to A*2402 moderately, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

HXB2 Location gp160 (767–775)
Author Location gp41
Epitope SYHRLRDFI
Epitope name E
Subtype A
Immunogen vaccine
Vector/Type: DNA with CMV promotor, modified vaccinia Ankara (MVA), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* Env, Gag, Nef, RT
Species (MHC) mouse (H-2K^{d})
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords subtype comparisons, vaccine-induced epitopes, variant cross-recognition or cross-neutralization, antagonism
References Larke *et al.* 2007

- Cross-clade vaccine recognition was studied using either single-, multi or several anatomically separated single-clade vaccines. Limited cross-clade response was seen with single-clade administrations. Multi-clade vaccines gave immune interference (antagonism and original antigenic sin), reducing CTL response. Simultaneously administered but anatomically separated vaccines from clades A, B, C decreased antagonism and increased immune responses.
- After immunization with Clade A vaccine containing Epitope E, SYHRLRDFI, T cells were able to respond to epitope variant SYHRLRDFv, as well as variants SYHRLRDci, SYHRLRDll and SYHRLRDli at <50% magnitude. Variants SYrhLRDFI, iYHhLRDll and SYrlLRDll were not recognized.

HXB2 Location gp160 (767–780)
Author Location gp41 (606–614 LAI)
Epitope SYHRLRDLLLIVTR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A31)
References Hammond *et al.* 1995

- Peptide only processed by a TAP-1/2-dependent pathway.
- CTL from an acute seroconverter.

HXB2 Location gp160 (767–780)
Author Location gp41
Epitope SYHRLRDLLLIVTR
Epitope name SR14(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3, A31)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A3- and -A31-restricted epitope SYHRLRDLLLIVTR elicited an immune response in Chinese HIV-1 positive subjects as part of peptide SLCLFSYHRLRDLLLIV.

HXB2 Location gp160 (769–777)
Author Location gp41 (769–777 BH10)
Epitope HRLRDLLLI
Immunogen HIV-1 infection
Species (MHC) human
References Safrit *et al.* 1994a

- Recognized by CTL derived from acute seroconverter.

HXB2 Location gp160 (770–778)
Author Location Env (679–777)
Epitope RLRDLLLIV
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords binding affinity
References Kmieciak *et al.* 1998a

- CTL responses in six patients to four Env epitopes were studied: D2: LLNATAIAV, 5.3: RLRDLLLIV, D1: KLTPLCVTL, and 4.3: QMHEDIISL – all have A2 anchor residues.
- The C terminal epitopes (D2 and 5.3) were highly variable and the variability was considered responsible for limited CTL response, while D1 and 4.3, N-terminal epitopes, were much more conserved and gave evidence of high levels of CTL response *in vitro*.
- Peptides 5.3 and D2 bound to HLA A*0201 with low affinity.

HXB2 Location gp160 (770–780)
Author Location gp41 (768–778 NL43)
Epitope RLRDLLLIVTR
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
References Takahashi *et al.* 1991

- CD8+ T cell clone.

HXB2 Location gp160 (770–780)
Author Location gp41 (775–785 LAI)
Epitope RLRDLLLIVTR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*0301 epitope.

HXB2 Location gp160 (770–780)

Author Location gp41 (770–780 BH10)
Epitope RLRDLLLIVTR
Immunogen HIV-1 infection
Species (MHC) human (A*3101)
References Safrit *et al.* 1994a; Safrit *et al.* 1994b

- Recognized by CTL derived from acute seroconverter.
- C. Brander notes that this is an A*3101 epitope in the 1999 database.

HXB2 Location gp160 (770–780)
Author Location gp160 (770–780 LAI)
Epitope RLRDLLLIVTR
Subtype B
Immunogen
Species (MHC) human (A*3101)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*3002 epitope.

HXB2 Location gp160 (770–780)
Author Location
Epitope RLRDLLLIVTR
Immunogen HIV-1 infection
Species (MHC) human (A03, A31)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope RLRDLLLIVTR when restricted by HLA-A03 elicited a magnitude of response of 450 SFC with a functional avidity of 0.5nM and binding affinity of 9.6nM. When restricted by HLA-A31, it elicited a magnitude of response of 450 SFC with a functional avidity of 0.05nM and binding affinity of 3.8nM.

HXB2 Location gp160 (770–780)
Author Location
Epitope RLRDLLLIVTR
Immunogen HIV-1 infection
Species (MHC) human (A03, A31)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- Based on a prediction of the minimum number of HLA alleles needed to cover the HLA representation in all responders to this epitope, a minimum set of 6 alleles was found: 2 alleles previously known to be associated (A03, A31) and 4 additional alleles (A02, A74, B44, Cw04).

HXB2 Location gp160 (770–780)
Author Location gp41 (768–778 NL43)
Epitope RLRDLLLIVTR
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords subtype comparisons
References Cao *et al.* 1997a

- The consensus peptide of clade B is RLRDLLLIVTR.
- The consensus peptide of clades A, C and E is RLRDFILIVTR and it is less reactive.
- The consensus peptide of clade D is SLRDLLLIVTR and it is less reactive.

HXB2 Location gp160 (770–780)
Author Location gp41 (775–785)
Epitope RLRDLLLIVTR
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A3)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location gp160 (770–780)
Author Location gp41 (770–780)
Epitope RLRDLLLIVTR
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant.

HXB2 Location gp160 (770–780)

CTL CD8+

Author Location Nef (73–82)
Epitope RLRDLLLIVTR
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant.
- In two of the subjects, RLRDLLLIVTR was the dominant epitope.

HXB2 Location gp160 (770–780)
Author Location gp41 (769–780)
Epitope RLRDLLLIVTR
Epitope name A3-RR11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 1/7 individuals began to have detectable responses to this epitope after STI.

HXB2 Location gp160 (770–780)
Author Location Env (770–780)
Epitope RLRDLLLIVTR
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 7 epitopes from this individual that varied over time, although the internal mutations did not become fixed. rlrdlllVItr variant residues were found. The V mutation arose at late time points, the I mutation arose at intermediate time points.

HXB2 Location gp160 (770–780)
Author Location Env (786–778)
Epitope RLRDLLLIVTR
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 14 patients recognized this epitope.

HXB2 Location gp160 (770–780)
Author Location gp160
Epitope RLRDLLLIVTR
Epitope name RR11(gp160)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3, A31)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- HLA-A*03-restricted epitope RLRDLLLIVTR elicited no immune response in Chinese HIV-1 positive subjects as part of peptide HRLRDLLLIVTRIVELL.
- Although the tested peptide sequence HRLRDLLLIVTRIVELL contains the exact sequence of a previously described HLA-A3 epitope, RLRDLLLIVTR, none of the 3 HLA-A3 carriers responded to it (author communication and Fig.1). When tested in Chinese HLA-A31 positive subjects, this peptide did elicit an immune response.

HXB2 Location gp160 (770–780)

Author Location gp41 (770–780)
Epitope RLRDLLLIVTR
Immunogen HIV-1 infection
Species (MHC) human (A31)
References Ferris *et al.* 1999; Hammond *et al.* 1995

- This epitope is processed by a TAP1/2 dependent mechanism.

HXB2 Location gp160 (770–780)
Author Location gp41 (770–780)
Epitope RLRDLLLIVTR
Immunogen HIV-1 infection
Species (MHC) human (A31)
Donor MHC A*0201, A31, B44, B60, Cw16, Cw3
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

HXB2 Location gp160 (770–780)
Author Location Env
Epitope RLRDLLLIVTR
Epitope name TW10
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A31)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords epitope processing, escape
References Draenert *et al.* 2004b

- This study characterizes the N-terminal flanking position of the epitope ISPRTLNAW, and mutations in this position are thought to impact processing. The A31 epitope RLRDLLLIVTR was used as a negative control in this study.

HXB2 Location gp160 (770–780)
Author Location gp41 (775–785)
Epitope RLRDLLLIVTR
Immunogen HIV-1 infection
Species (MHC) human
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the HLA A2+ was HLA A*0201, A31, B8, B51 and responded to this epitope that has been previously noted to be HLA A3.1, as well as seven others.

HXB2 Location gp160 (777–785)
Author Location gp41 (782–790 LAI)
Epitope IVTRIVELL
Subtype B
Immunogen
Species (MHC) human (A*6802)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*6802 epitope.

HXB2 Location gp160 (777–785)
Author Location gp41
Epitope IVTRIVELL
Epitope name IL9(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A68)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A68-restricted epitope IVTRIVELL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide LIVTRIVELLGRRGWEAL.

HXB2 Location gp160 (781–794)
Author Location Env
Epitope HSSLKGLRRGREGLK
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses

CTL CD8+

to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide HSSLKGLRRGREGLK from subtype CRF01_AE.

HXB2 Location gp160 (781–795)
Author Location
Epitope IVELLGRRGWEVLKY
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101; B*0801, B*1401
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b
- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- IVELLGRRGWEVLKY was recognized by a placebo patient after infection.

HXB2 Location gp160 (781–802)
Author Location gp41 (788–809 HXB2)
Epitope IVELLGRRGWEALKYWWNLLQY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Lieberman *et al.* 1992
- CTL epitope defined by T cell line and peptide mapping.

HXB2 Location gp160 (781–802)
Author Location gp120 (788–809)
Epitope IVELLGRRGWEALKYWWNLLQY
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1995
- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

HXB2 Location gp160 (786–794)
Author Location gp41 (751–759)
Epitope GRRGWEALK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*2705)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords Th1, characterizing CD8+ T cells
References Kleen *et al.* 2004
- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- One of seven patients responded to this peptide with GzB producing cells, and a different patient responded with IFN-gamma producing cells.

HXB2 Location gp160 (786–794)
Author Location gp41 (791–799 LAI)
Epitope GRRGWEALK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords review
References McMichael & Walker 1994
- Review of HIV CTL epitopes.
- Also: J. Liebermann 1992 and pers. comm. J. Liebermann.

HXB2 Location gp160 (786–794)
Author Location Env
Epitope GRRGWEALK
Epitope name GK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27, B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008
- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- GK9, GRRGWEALK, is a known HLA-B27- and HLA-B57-restricted epitope used as a positive control for eliciting CTL IFN-gamma responses.

HXB2 Location gp160 (786–795)
Author Location gp41 (791–800 LAI)
Epitope GRRGWEALKY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*2705)
Keywords optimal epitope
References Llano *et al.* 2009
- C. Brander notes this is a B*2705 epitope.

HXB2 Location gp160 (786–795)
Author Location
Epitope GRRGWEALKY

Immunogen HIV-1 infection
Species (MHC) human (B*2705)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope GRRGWEALKY elicited a magnitude of response of 215 SFC with a functional avidity of 5nM.

HXB2 Location gp160 (786–795)
Author Location gp41 (791–800 LAI)
Epitope GRRGWEALKY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Lieberman 1998

- Optimal peptide mapped by titration J. Lieberman, pers. comm.

HXB2 Location gp160 (786–795)
Author Location gp41 (786–795)
Epitope GRRGWEALKY
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Day *et al.* 2001

HXB2 Location gp160 (787–795)
Author Location gp160 (787–795)
Epitope RRGWEVLKY
Immunogen HIV-1 infection
Species (MHC) human (A*0101)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location gp160 (787–795)
Author Location gp41 (787–795)
Epitope RRGWEVLKY
Immunogen HIV-1 infection
Species (MHC) human (A1)
Donor MHC A1A1, B14, B8, Cw7, Cw8
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

HXB2 Location gp160 (787–795)
Author Location gp41
Epitope RRGWEVLKY
Epitope name A1-RY9(gp41)
Immunogen HIV-1 infection
Species (MHC) human (A1)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location gp160 (787–795)
Author Location gp41
Epitope QRGWEVLKY
Epitope name QY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A1)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

CTL CD8+

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- Epitope QRGWEVLKY varied to lRGWEiLKY in an untreated patient. Previously published HLA-restriction for QY9 is HLA-A1.

HXB2 Location gp160 (787–795)
Author Location gp41
Epitope `RRGWEVLKY`
Epitope name RY9(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A1)
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords non-susceptible form
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- The tested peptide sequence, LLGRRGWEaLKYLWNLL, contains a variant, RRGWEaLKY that differs by 1 substitution from the previously described HLA-A1 optimal epitope RRGWEVLKY. None of the 4 HLA-A1 carriers responded to the variant RRGWEaLKY.

HXB2 Location gp160 (787–795)
Author Location
Epitope `RRGWEVLKY`
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A1, A2; B38, B8
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location gp160 (787–805)
Author Location (C consensus)
Epitope `QRGWEALKYLGSLVQYWGL`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

HXB2 Location gp160 (792–806)
Author Location Env
Epitope `GLKYLWNLLLYWGRE`
Subtype A
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 1 subject responded to peptide GLKYLWNLLLYWGRE from subtype A.

HXB2 Location gp160 (794–802)
Author Location gp160 (794–802 LAI)
Epitope `KYCWNLLQY`
Subtype B
Immunogen
Species (MHC) human (A*3002)
Keywords optimal epitope
References Goulder *et al.* 2001a; Llano *et al.* 2009

- C. Brander notes this is an A*3002 epitope.

HXB2 Location gp160 (794–802)
Author Location gp41
Epitope `KYCWNLLQY`
Epitope name KY9 (gp41)
Immunogen HIV-1 infection

Species (MHC) human (A*3002)
References Goulder *et al.* 2001a

- HLA-A*3002 is very common in African populations, 50% of Zimbabweans express HLA-A30, 44% in African Zulu, so five new HIV epitopes were characterized that are presented by this HLA molecule.
- A rapid method was developed combining ELISPOT with intracellular IFN-γ staining of PBMCs to map optimal epitopes, then HLA presenting molecules were defined – this method was completed within 48 to 72 hours of receipt of blood.
- Two individuals were studied: Subject 199 (HLA A*0201/*3002 B*4402/51 Cw2/5), a Caucasian, and Subject 6007 (HLA A*3002/ B53/*5801 Cw4/7) an African-Caribbean.
- In both HLA-A*3002 individuals the response to RSLYNTVATLY was dominant.
- In subject 199 four additional A*3002 epitopes were identified.
- Three quantitative assays, ELISPOT, precursor frequency and chromium release, confirmed a hierarchy of response: RY11 (p17) > KY9 (gp41) > KY9 (RT-53) > IY9 (gp41)

HXB2 Location gp160 (794–802)
Author Location gp41 (283–291)
Epitope KYCWNLLQY
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location gp160 (794–802)
Author Location
Epitope KYCWNLLQY?
Epitope name KIY9
Immunogen HIV-1 infection
Species (MHC) human (A*3002)
Country United States, South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords memory cells
References Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

HXB2 Location gp160 (794–802)
Author Location Env
Epitope KYCWNLLQY
Epitope name A30-KQY9(env)
Immunogen HIV-1 infection
Species (MHC) human (A30)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location gp160 (794–802)
Author Location gp41
Epitope KYLWNLLQY
Epitope name KY9(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope KYLWNLLQY elicited an immune response in Chinese HIV-1 positive subjects as part of peptide EALKYLWNLLQYWIQELK. This epitope differs from the previously described HLA-A30-restricted epitope sequence, KYCWNLLQY, at 1 residue, KYlWNLLQY.
- 3 of the 15 HLA-A30 carriers responded to an KYlWNLLQY-containing peptide with average magnitude of CTL response of 110 SFC/million PBMC (author communication and Fig.1).

HXB2 Location gp160 (794–814)
Author Location gp41 (SF2)
Epitope KYCWNLLQYWSQELKNSAVSL
Immunogen HIV-1 infection
Species (MHC) human
References Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined.

HXB2 Location gp160 (795–816)

CTL CD8+

Author Location gp41 (802–823 HXB2)
Epitope YWWNLLQYWSQELKNSAVNLLN
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1992

- CTL epitope defined by T cell line and peptide mapping.

HXB2 Location gp160 (799–807)
Author Location Env (800–808 subtype B)
Epitope LLQYWSQEL
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN *HIV component:* gp160
Species (MHC) human (A*0201)
Keywords binding affinity
References Kundu *et al.* 1998a

- Ten HIV-1 + HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period.
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity.
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual.
- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses.

HXB2 Location gp160 (799–808)
Author Location Env
Epitope LLLYWGRELK
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0201, A*0205, B*2703, B*4201, Cw*0202, Cw*1701; A*0201, A*0205, B*1503, B*5801, Cw*0401, Cw*0701; A*6802, A*7401, B*1510, B*4901, Cw*0304, Cw*0701; A*0101, A*2301, B*0702, B*4501, Cw*0702, Cw*1601
Country Kenya
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2008

- To evaluate the use of IFN-gamma ELISpot and proliferation assays, the two were compared in a cohort of HIV-1-infected Kenyan sex-workers. ELISpot does not always correlate with viral load and replication or disease progression. The exclusive use of these assays makes definition of CTL response in disease incomplete, especially for memory T cells.
- Despite assaying for 24 INF-gamma and 41 proliferative responses, only 5 of these responses overlapped in the same subject. 18 peptide-epitopes including 10 epitopes and their variants were used in this study.
- LLLYWGRELK elicited proliferation in 4 subjects; and ELISpot response in 1 separate subject.

HXB2 Location gp160 (805–814)
Author Location gp41 (810–819 LAI)
Epitope QELKNSAVSL
Subtype B
Immunogen
Species (MHC) human (B*4001)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*4001,B60 epitope.

HXB2 Location gp160 (805–814)
Author Location Env (805–814)
Epitope QELKNSAVSL
Epitope name QL10
Immunogen HIV-1 infection
Species (MHC) human (B*4001)
Donor MHC A*0201, A*2402, B*4001, B*5001, Cw03, Cw04
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords immunodominance, escape, variant cross-recognition or cross-neutralization
References Draenert *et al.* 2006

- HIV-specific cellular and humoral immune responses were examined in monozygotic male twins infected simultaneously with the same virus. 15 of 17 targeted epitopes were identical in the twins, including two immunodominant responses. 3 of 4 declining responses in the twins showed mutations at the same residue. Evolving antibody responses cross-neutralized the other twin's virus. The results were compared with a third brother, infected by the twins' virus 13 months after their seroconversion. The data show similarity in disease course in persons of identical genetic background infected with the same strain of HIV-1.
- This epitope, QELKNSAVSL (QL10) was restricted by HLA-B*4001. A variant that arose was QELKkSAVSL.

HXB2 Location gp160 (805–814)
Author Location gp41
Epitope QELKNSAVSL
Epitope name QL10(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B40)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B40-restricted epitope QELKNSAVSL elicited an immune response in Chinese HIV-1 positive subjects LLQYWIQELKNSAVSLL.

- 1 of the 20 HLA-B40 carriers responded to QELKNSAVSL-containing peptide with average magnitude of CTL response of 190 SFC/million PBMC (author communication and Fig.1).

HXB2 Location gp160 (805–814)
Author Location gp41 (SF2)
Epitope QELKNSAVSL
Immunogen HIV-1 infection
Species (MHC) human (B60)
References Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes.
- B60 is present in 10-20% of the Caucasoid and very common in Asian populations.

HXB2 Location gp160 (805–814)
Author Location gp41 (805–814)
Epitope QELKNSAVSL
Immunogen HIV-1 infection
Species (MHC) human (B60, B61)
Keywords immunodominance
References Day *et al.* 2001

- No immunodominant responses were detected to five B61-restricted epitopes tested.
- All five B60-restricted epitopes were reactive in another subject, and the B60-restricted responses together contributed over one-third of the total CTL response.

HXB2 Location gp160 (805–814)
Author Location Env (799–813 BH10, LAI)
Epitope QELKNSAVSL
Immunogen HIV-1 infection
Species (MHC) human
References Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is LLQYWSQELKNSAVS) has similarity with the complement component C6 fragment LTQFSSEELKNSGLT.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is NSAVSLLNATAIAVA) also has similarity with the human INT-2 proto-oncogene protein precursor (fibroblast growth factor-3) fragment NSAYSILEITAVEVG.

HXB2 Location gp160 (813–822)
Author Location Env (813–822)
Epitope SLLNATAIAV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- Responses to epitope SLLNATAIAV were seen in early chronic infection. This was one of the epitopes targeted by broad HLA-A2-restricted CTL responses.

HXB2 Location gp160 (813–822)
Author Location gp41 (814–823 LAI)
Epitope SLLNATDIAV
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN
HIV component: gp160
Species (MHC) human (A*0201)
References Dupuis *et al.* 1995

- Of two CTL clones, one reacted only with 815-823, the other with 814-823 and 815-823.
- Noted to be A*0201 in Brander *et al.*, 1999 database.

HXB2 Location gp160 (813–822)
Author Location Env (814–823 subtype B)
Epitope SLLNATDIAV
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN
HIV component: gp160
Species (MHC) human (A*0201)
Keywords binding affinity
References Kundu *et al.* 1998a

- Ten HIV-1 + HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period.
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity.
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual.
- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses.
- CTL to overlapping peptides in this region gave a positive response in the greatest number of patients.

- ALTERNATIVE EPITOPES: LLNATDIAV and LLNATDIAVA – CTL were induced by vaccine in those that had the sequence SLLNATAIAVA in their own infection, but not in those with: NLLNTIAIAVA or NLFNTTAIAVA or SLLNATAITVA.

HXB2 Location gp160 (813–822)
Author Location gp41 (818–827 LAI)
Epitope SLLNATDIAV
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN *HIV component:* gp160
Species (MHC) human (A*0201)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*0201 epitope.

HXB2 Location gp160 (813–822)
Author Location gp41 (814–823 LAI)
Epitope SLLNATDIAV
Epitope name LR27
Subtype B
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade LAI *Adjuvant:* Incomplete Freund's Adjuvant (IFA), Montanide (ISA 720), P30, PLG
Species (MHC) mouse (A*0201)
Keywords binding affinity, vaccine-specific epitope characteristics, immunodominance
References Peter *et al.* 2001

- The stability of peptide binding to HLA-A2.1 was determined for six HLA-A2.1 peptides included in this vaccine study – ILKEPVHGV (RT), SLYNTVATL (p17), SLLNATDIAV (gp41) and LLWKGEGAV (RT) all bound with high affinity comparable to a influenza epitope reference (GILGFVFTL), while RGPGRAFVTI and VIYQYMDDL bound with a lower affinity (relative binding activity = 0.01).
- The four high-affinity peptides formed stable complexes with half-lives ranging between 8 and 32 hours, while the low affinity peptides had half lives of less than an hour.
- HLA-A2.1 transgenic mice were immunized with the six HIV-1 peptides and P30, as a universal T-helper epitope, with IFA or Montanide or microspheres as adjuvants.
- All peptides except VIYQYMDDL induced a stong CTL response in Cr-release assays - stronger responses were observed when peptides were delivered alone, indicating immunodominance when the combination was used.

HXB2 Location gp160 (813–822)
Author Location gp41 (814–823 LAI)
Epitope SLLNATDIAV
Epitope name LR27
Subtype B
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade LAI *Adjuvant:* Incomplete Freund's Adjuvant (IFA), IL-12, P30
Species (MHC) mouse (A*0201)
Keywords vaccine-specific epitope characteristics, immunodominance
References Peter *et al.* 2002

- When HIV-1 peptides were used to vaccinate HLA-A2.1 transgenic A2-Kb mice, strong responses to five peptides were observed when the peptides were given individually, but immunodominance limited the response to some of the peptides when they were given in combination Peter *et al.* [2001]. IL-12 can counteract immunodominance in BALB/c mice, so it was given with the multiple epitope vaccination, and was instead found to specifically eliminate the HLA-A2.1-epitope CTL responses, but not Kb CTL responses. This was possibly a consequence of transient depletion of T-cells, B cells and macropahges in the spleen.

HXB2 Location gp160 (813–822)
Author Location gp41 (814–823)
Epitope SLLNATDIAV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords dendritic cells
References Kundu *et al.* 1998b

- Allogeneic dendritic cells (DCs) were obtained from HLA-identical siblings, pulsed with rgp160 MN or A2-restricted HIV-1 epitope peptides, and infused monthly into six HIV-infected patients.
- 1/6 showed increased env-specific CTL and increased lymphoproliferative responses, 2/6 showed increase only in proliferative responses, and 3/6 showed no change – pulsed DCs were well tolerated.
- SLLNATDIAV is a conserved HLA-A2 epitope included in this study – 4/6 patients had this sequence as their HIV direct sequence, and 3 of these had a detectable CTL response – the other two had either the sequence SLFNAIDIAV or SLLNTTDIVV and no detectable CTL response.
- CTL demonstrated against peptide-coated target, epitope is naturally processed and enhancible with vaccine.

HXB2 Location gp160 (813–822)
Author Location gp41 (818–827)
Epitope SLLNATDIAV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the A2+ individuals that didn't respond to SLYNTVATL reacted with seven other epitopes, including this epitope.

HXB2 Location gp160 (813–822)
Author Location gp41 (SF2)
Epitope SLLNATAIAV
Epitope name SV10
Immunogen HIV-1 infection
Species (MHC) human (A2)

Keywords acute/early infection
References Goulder *et al.* 2001a
- Dominant CTL epitope in acute infection of patient AC13– response to this epitope corresponded to reduction of initial viremia.
- Several other subdominant CTL epitopes were identified in the acute phase, but a response to SL9, SLYNTVATL, was not evident until 18 months post-presentation.

HXB2 Location gp160 (813–822)
Author Location gp41 (77–85 SF2)
Epitope SLLNATDIAV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b
- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A2+ individuals that had a CTL response to this epitope broken down by group: 1/10 group 1, 2/6 group 2, and 1/4 group 3.

HXB2 Location gp160 (813–822)
Author Location gp41 (814–823 CM243 subtype CRF01)
Epitope SLLNATAIAV
Epitope name E813-82
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HIV exposed persistently seronegative (HEPS)
References Sriwanthana *et al.* 2001
- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was reactive in HIV+ control study subjects 125 and 144 who carried HLA-A2.

HXB2 Location gp160 (813–822)
Author Location gp41 (814–823 CM243)
Epitope SLLNATAIAV
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords subtype comparisons
References Bond *et al.* 2001
- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- 1/4 tested FSWs recognized the E clade version of this epitope, which differs from the previously defined B clade version by one amino acid, SLLNATDIAV.
- This epitope was somewhat conserved 4/8 subtypes: CRF01 (E), B, D, and F.

HXB2 Location gp160 (813–822)
Author Location gp41 (813–822)
Epitope SLLNATDIAV
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001
- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.

HXB2 Location gp160 (813–822)
Author Location gp41 (813–822 IIIB)
Epitope SLLNATAIAV
Epitope name D2
Subtype B
Immunogen vaccine
Vector/Type: DNA, DNA with protein boost *Strain:* B clade IIIB *HIV component:* gp160, gp160ΔV3 *Adjuvant:* IL-12
Species (MHC) mouse (A2)
Keywords vaccine-specific epitope characteristics
References Kiszka *et al.* 2002
- Transgenic mice expressing a HLA-A2/Kb chimeric protein were vaccinated with a full length gp160 or with gp160deltaV3, with the V3 loop deleted. Mice given gp160deltaV3 had a broader immune response than those given gp160, with increased responses to conserved HLA-A2 epitopes in the C1 region of gp120, KLTPLCVTL, and the C-term region of gp41, SLLNATAIAV.
- Greater resistance was conferred by the gp160deltaV3 than the gp160 vaccine to a challenge of vaccinia expressing heterologous gp160 from primary isolates (VI-06 and 89.6), and the resistance was conferred by CD8+ T-cells.

HXB2 Location gp160 (813–822)
Author Location Env (813–)
Epitope SLLNATDIAV
Epitope name Env813
Immunogen HIV-1 infection
Species (MHC) human (A2)

Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This epitope was one of the previously identified HLA-A2 epitopes studied.
- None of the 17 HIV-infected HLA-A2+ people in this study recognized this epitope.

HXB2 Location gp160 (813–822)
Author Location gp160 (813–822)
Epitope SLLNATDIAV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords acute/early infection, optimal epitope
References Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was recognized both in acute and chronic infection, but slightly more frequently in chronic infection.

HXB2 Location gp160 (813–822)
Author Location Env
Epitope SLLNATAIAV
Epitope name A2-SAV10(Env)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location gp160 (813–822)
Author Location gp41
Epitope SLLNATAIAV
Epitope name SAV10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords superinfection
References Streeck *et al.* 2008b

- Loss of viral replication control by an elite controller after superinfection was found to coincide with rapid recombination events in 2, ∼50 residue regions of Gag and Env that include immunodominant epitopes KK10 (KRWIILGLNK) and CL9 (CAPAGFAIL). Viral escape was seen at both epitopes and consequent CTL responses against the epitope-variants.
- CTL responses to previously described HLA-A2-restricted SLLNATAIAV were seen, post-superinfection and -recombination.

HXB2 Location gp160 (813–822)
Author Location gp41
Epitope SLLNATDIAV
Epitope name gp41 SV10
Immunogen HIV-1 infection
Species (MHC) human (A68)
Keywords binding affinity, subtype comparisons, supertype, computational epitope prediction
References Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- This epitope binds to three HLA-A2 supertype alleles: A*6802 (highest affinity), A*0202 and A*0203 (but not A*0201 and not A*0206)
- This epitope did not elicit an ELISPOT response in 22 chronic HIV HLA-A2 infections, but elicited a strong response in 1/12 acute HLA-A2 infections – this individual, AC13, was HLA A*0201/68 B44/14 and also had a strong response to HLA-A2 vpr epitope AIIRILQQL.

HXB2 Location gp160 (813–822)
Author Location gp41
Epitope SLLNATAIAV
Epitope name SV10(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ

Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope SLLNATAIAV elicited an immune response in Chinese HIV-1 positive subjects as part of peptide ELKNSAVSLLNATAIAVA. This epitope differs from the previously described HLA-A2-restricted epitope sequence, SLLNATDIAV, at 1 residue, SLLNATaIAV.
- 2 of the 55 HLA-A2 carriers responded to SLLNATAIaV-containing peptide with average magnitude of CTL response of 270 SFC/million PBMC (author communication and Fig.1).

HXB2 Location gp160 (813–828)
Author Location gp41 (MN)
Epitope `SLLNATAIAVAEGTDR`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A2
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, HAART, ART
References Chitnis *et al.* 2003

- 17 perinatally HIV-1 infected children (0.08-16 years) were evaluated for HLA-A2-restricted IFN-gamma CD8+ CTL responses against 4 immunodominant peptides that carry HLA-A2 epitopes. Two peptides were from gp120 (one at position 112, one from the V3 loop), and one each was from gp41 and Gag. 15/17 patients responded to the Gag peptide, 13/17 to the gp41 and the non-V3 gp120 peptides, and 11/17 responded to the V3 loop. 4 children recognized all 4 peptides.

HXB2 Location gp160 (814–822)
Author Location Env (815–823)
Epitope `LLNATAIAV`
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords binding affinity
References Kmieciak *et al.* 1998a

- CTL responses in six patients to four Env epitopes were studied: D2: LLNATAIAV, 5.3: RLRDLLLIV, D1: KLTPLCVTL, and 4.3: QMHEDIISL—all have A2 anchor residues.
- The C terminal epitopes (D2 and 5.3) were highly variable and the variability was considered responsible for limited CTL response, while D1 and 4.3, N-terminal epitopes, were much more conserved and gave evidence of high levels of CTL response *in vitro*.
- Peptides 5.3 and D2 bound to HLA A*0201 with low affinity and were variable, particularly D2.
- Substitutions in peptide D2: llnTIaiav did not abrogate the response, but diminished it.
- In a longitudinal study, the CTL response to the variable D2 epitope diminished over time, while the response to the conserved epitope D1 stayed higher.

HXB2 Location gp160 (814–822)
Author Location Env
Epitope `LLNATAIAV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201, A2)
Donor MHC A1, A19, B*3501, B44, Cw16, Cw7; A*0201, A19, B14, B44, Cw16, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
References Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-A2/A*0201 restricted epitope, LLNATAIAV was mutated to LLNAiAIAV in the daughter D2 isolate.

HXB2 Location gp160 (814–822)
Author Location (C consensus)
Epitope `LLDTIAIAV`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0205)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.

- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location gp160 (814–822)
Author Location (C consensus)
Epitope LLDTIAIAV
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0205)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- LLDTIAIAV is an optimal epitope.

HXB2 Location gp160 (814–822)
Author Location gp41 (815–823 LAI)
Epitope LLNATDIAV
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN *HIV component:* gp160
Species (MHC) human (A2)
References Dupuis *et al.* 1995

- Of two CTL clones, one reacted only with 815-823, the other with 814-823 and 815-823.

HXB2 Location gp160 (814–822)
Author Location Env (815–823)
Epitope LLNATAIAV
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Kmieciak *et al.* 1998b

- Increased CTL response to cells expressing a VV construct ΔV3 mutant compared with a full-length env gene product.

HXB2 Location gp160 (822–832)
Author Location gp41 (SF2)
Epitope VAEGTDRVIEI
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of individuals that had a CTL response to this epitope (HLA presenting molecule uncertain) broken down by group: 0 group 1, 1 group 2, and 0 group 3.

HXB2 Location gp160 (824–832)
Author Location gp160 (828–836 WEAU)
Epitope EGTDRIVIEI
Epitope name gp160 EI9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*2902, B*0801, B*4403
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, immunodominance, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.
- This was one of five reasonably strong responses in early infection in the patient WEAU, and the epitope sequence did not vary during the first year of the infection.

HXB2 Location gp160 (827–841)
Author Location gp41 (834–848 IIIB)
Epitope DRVIEVVQGAYRAIR
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Clerici *et al.* 1991a

- Helper and cytotoxic T cells can be stimulated by this peptide (Th4)

HXB2 Location gp160 (827–841)
Author Location gp41 (834–848 IIIB)
Epitope DRVIEVVQGAYRAIR

Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^d, H-2^p, H-2^q, H-2^u)
References Shirai *et al.* 1992

- In a murine system multiple class I molecules can present to CTL.

HXB2 Location gp160 (827–841)
Author Location gp41 (834–848 IIIB)
Epitope DRVIEVVQGAYRAIR
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* gp160
Species (MHC) mouse (H-2^d, H-2^p, H-2^q, H-2^u)
References Shirai *et al.* 1996b

- Multiple murine MHC can cross-present this epitope (HP53), and P18 RIQRGPGRAFVTIGK, to specific CTL.

HXB2 Location gp160 (827–841)
Author Location gp41 (834–848 IIIB)
Epitope DRVIEVVQGAYRAIR
Immunogen HIV-1 exposed seronegative
Species (MHC) human
References Pinto *et al.* 1995

- CTL and T helper cell reactivity in healthcare workers exposed to HIV.

HXB2 Location gp160 (827–841)
Author Location gp41 (HIV-1 EVK, HIV-1 GKV4046,)
Epitope DRVIEVVQGAYRAIR
Epitope name N15
Subtype B
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, T-cell Elispot
Keywords assay standardization/improvement, vaccine-specific epitope characteristics, vaccine antigen design, antibody generation
References Karpenko *et al.* 2007

- A combined VLP-based vaccine, CombiHIVcac, was designed comprising TBI with 4 T-cell epitopes and 5 B-cell epitopes, as well as TCI with over 80 T-cell epitopes from Env, Gag, Pol and Nef conserved across A, B and C HIV-1 subtypes. The vaccine induced humoral and cellular immunity in mice infected with 3 HIV-1 strains. Virus-neutralizing activity was as efficient as HIV-1 patient sera inhibition of viral replication. IFN-gamma and IL-2 ELISpot showed that CTL responses were induced, though at 2 and 10 times lower than T-helper responses as measured by IL-4 ELISpot. Toxicity studies showed the vaccine to be promising with no allergenic properties.
- This multiple class I restricted peptide, DRVIEVVQ-GAYRAIR, is from the TCI component of the vaccine. It induced CTL responses as measured by ELISpot. MHC H-2d mice were used in the study.

HXB2 Location gp160 (828–836)
Author Location Env (829–837 subtype B)
Epitope RVIEVLQRA
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN *HIV component:* gp160
Species (MHC) human (A*0201)
Keywords binding affinity
References Kundu *et al.* 1998a

- Ten HIV-1 + HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period.
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity.
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual.
- CTL responses after reimmunization may include recall responses – individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses.

HXB2 Location gp160 (828–836)
Author Location gp41 (829–837 LAI)
Epitope RVIEVLQRA
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN *HIV component:* gp160
Species (MHC) human (A2)
References Dupuis *et al.* 1995

- CTL from HLA-A2 positive subject react with this peptide.

HXB2 Location gp160 (828–836)
Author Location gp41 (829–837 CM243 subtype CRF01)
Epitope KVIEVAQGA
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords subtype comparisons
References Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- 1/4 tested FSWs recognized the E clade version of this epitope, which differs from the previously defined B clade version by three amino acids, RvievLqRa.
- This epitope was only conserved in CRF01 (subtype E), and identities were rare.

HXB2 Location gp160 (830–854)
Author Location gp41 (831–853)
Epitope IEVVQGAYRAIIRHIPRRIRQGLERI
Immunogen HIV-1 infection
Species (MHC) human
References Price *et al.* 1995

- Study of cytokines released by HIV-1 specific activated CTL.

CTL CD8+

HXB2 Location gp160 (831–838)
Author Location Env (830–837)
Epitope EVAQRAYR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*3303)
References Hossain *et al.* 2001; Takiguchi *et al.* 2000

- HLA-A33 a very common allele in Asia, with HLA-A*3303 the most common among the Japanese. New A*3303 epitopes were defined to better characterize the immune response in this population.
- The anchor motif for HLA*3303 (A, I, L, V, F, Y in position 2 (F and Y bind most strongly), and R (K is also tolerated) in the C-terminal position) was used to define 82 potentially reactive peptides in Env; 37/82 peptides bound to A*3303; 3/37 peptides could induce peptide-specific CTL in bulk PBMC cultures from 1/3 HLA A*3303 positive individuals tested.
- 2/3 peptides that reacted with the bulk culture, EVAQRAYR and VIEVAQRAYR, were overlapping, with one encompassing the other, but EVAQRAYR was shown to be the one that was reactive with a CTL clone.
- CTL clones were isolated that killed target cells in a concentration dependent manner after pulsing with the EVAQRAYR peptide, that could also kill cells transfected with env expressed from a vaccinia vector. Bulk cultures were tested from six additional people, and only 2/6 reacted with this peptide, but the peptide is in a highly variable region.

HXB2 Location gp160 (831–838)
Author Location gp41 (320–327)
Epitope EVAQRAYR
Immunogen HIV-1 infection
Species (MHC) human (A*3303)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location gp160 (831–838)
Author Location gp41
Epitope EVVQRAYR
Epitope name ER8(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope EVVQRAYR elicited an immune response in Chinese HIV-1 positive subjects as part of peptides AVAEGTDRVIEVVQRAYR and VIEVVQRAYRAIL-HIPTR. This epitope differs from the previously described HLA-A33-restricted epitope, EVAQRAYR, at 1 residue, EVvQRAYR.
- 2 of the 20 HLA-A33 carriers responded to an EVvQRAYR-containing peptide with average magnitude of CTL response of 55 SFC/million PBMC (author communication and Fig.1).

HXB2 Location gp160 (833–841)
Author Location gp160 (837–845 WEAU)
Epitope VQRTCRAIL
Epitope name gp160 VL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*2902, B*0801, B*4403
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords dynamics, immunodominance, acute/early infection, characterizing CD8+ T cells, viral fitness and reversion
References Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape,within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.
- This was one of five reasonably strong responses in early infection in the patient WEAU, and the epitope sequence did not vary during the first year of the infection.

HXB2 Location gp160 (833–847)
Author Location
Epitope LQRAGRAILHIPTRI
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* Other *HIV component:* gp160
Species (MHC) human
Donor MHC A3, A33; B15 (63), B27
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location gp160 (835–843)
Author Location Env (834–842 SF2)
Epitope RAYRAILHI
Immunogen HIV-1 infection
Species (MHC) human (B*5101)
Keywords rate of progression
References Tomiyama *et al.* 1999

- HLA-B27, -B51, and -B57 are associated with slow progression to AIDS, while HLA-B35, -B8, -B24 are associated with a rapid progression to AIDS (Nat. Med. 2:405, 1996;Lancet 22:1187, 1986;Hum Immunol 22:73, 1988;Hum Immunol 44:156, 1995)
- 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%
- Of the 172 HIV-1 peptides with HLA-B*5101 anchor residues, 33 bound to HLA-B*5101, seven of these peptides were reactive with CTL from 3 B*5101 positive individuals, and six were properly processed.
- This peptide could stimulate CTL from one person, however this CTL clone did not recognize B*5101 positive target cells infected with HIV-1 recombinant vaccinia expressing Env, so it was not confirmed that this peptide was a properly processed epitope.

HXB2 Location gp160 (835–843)
Author Location Env (835–843)
Epitope RAYRAILHI
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 7 epitopes from this individual that varied over time, although the internal mutations did not become fixed. The rTFrailhi variant residues arose at early time points, rIyrailhX variant residues arose at intermediate time points.

HXB2 Location gp160 (837–856)
Author Location gp120 (844–863 LAI)
Epitope YRAIRHIPRRIRQGLERILL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Shankar *et al.* 1996

HXB2 Location gp160 (837–856)
Author Location gp41 (844–863 HXB2)
Epitope YRAIRHIPRRIRQGLERILL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Lieberman *et al.* 1992

- CTL epitope defined by T cell line and peptide mapping.

HXB2 Location gp160 (837–856)
Author Location gp120 (844–863)
Epitope YRAIRHIPRRIRQGLERILL
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

HXB2 Location gp160 (837–856)
Author Location gp120 (844–863 SF2)
Epitope YRAIRHIPRRIRQGLERILL
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-A2, A26, B7, and B38.

HXB2 Location gp160 (840–854)
Author Location Env
Epitope ILHIPRRIRQGLERA
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons
References Aidoo *et al.* 2008

- Factors affecting cross-subtype immunity were evaluated by west Cote d'Ivoire subjects' INF-gamma ELISpot responses to OLPs from a CRF02_AG candidate vaccine, a west Kenyan subtype A virus and a Thai CRF01_AE sequence. 15 test subject sequences were primarily CRF02_AG or CRF02_AG-like, but also pure subtypes A and D. Cross-reactive responses to Gag as well as Env peptides were seen, though the response magnitude to Env was lower, perhaps due to its greater sequence variation.
- 2 subjects responded to peptide ILHIPRRIRQGLERA from subtype CRF01_AE.

CTL CD8+

HXB2 Location gp160 (841–855)
Author Location Env (837–851)
Epitope LHIPTRIRQGLERAL
Epitope name EE211
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords rate of progression, acute/early infection, memory cells
References Sabbaj *et al.* 2007

- CD127 hi memory CTLs were correlated with different patient groups - subjects with chronic HIV-1 infection or controllers or those treated early with ART. For patients with chronic infection, CD127 hi CTL levels decrease greatly. Early ART treatment alone maintained these long-lived memory T cells.
- In response to peptide EE211, LHIPTRIRQGLERAL, a patient with early ART had IFN-gamma secretion by both CD127 hi and lo cells before treatment but was maintained in CD127 hi cells after treatment. CD127 hi cells were responsible for producing IL-2 and TNF-alpha after ART.

HXB2 Location gp160 (842–856)
Author Location gp41 (SF2)
Epitope HIPRRIRQGLERALL
Immunogen HIV-1 infection
Species (MHC) human
References Altfeld *et al.* 2001a

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- The only Env peptide recognized was gp41 HIPRRIRQGLERALL.

HXB2 Location gp160 (842–856)
Author Location gp41
Epitope HIPRRIRQGLERALL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, HIPRRIRQGLERALL, had an overall frequency of recognition of 16.7% - 15.3% AA, 23.1% C, 15.9% H,14.3% WI.

HXB2 Location gp160 (843–851)
Author Location gp41 (843–851)
Epitope IPRRIRQGF
Epitope name IF9
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (B*07)
Country Kenya
Assay type Cytokine production, proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2007

- The authors suggest that epitope variation has different effects on the HIV- specific immune responses of effector memory T cells (Tem) and central memory T cells (Tcm). They show a lack of correlation between IFN-gamma ELISPOT (Tem typical) and proliferation (Tcm typical) assays for specific epitopes in subjects. Since proliferating CTL also correlate with high intracellular IFN-gamma levels, they surmise that proliferating Tcm differentiate to express Tem functions.
- They also show that proliferating CTL numbers correlate with higher CD4 cell counts.
- Several patients responded strongly to epitope variants that were not part of their autologous HIV-1 sequences. Thus they suggest more comprehensive functional characterizations than the usual overnight IFN-gamma ELISPOTs as well as assessments of Tem versus Tcm specific responses rather than general CTL immune responses.
- 4 variants of this index epitope IPRRIRQGF, IF9, were tested - IPtRIRQGl, IPRRIRQGa, IPtRIRQGF, IPvRIRQGl. Variant IPRRIRQGa that is relatively rare induced a high proliferation rate in T cells. IF9 has previously published restriction to HLA-B*07.

HXB2 Location gp160 (843–851)
Author Location gp41 (332–340)
Epitope IPRRIRQGL
Epitope name IL9

Immunogen HIV-1 infection
Species (MHC) human (B*07)
Assay type CTL suppression of replication
Keywords class I down-regulation by Nef
References Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Late protein Env epitope IPRRIRQGL-recognizing CTLs were affected by Nef.

HXB2 Location gp160 (843–851)
Author Location gp41 (848–856 LAI)
Epitope IPRRIRQGL
Subtype B
Immunogen
Species (MHC) human (B*0702)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*0702 epitope.

HXB2 Location gp160 (843–851)
Author Location
Epitope IPRRIRQGL
Immunogen HIV-1 infection
Species (MHC) human (B07)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope IPRRIRQGL elicited a magnitude of response of 163 SFC with a functional avidity of 1nM and binding affinity of 8.3nM.

HXB2 Location gp160 (843–851)
Author Location gp41 (848–856 LAI)
Epitope IPRRIRQGL
Subtype B
Immunogen
Species (MHC) human (B7)
Keywords mother-to-infant transmission
References Brander & Walker 1995

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.

HXB2 Location gp160 (843–851)
Author Location
Epitope IPRRIRQGL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords immunodominance, escape
References Soudeyns *et al.* 1999

- Following primary infection, progressive diversification and accumulation of mutations of HIV-env nucleotide sequences was observed, focused in V2 in one individual and in V8 in another.
- The patient with the V2 diversification showed only transient CTL against Env and Nef.
- The patient with the V8 diversification had an immunodominant CTL response to V8 epitope IPRRIRQGL, and multiple escape variants emerged within a year: ipTrirqgl and ipTrirqgF, which abrogated the CTL response *in vitro*, and also iprrLqgl and iprrirqDl which gave diminished responses.

HXB2 Location gp160 (843–851)
Author Location gp41 (848–856 LAI)
Epitope IPRRIRQGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords subtype comparisons
References Cao *et al.* 1997a

- The consensus peptide of clades A, B, D, and F is IPRRIRQGL.
- The consensus peptide of clade C is iprrirqgF, and it is equally reactive.

HXB2 Location gp160 (843–851)
Author Location gp41 (848–856 subtype B)
Epitope IPRRIRQGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords subtype comparisons, acute/early infection
References Wilson *et al.* 1998b

- The extent of CTL interclade cross-reactivity from CTL isolated from individuals newly infected with B clade virus was studied, and extensive cross-reactivity was observed.
- Two HLA B7 individuals had CTL response to B_LAI, A_92UG037 and C_92BR025 gp160, but were B clade strain MN non-responders – the authors note that the B7 epitope IPRRIRQGL is conserved between the LAI and clade A and C strains, but that MN has a non-conservative Arg to Thr substitution at position three that may be contributing to the specificity of the response in the HLA B7 individuals.

HXB2 Location gp160 (843–851)
Author Location gp41 (843–851 HXB2)
Epitope IPRRIRQGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords rate of progression, immunodominance
References Hay *et al.* 1999

- CTL response to IPRRIRQGL was the immunodominant response in a rapid progressor – there was a subdominant response to SPAIFQSSM in Pol, and interestingly, no response to commonly immunodominant HLA A*0201 epitope SLYNTVATL, although this individual was HLA A*0201.
- The individual showed a strong initial CTL response at the time of the initial drop in viremia, but it was quickly lost, although memory cells persisted.
- Despite the initial narrow response to two epitopes, no other CTL responses developed.
- No HIV-specific lymphoproliferative responses were detected in this patient, and neutralizing antibody response was weak.
- Variants were observed *in vivo*, the most common form of the viral epitope at presentation at 3 months was the only form that did not elicit a CTL response: iprrTrqgl; the other forms detected were iprrirqgF, iprriLqgF, VprrirqgF and they could elicit a CTL response although the response to iprriLqgF was reduced.
- A second rapid progressor had a detectable CTL response exclusively to this epitope.

HXB2 Location gp160 (843–851)
Author Location gp41 (subtype A)
Epitope IPRRIRQGF
Subtype A
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords subtype comparisons
References Cao *et al.* 2000

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, Pol, RT or Nef from HIV-1 clades A, B, and D.
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype.
- This optimal epitope sequence, recognized by CTL derived from a Ugandan with an A subtype infection, is cross-reactive with subtypes A and B, but not in subtype D.

HXB2 Location gp160 (843–851)
Author Location gp41
Epitope IPRRIRQGL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords rate of progression, acute/early infection
References Islam *et al.* 2001

- Subject 053i was followed longitudinally from acute infection through death, and had rapid progression to AIDS.
- This individual had a dominant response to IPRRIRQGL with strong *in vivo* activated responses and *in vitro* stimulated memory responses and a subdominant response to SPAIFQSSM – during the course of disease progression (4 Years), the functional CTL responses were lost and no sequence variation occurred with in both epitopes.
- At 3 months post-presentation, seven IPRRIRQGL CTL clones were obtained, five used the T-cell receptor Vβ 6S1 and Jβ 2.7 and had the CDR3 WAASS, two used Vβ16S1, ERSPPGD, Jβ 2.7 and one CTL clone isolated at 39 months was Vβ 14S1, CR3 PTAAG, and Jβ 2.1 – all of these clones persisted over the course of the infection, even to time of death, despite the loss of CTL functional responses over time.

HXB2 Location gp160 (843–851)
Author Location gp41 (843–851 SF2)
Epitope IPRRIRQGL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 2/4 group 1, 1/3 group 2, and 1/1 group 3.

HXB2 Location gp160 (843–851)
Author Location gp41 (848–856)
Epitope IPRRIRQGL
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B7)
Keywords HIV exposed persistently seronegative (HEPS), immunodominance
References Kaul *et al.* 2001a

- IPRRIRQGL cross-reacts with clades A, B and D.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B7 women, 2/5 HEPS and 5/6 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in 2 of the 5/6 HIV-1 infected women that responded to the epitope, but in neither of the 2/5 HEPS cases.

- Subject ML 1203 started with CTL responses to A*6802 DTVLEDINL and to B7 FPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A*6802 ETAYFILKL which became dominant, B7 TPGPGV/IRYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV.

HXB2 Location gp160 (843–851)
Author Location gp41 (843–851)
Epitope `IPRRIRQGL`
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes.
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

HXB2 Location gp160 (843–851)
Author Location gp41 (SF2)
Epitope `IPRRIRQGL`
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.

HXB2 Location gp160 (843–851)
Author Location gp41 (842–852)
Epitope `IPRRIRQGL`
Epitope name B7-IL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), immunodominance, acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- Only two epitopes were detected during acute infection in patient AC-06, B7 restricted gp41 epitope IPRRIRQGL and Gag GPGHKARVL. GPGHKARVL was the first targeted peptide, and remained immunodominant through the 34 month study period.
- 6/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 2/4 individuals had detectable responses to this epitope after STI.

HXB2 Location gp160 (843–851)
Author Location gp41
Epitope `IPRRIRQGL`
Epitope name B7-IL9(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A24, B27, B7
Keywords HAART, ART, supervised treatment interruptions (STI)
References Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (`http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html`) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient C displayed the greatest response to B27-KK10(p24), and in decreasing order also responded to A24-RW8(Nef), B7-IL9(gp41), A24-RL9(gp41), A24-YL8(gp41), and B7-TM9(Nef).

HXB2 Location gp160 (843–851)
Author Location Env
Epitope `IPRRIRQGL`
Epitope name EW10
Immunogen HIV-1 infection

CTL CD8+

Species (MHC) human (B7)
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords class I down-regulation by Nef
References Bobbitt *et al.* 2003

- Nef, through Nef-mediated MHC-1 down-regulation, is not the only viral protein to influence levels of HIV-specific CTL recognition. The Rev L60F mutation, a common natural variant, can decrease CTL recognition of late gene products. The Rev mutation impacts the early to late gene switch, reducing late gene product production (Gag, Pol, Env, Vpu, Vpr and Vif), while increasing Nef production, both of which reduce the impact CTL recognition of late gene products. As expected, Rev L60F rendered HIV infected cells more resistant to CTL that recognized epitopes from the late proteins Env and Gag. Gag expression is reduced more than Env, and Gag-specific CTL were more profoundly affected. Conversely CTL against an epitope in an early gene product, Tat, were more effeciently recognized when infected with viruses carrying the Rev L60F mutation.
- Patients in the asymptomic phase with active immune responses had more CTL resistant viruses, with lower Rev activity, lower Gag expression and greater resistance to Gag-specific CTL killing, while viruses isolated from people with AIDS were more sensitive to CTL killing.

HXB2 Location gp160 (843–851)
Author Location gp41 (843–851)
Epitope IPRRIRQGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A1, A3, B14, B7, Cw*0702, Cw*0802
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

HXB2 Location gp160 (843–851)
Author Location gp41
Epitope IPRRIRQGL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords HIV exposed persistently seronegative (HEPS)
References Koning *et al.* 2004

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A*11, A*31 and Cw*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
- 3/9 HLA B7+ infection-resistant men, compared to 0/4 pre-seroconversion men who went on to become infected, reacted to this epitope.

HXB2 Location gp160 (843–851)
Author Location Env (333–341)
Epitope IPRRRIRQGL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 3/7 patients recognized this epitope.

HXB2 Location gp160 (843–851)
Author Location (B consensus)
Epitope IPRRIRQGL
Epitope name IL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A31, A68, B07, B70, Cw1, Cw7
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger

intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location gp160 (843–851)
Author Location gp41
Epitope IPRRIRQGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country United Kingdom
Assay type Tetramer binding, T-cell Elispot, Intracellular cytokine staining
Keywords rate of progression, acute/early infection, characterizing CD8+ T cells, immune dysfunction
References Papagno *et al.* 2004
- Acute HIV-1 infection induces massive activation of HIV-specific and non-HIV-specific CD8+ T-cells resulting in differentiation of these cells. High differentiation of CD8+ T-cells is correlated with disease progression. Differentiation is a natural process but it can be driven by elevated immune activation, such as in HIV infection.

HXB2 Location gp160 (843–851)
Author Location gp41 (333–334)
Epitope IPRRIRQGL
Epitope name IPR
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A2, A68.1, B*07, B*3503, Cw*0401, Cw*0702, DQ2, DQ6, DR15, DR17, DR51, DR52
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Oxenius *et al.* 2004b
- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses,and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relatively efficiency of the variant eptiopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- This was one of 8 reactive epitopes found not to vary over time.

HXB2 Location gp160 (843–851)
Author Location gp120
Epitope IPRRIRQGL
Epitope name IL9
Immunogen
Species (MHC) (B7)
Keywords review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion
References Lichterfeld *et al.* 2005
- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

HXB2 Location gp160 (843–851)
Author Location gp41
Epitope IPRRIRQGL
Epitope name B7-IL9(gp41)
Immunogen HIV-1 infection
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006
- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location gp160 (843–851)
Author Location gp41
Epitope IPRRIRQGL
Epitope name IL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords superinfection
References Streeck *et al.* 2008b
- Loss of viral replication control by an elite controller after superinfection was found to coincide with rapid recombination events in 2, ∼50 residue regions of Gag and Env that include immunodominant epitopes KK10 (KRWIILGLNK) and CL9 (CAPAGFAIL). Viral escape was seen at both epitopes and consequent CTL responses against the epitope-variants.
- CTL responses to previously described, HLA-B7-restricted IPRRIRQGL were seen post-superinfection and -recombination.

HXB2 Location gp160 (843–851)

CTL CD8+

Author Location Env
Epitope IPRRIRQGL
Epitope name Env1137
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Epitope IPRRIRQGL elicits IFN-gamma ELISpot responses in 5/7 subjects; and bound HLA-B7 with high and medium affinities in soluble and cell-based assays respectively. The authors claim previously published HLA restrictions of this epitope include B7, A2, A26 and B38 (LANL database), B*0702 (Immune Epitope Database).

HXB2 Location gp160 (843–851)
Author Location gp160 (clade A, B, C, D)
Epitope IPRRIRQGL
Subtype A, B, C, D
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*6802A*6802, B*1303, B*1401, Cw*0602, Cw*1701
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References McKinnon *et al.* 2005

- Interclade cross-reactivity of clades A, B, C, and D was tested using recombinant vaccinia-based IFN-gamma Elispot assay. 47/74 women had a positive Elispot response to at least one clade, and cross-clade responses were frequent. Clade A responses were most frequent, as expected, as clade A dominates the Kenyan epidemic (85% of the 47 women responded to clade A Env, 74% to B, 62% to C, and 43% to D). Cross-clade CD8 T-cell responses were common and directed at conserved epitopes.
- There was a greater magnitude of response to A clade peptides in individuals who responded to more than 1 clade; a 2-fold higher response was observed in clade A in 36% (9/25) of these individuals, and the response to A peptides was never lower. IPRRIRQGL responses were detected in all 4 clades in 1 woman: clade A gave a high response; IPRRIRQGL was identical clade B; clade C and D had lower responses and carried variant peptides IPRRIRQGf and IvRRIRQGL.

HXB2 Location gp160 (843–851)
Author Location gp160
Epitope IPRRIRQGL
Subtype A, B, C, D
Immunogen HIV-1 infection, vaccine
Vector/Type: vaccinia *Strain:* A clade, B clade, D clade NDK, C clade consensus *HIV component:* Env
Species (MHC) human
Donor MHC A*0205, A*3402, B*4201, B*5802, Cw*0602, Cw*1701
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References McKinnon *et al.* 2005

- Interclade cross-reactivity of clades A, B, C, and D was tested using recombinant vaccinia-based IFN-gamma Elispot assay. 47/74 women had a positive Elispot response to at least one clade, and cross-clade responses were frequent. Clade A responses were most frequent, as expected, as clade A dominates the Kenyan epidemic (85% of the 47 women responded to clade A Env, 74% to B, 62% to C, and 43% to D). Cross-clade CD8 T-cell responses were common and directed at conserved epitopes.
- There was a greater magnitude of response to A clade peptides in individuals who responded to more than 1 clade; a 2-fold higher response was observed in clade A in 36% (9/25) of these individuals, and the response to A peptides was never lower. An IPRRIRQGL response was detected in a women who had Env responses to 3 clades, A, B, and C, and clade A and B gave the highest responses. IPRRIRQGL was identical in A and B, had the form IPRRIRQGf in C, and IvRRIRQGL in D.

HXB2 Location gp160 (843–851)
Author Location
Epitope IPRRIRQGL
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A*2501, A*3002; B*0702, B*1801
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location gp160 (843–851)
Author Location Env
Epitope IPRRIRQGL

Subtype B, C, A1, AE
Immunogen HIV-1 infection
Species (MHC) human
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- Epitope IPRRIRQGL was cross-recognized with IPRRIRQGf by 3 subjects, but recognized exclusively by one subtype C infected patient. Predicted HLA restriction for this epitope was to suptertype B7.

HXB2 Location gp160 (843–851)
Author Location Env
Epitope IPRRIRQGF
Subtype B, CRF06_cpx, A1, AE
Immunogen HIV-1 infection
Species (MHC) human
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- Epitope IPRRIRQGF was cross-recognized with IPRRIRQGl by 3 subjects, but recognized exclusively by one subtype CPX06 infected patient, an example of cross-recognition pattern (c) above. Predicted HLA restriction for this epitope was supertype B7.

HXB2 Location gp160 (843–851)
Author Location gp41
Epitope IPTRIRQGL
Epitope name IL9(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope IPTRIRQGL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide YRAILHIPTRIRQGLERA. This epitope differs from the previously described HLA-B7-restricted epitope sequence, IPRRIRQGL, at 1 residue, IPtRIRQGL.
- 1 of the 9 HLA-B7 carriers responded to IPtRIRQGL-containing peptide with average magnitude of CTL response of 70 SFC/million PBMC (author communication and Fig.1).

HXB2 Location gp160 (843–851)
Author Location Env
Epitope IPRRIRQGL
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*6802, A*7401, B*1510, B*4901, Cw*0304, Cw*0701; B*0702, B*1503, Cw*0202, Cw*0702; A*2902, A*3601, B*1510, B*4201, Cw*0304, Cw*1701
Country Kenya
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2008

- To evaluate the use of IFN-gamma ELISpot and proliferation assays, the two were compared in a cohort of HIV-1-infected Kenyan sex-workers. ELISpot does not always correlate with viral load and replication or disease progression. The exclusive use of these assays makes definition of CTL response in disease incomplete, especially for memory T cells.
- Despite assaying for 24 INF-gamma and 41 proliferative responses, only 5 of these responses overlapped in the same subject. 18 peptide-epitopes including 10 epitopes and their variants were used in this study.

CTL CD8+

- IPRRIRQGL elicited proliferation in 2 subjects; ELISpot response in 1 subject; both ELISpot responses and proliferation in 1 subject.

HXB2 Location gp160 (843–851)
Author Location Env
Epitope IPRRIRQGF
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*6802, A*7401, B*1510, B*4901, Cw*0304, Cw*0701; A*0301, A*3001, B*1803, B*4201, Cw*0401, Cw*1701; B*0702, B*1503, Cw*0202, Cw*0702; A*0101, A*2301, B*0702, B*4501, Cw*0702, Cw*1601; A*2902, A*3601, B*1510, B*4201, Cw*0304, Cw*1701
Country Kenya
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2008

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- Despite assaying for 24 INF-gamma and 41 proliferative responses, only 5 of these responses overlapped in the same subject. 18 peptide-epitopes including 10 epitopes and their variants were used in this study.
- IPRRIRQGF elicited proliferation in 1 subject; ELISpot responses in 2 subjects; both responses in 1 subject.

HXB2 Location gp160 (843–851)
Author Location Env
Epitope IPRRIRQGA
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*6802, A*7401, B*1510, B*4901, Cw*0304, Cw*0701; A*0301, A*3001, B*1803, B*4201, Cw*0401, Cw*1701; B*0702, B*1503, Cw*0202, Cw*0702; A*2902, A*3601, B*1510, B*4201, Cw*0304, Cw*1701
Country Kenya
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References McKinnon *et al.* 2008

- To evaluate the use of IFN-gamma ELISpot and proliferation assays, the two were compared in a cohort of HIV-1-infected Kenyan sex-workers. ELISpot does not always correlate with viral load and replication or disease progression. The exclusive use of these assays makes definition of CTL response in disease incomplete, especially for memory T cells.
- Despite assaying for 24 INF-gamma and 41 proliferative responses, only 5 of these responses overlapped in the same subject. 18 peptide-epitopes including 10 epitopes and their variants were used in this study.
- IPRRIRQGA elicited proliferation in 1 subject; ELISpot responses in 2 subjects; both responses in 1 subject.

HXB2 Location gp160 (845–856)
Author Location gp41 (852–863 HXB2)
Epitope RRIRQGLERILL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A30, B8)
References Lieberman *et al.* 1992

- CTL epitope defined by T cell line and peptide mapping.

HXB2 Location gp160 (845–856)
Author Location gp41 (852–863 LAI)
Epitope RRIRQGLERILL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Shankar *et al.* 1996

HXB2 Location gp160 (845–856)
Author Location gp160 (845–856)
Epitope RRIRQGLERILL
Epitope name RL12
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords rate of progression, immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-B8-restricted epitope RRIRQGLERILL elicited increasing CTL responses at the last 2 time points. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location gp160 (846–854)
Author Location
Epitope RIRQGLERA
Epitope name Env-RA9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0205)
Donor MHC A*0205, A*3002, B*1402, B*5301, Cw*0401, Cw*0802
Keywords HAART, ART

References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- This epitope was newly defined in this study.
- Patient 00RCH28 was African American, not on HAART, had a viral load of 5900 and CD4 count of 889, and she also recognized IN(219-227), KIQNFRVYY, A*3002.
- Among HIV+ individuals who carried HLA A02, 6/21 (29%) recognized this epitope.

HXB2 Location gp160 (846–854)
Author Location gp41 (335–343)
Epitope `RIRQGLERA`
Immunogen HIV-1 infection
Species (MHC) human (A*0205)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location gp160 (846–854)
Author Location gp41 (846–859)
Epitope `RIRQGLERA`
Immunogen
Species (MHC) human (A*0205)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 30/50 Brazilian HIV sequences.

HXB2 Location gp160 (846–854)
Author Location Env (846–854)
Epitope `RIRQGLERA`
Immunogen HIV-1 infection
Species (MHC) human (A*0205)
Keywords escape, optimal epitope
References Liang *et al.* 2008

- 1100 unique full-length Env sequences were analyzed and the positive selection (PS) pressure determined. The QUASI method was used across Clades A, B, C and D, to find PS sites dispersed across Env.
- Frequency of PS sites is stable over time.
- 25% to 61% PS sites are shared between subtypes A, B, C and D, so it is inferred that immune responses are targeted against the same general regions.
- Significant correlations between PS sites and neutralizing antibody response, helper response, antibody plus CTL response are found. This suggests that the NAb response might be the driving force behind HIV-1 Env evolution.
- PS-free sites that are targeted greatly by NAb and CTL were found. Functional reasons for the lack of positive selection in such regions must exist.
- PS-site-rare regions (conserved regions of Env) were examined for PS, and epitopes located in such regions. Epitope RIRQGLERA, restricted by HLA-A*0205 is on a region free from positive selection. It is found in Kenyan populations and is associated with low transmission of HIV.

HXB2 Location gp160 (846–854)
Author Location gp41
Epitope `RIRQGLERA`
Epitope name A0205-RA9(gp41)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location gp160 (846–854)
Author Location gp41
Epitope `RIRQGLERA`
Epitope name RA10(gp41)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide TRIRQGLERALL contains the exact sequence of a previously described HLA-A2 optimal epitope, RIRQGLERA, none of the 55 HLA-A2 carriers responded to it.

HXB2 Location gp160 (848–856)
Author Location gp160 (848–856)
Epitope `RQGLERALL`
Immunogen

CTL CD8+

Species (MHC) human (B8)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B8 epitope.

HXB2 Location gp160 (848–856)
Author Location
Epitope `RQGLERALL`
Immunogen
Species (MHC) (B8)
Keywords review, immunodominance, escape, vaccine antigen design
References Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection.

HXB2 Location gp160 (848–856)
Author Location
Epitope `RQGLERALL`
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101; B*0801, B*1401
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- RQGLERALL was recognized by a placebo patient after infection.

HXB2 Location gp160 (848–856)
Author Location
Epitope `RQGLERALL`
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A1, A2; B38, B8
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location gp160 (849–856)
Author Location gp41 (849–856)
Epitope `QGLERALL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A1A1, B14, B8, Cw7, Cw8
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

II-B-22 Env CTL/CD8+ epitopes

HXB2 Location Env
Author Location
Epitope
Immunogen computer prediction
Species (MHC) (A*0201, B*3501)
Keywords subtype comparisons, computational epitope prediction
References Schönbach *et al.* 2002

- Computational methods (artificial neural networks, hidden Markov models, binding matrices based on HLA association rates) were used to identify HLA-A*0201 and HLA-B*3501

CTL CD8+

HIV T-cell epitope candidates from 533 Gag, Env and Pol sequences of which 374 were derived from HIV-1, 97 were derived from HIV-2 and 62 from SIV. Comparisons to known epitopes and between clades were made.

HXB2 Location Env
Author Location Env
Epitope
Epitope name Env584-9
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Country Japan
Assay type Tetramer binding
Keywords supervised treatment interruptions (STI)
References Tanuma *et al.* 2008

- A longitudinal study of 3 immunodominant epitopes in early-ART patients given 5 STI series was undertaken to determine escape mechanisms during STI. Since all 12 patients' Nef138-10, RYPLTFGWCF, escaped to its Y2F variant RfPLTFGWCF, it is suggested that mutations in the immunodominant CTL epitope may be one mechanism of escape, limiting immune control.
- Frequency of epitope Env584-9 did not correlate with plasma viral load.

HXB2 Location Env
Author Location
Epitope
Subtype A, B, C
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost, canarypox prime with gp160 boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* Gag, gp120, gp41, Nef, Pol
Species (MHC) human (A1, A2, A24, A25, A26, A30, A31, B17, B39, B51, B57, B60, B62, B70, B8)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Ferrari *et al.* 2001

- Different HIV strains were used for different regions: gp41 LAI, Gag LAI, gp120 MN, gp120 SF2
- HLA-B62 responses dominated the responses against an Env vaccine in an individual (022JAV) who was HLA A2, A26, B35, B62. The strongest response was against the MN peptide 381-400; a response diminished by half was observed against vaccinia expressed clade A and clade C relative to clade B.
- Class I presentation of Env CTL responses in vaccinee 022A12K: A25 > B39, A1 and B8 were undetectable.
- Class I presentation of Env CTL responses in vaccinee 022A12N: B57 » A2 > A26 and B60.
- Class I presentation of Env CTL responses in vaccinee 034GP3: A31 > A24 > B62 > B51.
- Class I presentation of Env CTL responses in vaccinee 0348PP: B17 > B70, A1 and A30 were undetectable.

HXB2 Location Env
Author Location gp120 (303–327)
Epitope
Immunogen HIV-1 infection
Species (MHC) human (A11, A2, A3, B27)
Keywords subtype comparisons
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.
- For this cluster of epitopes spanning the tip of the V3 loop, they suggest including a sequence from each clade.

HXB2 Location Env
Author Location
Epitope
Subtype B
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost, canarypox prime with gp160 boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* Gag, gp120, gp41, Nef, Pol
Species (MHC) human (A2, B8)
Keywords vaccine-induced epitopes
References Ferrari *et al.* 2001

- Different HIV strains were used for different regions: gp41 LAI, Gag LAI, gp120 MN, gp120 SF2
- No HLA-A*0201 or B8 responses were made against the Env vaccine in individuals carrying these alleles, despite these being common presenting molecules for CTL responses to natural infections.

HXB2 Location Env
Author Location Env
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Keywords rate of progression
References Jin *et al.* 2002

- Patients with HLA-B*35 variants B*3502, B*3503, B*3504, and B*5301 tend to proceed to AIDS more quickly than those with B*3501.
- Of 32 patients with HLA-B*35 alleles CD8+ CTL responses were quantified using an intracellular cytokine staining assay – 75% had responses to Pol, 69% to Gag, 50% to Nef, and 41% to Env.
- The overall magnitude of CTL responses did not differ between those bearing B*3501 and the others. A higher percentage of Gag responses was observed in those that had lower RNA levels that carried B*3501, and there was a negative association with viral load and CTL activity. The data is consistent with higher levels of CTL responses contributing to protection in B*3501 individuals, but not in B*3502, B*3503, B*3504, and B*5301 individuals.

HXB2 Location Env
Author Location gp41 (842–850 IIIB, BH8)
Epitope
Immunogen HIV-1 infection
Species (MHC) human (B7)

References Pantaleo *et al.* 1997; Soudeyns & Pantaleo 1997

- Clonotype-specific PCR and analysis of *in vivo* HIV-specific CTL showed that in early infection HIV-specific CTL clones preferentially accumulate in blood rather than lymph nodes and that they accumulate prior to down-regulation of virus.

HXB2 Location Env
Author Location gp160 (MN)
Epitope
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade MN *HIV component:* gp120, gp160
Species (MHC) mouse (H-2^d)
References Vinner *et al.* 1999

- Mammalian codon optimization renders gp160 expression Rev independent, increases gp160 expression levels, and DNA vaccination of BALB/c mice yields a higher antibody response with an earlier onset than wild type.
- Secreted gp120 gave higher antibody titers than membrane bound gp160.
- In contrast to antibodies, synthetic codon-optimized DNA did not alter the CTL response, wild type genes generated equally strong CTL responses.

HXB2 Location Env
Author Location (IIIB)
Epitope
Immunogen vaccine
Vector/Type: peptide *HIV component:* V3 *Adjuvant:* Cholera toxin (CT), GM-CSF, IL-4
Species (MHC) mouse (H-2^d)
References Kato *et al.* 2000

- A multicomponent peptide vaccine VC1 with cholera toxin adjuvant was given to mice.
- Immunization of BALB/c mice with VC1 and CT induced a strong CTL response which was enhanced by IL-12 expressing plasmids.
- Immunization with VC1 and CT resulted in HIV-1 specific IgA antibody responses, which were increased by the combination of IL-4 or GM-CSF expressing plasmids.

HXB2 Location Env
Author Location gp160 (IIIB)
Epitope
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* PLG
Species (MHC) mouse (H-2^d)
References Kaneko *et al.* 2000

- A PLG-microparticle encapsulated DNA encoding gp160 was given to mice.
- Oral DNA vaccination of BALB/c mice induced mucosal and systemic gp160 glycoprotein-specific cellular and humoral immune responses, and mice vaccinated orally had higher resistance to HIV-env expressing vaccinia intrarectal challenge than mice vaccinated i.m.

HXB2 Location Env
Author Location Env
Epitope
Immunogen vaccine
Vector/Type: DNA with CMV promotor with cationic liposome *HIV component:* gp160, Rev
Species (MHC) mouse (H-2^d)
References Ishii *et al.* 1997

- pCMV160/Rev is a DNA vaccine candidate carrying gp160 and Rev linked to a cytomegalovirus (CMV promotor)

HXB2 Location Env
Author Location Env
Epitope
Immunogen vaccine
Vector/Type: adeno-associated virus (AAV) *HIV component:* Env, Rev, Tat *Adjuvant:* IL-2
Species (MHC) mouse (H-2^d)
References Xin *et al.* 2001

- An AAV vector expressing HIV-1 env, tat, and rev genes (AAV-HIV vector) was used to vaccinate BALB/c mice.
- A single injection stimulated and long lasting serum IgG, fecal IgA, and HIV-specific CTL.
- Boosting enhanced the humoral response, and IL2 enhanced T-cell immunity.

HXB2 Location Env
Author Location Env
Epitope
Immunogen vaccine
Vector/Type: vaccinia, influenza *Strain:* B clade IIIB *HIV component:* Env, V3
Species (MHC) mouse (H-2^d)
References Gonzalo *et al.* 1999

- The use of two different live vectors for priming and boosting has a synergistic effect on the immune response against HIV-1– a 5-6 fold enhanced CTL response in Balb/c mice occurred when they were immunized with rec influenza virus (Flu-Env) expressing the V3 loop epitope from HIV-1 strain IIIB, and boosted with a vaccinia virus recombinant (VV-Env) expressing the complete HIV-1-IIIB env protein, comared to either immunogen alone.

HXB2 Location Env
Author Location Env (subtype B)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: rabies virus *Strain:* B clade 89.6, B clade NL43 *HIV component:* gp160
Species (MHC) mouse (H-2^d)
References McGettigan *et al.* 2001

- BALB/c were immunized with a replication competent recombinant rabies virus (RV) vaccine expressing HIV-1 gp160.
- A single vaccination induced induced strong and long-lasting (4.5 months) gp160-specific CTL cytotoxic responses.

CTL CD8+

- Although the greatest specific lysis was achieved when the vaccine strain was also used as the *in vitro* the target strain to assess the response, there was extensive CTL cross-reactivity against other B clade HIV-1 envelope proteins, implying CTL recognition of multiple epitopes within the HIV-1 envelope protein.

HXB2 Location Env
Author Location gp120 (V3)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* B clade BRVA, B clade IIIB, B clade JY1, B clade LR150, B clade MN, B clade RF *HIV component:* V3
Species (MHC) mouse (H-2^{d})
Assay type CD8 T-cell Elispot - IFNγ
References Vázquez-Blomquist *et al.* 2003

- Priming mice with recombinant MVA and boosting with fowlpox was shown to increase the number of specific IFN-gamma secreting cells relative to reversing the order (fowlpox prime, MVA boost) or priming with a Semliki Forest Virus DNA vector and boosting with recombinant MVA or fowlpox. The authors speculate why the order might be important. Fowlpox has more proteins, so there may be more CTL epitope competition; alternatively pox viruses may modulate the immune response through chemokine homologs.
- The antigen tested was a V3 loop polyepitope vaccine combining multiple V3 loop variants given by an intraperitoneal route to BALB/c mice.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* gp120 *Adjuvant:* Cholera toxin (CT)
Species (MHC) mouse (H-2D^{d})
Assay type T-cell Elispot, Chromium-release assay
References Bagley *et al.* 2003

- BALBc mice were immunized intramuscularly with single plasmids encoding gp120, or cholera toxin catalytic domain (CTA1) and gp120, or with a dicistronic DNA vaccine expressing both CTA1 and gp120. Vaccination including CTA elicited stronger and longer lasting Ab responses and T-cell responses to gp120.

HXB2 Location Env
Author Location gp120 (318–327 IIIB)
Epitope
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* gp120
Species (MHC) mouse (H-2D^{d})
Assay type Cytokine production, Intracellular cytokine staining, Th support of CTL response, Chromium-release assay
Keywords epitope processing, Th1, vaccine antigen design
References Vatakis *et al.* 2005

- Mice were vaccinated with three DNA epitope vaccines, differing in the affinity of the helper epitope to the MHC class II molecule. It was observed that a TH epitope with lower affinity decreased the magnitude of the CTL responses and decreased the numbers of epitope-specific T-helper cells and CTLs. Also, cytokine secretion and proliferative responses were diminished.

HXB2 Location Env
Author Location
Epitope
Epitope name p11c, p68A, p41A, p199A
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade 89.6P *HIV component:* Env
Species (MHC) macaque (Mamu-A*01)
Assay type Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords vaccine-specific epitope characteristics, immunodominance, vaccine antigen design
References Subbramanian *et al.* 2006

- Multiepitope plasmid DNA vaccine constructs were shown to elicit CTL populations that do not show skewing of recognition of dominant epitopes in macaques, but repeated boosting of the vaccinated macaques uncovered and amplified the usual CTL epitope dominance hierarchy. This study suggests that heterlogous prime-boost regimens can be effective in augmenting the magnitude of CTL responses, but cannot alter the dominance hierarchy established immediately after the exposure to antigen.
- Also, for live recombinant boost studies, results of in vitro peptide stimulation of PMBCs predict reliably the actual breadth of CTL responses that would expand out in antigen-primed T-cell populations.

HXB2 Location Env
Author Location Env (SIV)
Epitope
Immunogen SIV infection
Species (MHC) macaque (Mamu-A*11, Mamu-B*03, Mamu-B*04, Mamu-B*17)
References Dzuris *et al.* 2000

- Cell binding assays for Mamu molecules were employed to describe the peptide binding motifs for Mamu-A*11, -B*03, -B*03, -B*04, and -B*17 CTL epitopes – a similarity for Mamu-A*11 and -B*03 and human HLA-B*44 and -B*27, respectively, was observed – all epitopes studied were SIV epitopes, so not specifically listed here.

HXB2 Location Env
Author Location gp160 (LAI, MN)
Epitope
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* Gag, gp120, gp41, Protease
Species (MHC) human

CTL CD8+

References Belshe *et al.* 1998

- The live canarypox vaccine ALVAC-HIV(vCP205) carrying MN gp120, LAI gp41, Gag and Protease, and boosted with SF-2 rpg120, was given to HIV-1 seronegative volunteers – HIV-specific Env or Gag CD8+ CTL were detected in 64% of the volunteers.

HXB2 Location Env
Author Location gp160 (LAV)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, dendritic cells
References Zheng *et al.* 1999

- Protein delivery (gp160 LAV, p66 LAV, and p24 NY5) to human dendritic cells (DC) with liposomes provides enhanced memory CTL response relative to delivery of protein alone.
- Chloroquine administration enhanced epitope presentation, and brefeldin A and peptide aldehyde inhibitors inhibited antigen presentation, suggesting epitopes were processed by classical proteasome pathway.

HXB2 Location Env
Author Location Env (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression, Th1
References Wasik *et al.* 2000

- HIV+ infants that progressed rapidly to AIDS had lower Th1 responses and decreased production of IL-2, as well as beta-chemokines, relative to other HIV+ infants.
- No HIV+ infants had no demonstrable CTL at birth, but Th1 responses accompanied by CTL responses developed in children with slowly progressive disease, and not in rapid progressors.
- CTLp frequencies were determined by limiting dilution using autologous B cells infected with vaccina/HIV constructs.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Soudeyns *et al.* 2000

- Analysis of T cell receptor beta chain variable region repertoire indicates that antiretroviral therapy (ART) and highly active antiretroviral therapy (HAART) decrease global CD8 T cell oligoclonality during primary HIV infection.
- A sharp decline in HIV-1 gp120-specific CTL clones was observed in HAART-treated subjects.

HXB2 Location Env
Author Location Env (LAI, MN)
Epitope
Immunogen vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp41, Protease, V3
Species (MHC) human
References Salmon-Ceron *et al.* 1999

- The vaccine used was a rec canarypox with HIV-1 gp120 MN, tm/gag/protease LAI (vCP205), alone or with p24E-V3 MN synthetic peptide (CLTB-36))
- Twenty HIV negative subjects were vaccinated in phase I trial with combinations of vCP205 and CLTB-36.
- Immunization with vCP205 induced HIV-1-specific ABs to gp120, V3, and p24 antigens, and CTL immune responses against vCP205 were detected after the fourth immunization in 33% of the subjects against Env, Gag and Pol, but the CLTB-36 peptide did not produce AB or CTL immune responses against p24 or gp160.

HXB2 Location Env
Author Location Env
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords TCR usage
References Gamberg *et al.* 1999

- 13/13 subjects with advanced HIV infections showed CD8 T cell proliferation and differentiation of CTL *in vitro*, and six individuals showed HIV-specific responses to Gag, Pol, Env or Nef antigens.
- Data suggests that the functional and genetic integrity of the CD8 T cell repertoire (TCR betaV gene intrafamily genetic diversity) remains intact through advanced HIV infection, although HIV-specific CTL activity decreases.

HXB2 Location Env
Author Location Env (LAI, MN)
Epitope
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade SF2 *HIV component:* Env, Gag, Nef, Protease
Species (MHC) human
References Gorse *et al.* 1999b

- The vaccine used was rec canarypox expressing HIV-1 env, gag, pol, nef and protease (vCP300) with or without administration of HIV-1 SF-2 rgp120.
- In vitro inducible CTL activity against HIV-1 Env, Gag, Pol, and Nef antigens was observed in 79% (15 of 19) of vaccine recipients.
- The combination of vCP300 and vP1291 together resulted in an overall increase in CTL induction and detection sensitivity.

HXB2 Location Env
Author Location Env (LAI)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Buseyne *et al.* 1998b

- In infants with positive CTL responses, most responses showed cross-clade reactivity with somewhat diminished recognition of epitopes from different subtypes.

HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* gp120, gp160
Species (MHC) macaque
References Shiver *et al.* 1997

- DNA vaccinations of Rhesus monkeys with a gp120 or gp160 DNA vaccine elicited a strong CD8 cytotoxic T cell response.

HXB2 Location Env
Author Location gp160
Epitope
Immunogen HIV-1 infection
Species (MHC) macaque
References Kent *et al.* 1997b

- Macaques can be infected with HIV, and clear the infection within 6 months, so it is of interest to examine their initial immune response.
- A strong CTL response against env, pol and gag antigens can be detected.
- The CTL response peaked by 4 weeks and declined dramatically by 8 weeks.
- The response in the lymph nodes and peripheral blood was comparable.

HXB2 Location Env
Author Location gp160
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Env, Gag, Pol, Vif *Adjuvant:* B7, IL-12
Species (MHC) mouse
References Kim *et al.* 1997c

- A gag/pol, vif or env DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules B7 and IL-12, gave a dramatic increase in both the cytotoxic and proliferative responses in mice.
- When IL-12 was present, CTL response could be detected even without *in vitro* stimulation.

HXB2 Location Env
Author Location gp160
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Env, Gag, Pol, Vif *Adjuvant:* B7, IL-12
Species (MHC) mouse
References Kim *et al.* 1997d

- A gag/pol or env DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules CD86, gave a dramatic increase in both the cytotoxic and proliferative responses in mice.
- When CD86 was present, CTL response could be detected even without *in vitro* stimulation.

HXB2 Location Env
Author Location gp120 (HXBc2)
Epitope
Immunogen vaccine
Vector/Type: DNA prime with gp160 boost *Strain:* B clade HXBc2 *HIV component:* gp160
Species (MHC) macaque
References Letvin *et al.* 1997

- Vaccination of Macaques mulatta (Rhesus monkeys) with an HXBc2 env DNA prime and a protein boost elicited a T cell proliferative response, a CTL response, and type-specific neutralizing antibodies.
- Vaccinated animals challenged with SHIV-HXB2 were protected from infection.

HXB2 Location Env
Author Location gp120 (MN)
Epitope
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade MN *HIV component:* Env, Rev
Species (MHC) human
References MacGregor *et al.* 1998

- An HIV DNA env and rev vaccine given to 15 asymptomatic HIV+ individuals at three different dosages, 30, 100 or 300 ug, was safe.
- The CTL response to gp120 was enhanced in 0/4 patients in the 30 µg group, 2/3 patients in the 100 µg group, and 0/3 in the 300 µg group – but the non-responding patients in the 300 µg group had a strong CTL response prior to vaccination, and the CTL results are inconclusive.

HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Trickett *et al.* 1998

- Twelve HIV-1 infected patients were re-infused with their own lymphocytes, cryopreserved from an earlier time point in the infection.
- Improvement in CD4+ and CD8+ T cells was seen in 7/12, and an increase in the CTL response to Env was seen in one patient.

HXB2 Location Env
Author Location gp120 (LAI)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Legrand *et al.* 1997

- Seventeen recently infected patients were tested for CTL response to HIV proteins Env, Gag, Pol, Rev, Nef, Vif and Tat.
- An early response (within a month following PI) was noted in 87% of the subjects to Gag, 75% to Env, and 50% to Nef.
- Early responses to Pol, Rev, Vif and Tat were rare.

HXB2 Location Env
Author Location gp120 (LAI)
Epitope
Subtype B

CTL CD8+

Immunogen vaccine
Vector/Type: vaccinia prime with gp120 boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* gp160
Species (MHC) human
References Corey *et al.* 1998

- Vaccinia-naive subjects were vaccinated with vaccinia-gp160 LAI and boosted with gp120 SF2, LAI, MN, or 160 MN.
- 26/51 had an anti-Env CTL response, and those that were boosted with gp120 tended to produce Abs that neutralized autologous laboratory strains with some cross-reactivity.

HXB2 Location Env
Author Location Env (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Betts *et al.* 1997

- 6/8 individuals from Zambia infected with C clade virus had CTL that were able to make response to B clade HIV-1 IIIB vaccinia-expressed Gag, Pol and Env proteins.
- A vigorous cross-clade response was not limited to a particular protein, and the level of recognition of different proteins varied among the six patients.

HXB2 Location Env
Author Location Env
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References De Maria *et al.* 1997

- CD3+ cells that also carry a natural killer cell receptor (NKR+) can exhibit down regulation of T cell function.
- Anti-NKR IgM MAb masked this inhibitory function and increased HIV-1 specific CTL activity in phytohemagglutinin-activated PBMC cultured in the presence of IL-2 from 3/5 patients, and in one other case anti-NKR MAb brought HIV-1 specific CTL activity to detectable levels.

HXB2 Location Env
Author Location Env (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Betts *et al.* 1999

- This study demonstrated an inverse correlation between HIV Type I plasma viral load and CTL activity directed against HIV-1 Pol, and stronger combined effects of Pol- and Env-specific CTL, in long-term survivors (LTS) of HIV-1 infection.

HXB2 Location Env
Author Location Env (LAI)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Buseyne *et al.* 1998a

- This study showed a correlation between strong CTL memory and breadth of response in 7-12 month old infants, and remaining AIDS-free for the first year of life, higher absolute CD4 and CD8 cells, and lower viral load.

HXB2 Location Env
Author Location Env
Epitope
Immunogen HIV-1 exposed seronegative
Species (MHC) human
References Goh *et al.* 1999

- 13/37 exposed uninfected individuals with repeated high-risk sexual exposure had HIV-1 specific CTL against Env, Gag, Pol, or a combination of proteins – CTL activity was correlated with a CCR5 wildtype genotype.
- In this group, the highest CTLp frequencies were directed at Gag, but the most common response was to Env and four individuals had responses to multiple HIV-1 proteins.

HXB2 Location Env
Author Location Env (LAI, MN)
Epitope
Immunogen vaccine
Vector/Type: canarypox *HIV component:* Gag, gp120, gp41, Nef, Protease, RT
Species (MHC) human
References Evans *et al.* 1999

- A Canarypox vaccine expressing gp120, gp41, Gag, Protease, Nef and Pol CTL epitopes gave rise to CTL that could be detected in 61% of the volunteers – responses to Gag, Env, Nef and Pol were detected 3-6 months after the last vaccination.

HXB2 Location Env
Author Location Env (LAI)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost *Strain:* B clade LAI *HIV component:* Env, Gag
Species (MHC) macaque
Keywords Th1, Th2
References Kent *et al.* 1998

- Priming with an HIV-DNA vaccine and boosting with a vaccinia construct induced greater levels of HIV T cell immunity than either vaccine alone.
- The proliferative response to Env and Gag after the DNA vaccination had a mean SI of 1.5-4, but after boosting with rHIV-fowlpox virus, there was a 6-17 fold increase in the mean SI for HIV Gag and Env. The T help response happened despite a fall in antibody titers, suggesting that the Th response was primarily Th1, not Th2. The CTL response was also enhanced.

HXB2 Location Env
Author Location Env (LAI, MN)
Epitope
Immunogen vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Protease

Species (MHC) human
References Salmon-Ceron *et al.* 1999

- A live attenuated canarypox vector expressing MN gp120 and LAI gp41/gag/protease could induce CTL and a lymphoproliferative response in healthy, uninfected volunteers.

HXB2 Location Env
Author Location Env (MN)
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Env, Gag, Pol *Adjuvant:* CD80, CD86
Species (MHC) chimpanzee
References Kim *et al.* 1998

- The study explores the use of co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses.

HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Immunogen vaccine
Vector/Type: Semliki-Forest Virus with virus-like particle boost *Strain:* B clade IIIB *HIV component:* Gag, gp120
Species (MHC) macaque
References Notka *et al.* 1999

- Immunization of SIV Pr56Gag-derived VLPs with HIV-1 gp120 anchored on their surface induced Abs, CTL and Th responses to HIV gp120; priming with the HIV antigens in Semliki-Forest Viruses enhanced the immunological outcome.
- Immunized monkeys challenged with SHIV showed a more rapid reduction of plasma viremia.

HXB2 Location Env
Author Location Env
Epitope
Immunogen HIV-1 exposed seronegative
Species (MHC) human
References Akridge *et al.* 1999

- This study suggests that HIV-1-resistance in exposed and uninfected individuals is not only associated with the 32-bp deletion in the HIV-1 co-receptor CCR5, but can be related to HIV-1 specific CTL immunity.

HXB2 Location Env
Author Location gp120 (BRU)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Aladdin *et al.* 1999

- In vitro measurements of CTL-activity by Cr release assay in bulk culture showed no correlation between CTL-activity (gp120, Gag, Pol and Nef) and disease progression as measured by viral load, CD4 and time to death.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Aladdin *et al.* 2000

- The administration of IL-2 caused an initial enhancement of CD4 cell counts that was accompanied by a decrease in CTL activity – IL-2 therapy did not reduce initial HIV viral load and viral replication was ultimately enhanced.

HXB2 Location Env
Author Location Env
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Jin *et al.* 1998a

- CTL precursor frequencies were determined in HIV-1 infected pregnant women, and higher CTLp frequencies to Pol and SF2 Nef, but not IIIB Nef, were found in non-transmitting mothers than in transmitting mothers – Nef CTL responses have been found in uninfected infants born to HIV+ women (Lazuriaga95);
- Very different CTLp frequencies were observed in env depending on whether IIIB, MN, RF, BK, or SF2 was used as antigen – no association between env specific CTL and transmission was observed.

HXB2 Location Env
Author Location Env
Epitope
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* Env
Species (MHC)
Keywords review
References Zavala *et al.* 2001

- This paper is a review of vaccinia in the context of vaccines strategies that use different vectors to prime and boost, and emphasizes a unique capacity of vaccinia to very efficiently boost memory T-cell responses.
- HIV is discussed in the context of Gonazalo *et al.* 1999, where a V3 CTL epitope expressed in reFlu was boosted most effectively by vaccinia expressing the full Env.

HXB2 Location Env
Author Location Env
Epitope
Immunogen vaccine
Vector/Type: DNA *Strain:* ZF1 *HIV component:* complete genome
Species (MHC) macaque
References Akahata *et al.* 2000

- Rhesus macaques were vaccinated by i.m. injection with naked plasmid DNA carrying an HIV-1 complete genome vaccine, strain ZF1, with a mutated zinc finger in the nucleocapsid to prevent packaging.
- Env and Gag specific CTL but no antibody responses were induced in 2/4 vaccinated monkeys (MM145 and MM153)

CTL CD8+

- 2/4 monkeys (MM146 and MM143) produced antibodies against p24 and/or gp160, but no CTL response was detected.
- PBMC from all vaccinated monkeys produced IFN-gamma, in response to HIV-1 gp160, indicating a Th response – this response was 5 times higher in MM145, the animal with the strongest CTL response.
- 4 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM145 and MM153 (with a homologous Env) decreased to near or below the detection limit.
- 6-8 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM146 and MM143 decreased near or below the detection limit.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Young *et al.* 2001

- Addition of recombinant rec human IL12 (rhIL12) to cultures increased HIV-specific lysis of HIV-Gag, Pol and gp120 vaccinia expressed antigens (11/15 tested increased lysis by > 5%) if the culture was derived from HIV+ individuals who had CD4 cells/ul > 500.
- 2/10 individuals with <200 CD4 cells/ul, and 3/10 individuals with 200-500 CD4cells/ul, had an increase of >5% upon treatment of the culture with rhIL12, so a few individuals in late stage disease had CD8 cells that maintained responsiveness to rhIL12.

HXB2 Location Env
Author Location Env (subtype A, B, D)
Epitope
Subtype A, B, D
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Cao *et al.* 2000

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in HIV infected Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, Pol, RT or Nef from HIV-1 clades A, B, and D.
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype.

HXB2 Location Env
Author Location Env
Epitope
Immunogen vaccine
Vector/Type: canarypox, protein *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* Env, Gag, Protease *Adjuvant:* MF59
Species (MHC) human
References AVEG022PT 2001

- Different HIV strains were used for different regions: MN (gp120), LAI (gp120, protease and gag), and SF2 gp120
- 26/42 subjects who received CP vac-env-pro vaccine had a CTL response measured by Cr-release, while only 3/17 who were vaccinated with rec gp120 had a CTL response.
- A combination of a CP vac-env-pro vaccine with rec gp120 gave CD8+ T-cells in 62% of subjects, and NAbs in 91% of subjects.

HXB2 Location Env
Author Location Env
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References White *et al.* 2001

- HIV-specific CTL activity was detected in the female reproductive tract of only 1/3 HIV-infected women who underwent a hysterectomy, although CTL could be identified in the PBMC of all three women.

HXB2 Location Env
Author Location Env (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Jin *et al.* 2000a

- The CTL precursor level (CTLp) was measured in long term non-progressors (LTNP) with low viral load using limiting dilution analysis and measuring CTL against Env Gag and Pol expressed in vaccinia in autologous targets.
- LTNPs have high memory CTL numbers and low viral load.

HXB2 Location Env
Author Location Env (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, rate of progression
References Jin *et al.* 2000a

- The CTL effector levels (CTLe) were compared in long term non-progressors (LTNP) with low viral load and in patients whose virus was well-suppressed by therapy, using a tetramer assay.
- LTNPs have high memory CTLe numbers and low viral load, while HAART patients had low CTLe numbers and low viral load.

HXB2 Location Env
Author Location Env
Epitope
Immunogen HIV-1 exposed seronegative
Species (MHC) human
Keywords review, HIV exposed persistently seronegative (HEPS)
References Rowland-Jones *et al.* 2001

- This is a review that summarizes observations about HIV-specific CTL found in the HIV-1 exposed persistently seronegative (HEPS) population.

- The CTL responses assayed by ELISPOT and by CTL precursor frequencies by limiting dilution analysis indicate that CTL in HEPS individuals tend to be of a lower magnitude than in chronic HIV-1 infections – the responses in HEPS cases are below the level of detection by tetramer assays.
- CD8+ CTL responses tend to be detectable in HEPS subjects only if they are recently exposed, and the response diminishes if exposure is reduced – it is not clear if there is a stable memory population in HEPS cases.
- CD8+ CTL responses in the HEPS population are associated with HIV-1 specific CD4+ T cell responses, assayed by proliferation assays, IL-2 secretion, and ELISPOT, and the authors consider the possibility that HIV-1-specific T-help responses improve the "quality" of the CD8+ response in HEPS individuals relative to HIV-1 infected individuals, who tend to have a poor HIV-1-specific T-help response.
- HIV-1 specific CD8+ CTL responses in HIV-1 infected individuals show reduced levels of perforin, and the T cells may not mature properly, and although similar studies have not been conducted in HEPS individuals this is considered as a possible difference in the CTL immune response in HEPS and HIV-1 infected people.

HXB2 Location Env
Author Location
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA *HIV component:* Env, Gag, Pol
Species (MHC) mouse
Keywords review
References Nabel 2002

- Env DNA constructs were designed that were codon optimized for human genes, express Env in the absence of the regulatory protein Rev, both increasing Env expression levels, deletions in the cleavage site and in the fusion domain. These constructs increased Ab responses to Env, while not diminishing CTL responses, when injected into mice.
- Removing N-linked glycosylation sites did not alter the humoral or cellular immune responses to this HIV protein, as has been seen in analogous SIV experiments.

HXB2 Location Env
Author Location
Epitope
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission
References De Maria *et al.* 1994; Kuhn *et al.* 2002

- 6/24 HIV uninfected infants (ages 15-50 months) born to HIV+ mothers had HIV-1 specific CTL responses to vaccinia-expressed Nef, Gag/Pol, Env.
- Reviewed in Kuhn *et al.* [2002].

HXB2 Location Env
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission, rate of progression
References Kuhn *et al.* 2002; Wasik *et al.* 1999

- In HIV-infected infants HIV-specific, CTL responses were not detectable in cord blood or in PBMC collected shortly after birth and were absent or remained very low in 3 infants with a rapidly progressive disease. For those who progressed more slowly, the HIV-specific CTL activity varied.
- The two infants with high levels of Env peptide-stimulated IL-2 responses had the highest CTLp frequencies.
- Stronger responses were detected after initiation of the antiretroviral therapy.
- Two babies that were not infected though born to HIV+ mothers had detectable though low HIV-specific CTLp responses to Env (1/2), Pol (2/2), Gag (1/2) cord blood and transiently in PBMC after birth.
- Reviewed in Kuhn *et al.* [2002].

HXB2 Location Env
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission
References Aldhous *et al.* 1994; Kuhn *et al.* 2002

- Six of nine HIV vertically infected infants had HIV-1 specific CTL responses to vaccinia expressed Tat (4/6), Pol (6/6), Env (1/6), or Gag (1/6), but not all responses were detected at all time points.
- Two of eleven babies that were not infected though born to HIV+ mothers had detectable responses Tat (1/2), Pol (2/2), Gag (1/2).
- Reviewed in Kuhn *et al.* [2002].

HXB2 Location Env
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission
References Kuhn *et al.* 2002; McFarland *et al.* 1994

- Only 9% of HIV+ infants had HIV-specific CTL against Env or Gag in unstimulated PBMC. After CD3 stimulation of PBMC, Gag and Env specific CTL were found in PBMC from 91% and 78% of HIV-infected children, respectively, with high precursor frequencies.
- 2/9 babies that were not infected though born to HIV+ mothers had detectable responses to Env.

CTL CD8+

- Reviewed in Kuhn *et al.* [2002].

HXB2 Location Env
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.

HXB2 Location Env
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Trabattoni *et al.* 2002

- CD8+ T-cells that were stimulated by HIV-1 Env expressing targets from 25 HIV+ patients receiving ART and 17 ART-naive patients were compared. CTL from the individuals receiving ART showed increased TNFalpha production and a reduction of perforin and granzyme expressing CTL, suggesting a functional defect in ART-treated individuals, and a potential benefit of immunomodulants during therapy.

HXB2 Location Env
Author Location (HXB2)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Edwards *et al.* 2002

- 96% (26/27) chronically infected HIV-1 infected patients elicited gamma-IFN CD8+ T-cell responses against Gag.
- Nef and/or Pol CTL responses were detected in 86% of the subjects.
- The magnitude and breadth of Gag and p24 T-cell responses correlated with absolute CD4 counts, and inversely correlated with viral load.
- Pol and Int CTL responses correlated positively with absolute CD4+ T-cell count.
- Nef and Env responses did not correlate with either CD4 counts or viral load.

HXB2 Location Env
Author Location Env
Epitope
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* gp160, Rev *Adjuvant:* cationic liposome, GM-CSF, IL-2
Species (MHC) mouse
Keywords Th2
References Ishii *et al.* 2001

- Vaccination route of HIV-1 DNA immunization with gp160 and Rev genes was compared including intranasal (i.n.), intramuscular (i.m.), and topical application of DNA directly on the skin after elimination of keratinocyte layers using a strong adhesive. Topical exposure resulted in high level CTL responses, IFN-gamma and IL-4 production, and delayed type hypersensitivity (DTH). Topical application favored Th2 responses.
- DNA delivered topically with adjuvant-like cationic liposomes gave a stronger response than DNA alone, and co-administration of the DNA vaccine with IL-12 and GM-CSF expression vectors enhanced cytotoxic activity and DTH.

HXB2 Location Env
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, dendritic cells
References Larsson *et al.* 2002b

- Autologous mature dendritic cells with rec vaccinia expressing Gag, Pol, Nef and Env could amplify CD8+ T-cell Elispot responses 4-38 fold in five HIV+ patients on successful HAART treatment, relative to autologous monocytes. Some weak responses could only be detected using mature dendritic cells as APCs, and this approach could be useful for detection of low frequency memory cells.

HXB2 Location Env
Author Location (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords immunotherapy
References Trickett *et al.* 2002

- Conditions were optimized for ex-vivo expansion of CD8+ and CD4+ T-cells with the goal of functional T-cell production for autologous immunotherapy. 10,000-fold expansions were obtained in 14 days with optimized concentrations of IL-2, anti-CD3 and anti-CD28 coated microspheres, and decreasing amounts of serum over the first 8 days.

HXB2 Location Env
Author Location (IIIB)
Epitope
Subtype B
Immunogen HIV-1 and HCV co-infection

Species (MHC) human
Keywords rate of progression
References Lauer *et al.* 2002

- HIV-1 and HCV immune responses were studied in 22 individuals who were co-infected with HIV-1 and hepatitis C virus (HCV). IFNgamma production was measured in an Elispot assay of CD8+ T-cells using targets expressing either Gag, RT, Env and Nef in a vaccinia construct, or one of seven HCV proteins.
- All 22 patients targeted at least one protein. 20/22 patients recognized RT, 17/22 patients recognized Gag, 13/22 subjects recognized Env and 11/22 patients recognized Nef. Robust CTL activity was independent of disease progression or viral load.
- Despite high HCV viral loads, very few HCV CD8+ T-cell Elispot responses were detected. In a control HCV infected person who did not have HIV-1, strong anti-HCV responses were mounted.
- HIV-specific CD4 proliferative responses were detected in 9/17 coinfected patients, but no HCV responses were detected.

HXB2 Location Env
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords responses in children
References Luzuriaga *et al.* 1995

- 2/3 infants infected in utero had detectable HIV-1 Gag and Env specific CTL responses, one by 4 months, one by 11 months of age. Levels of the responses varied at different time point. Pol responses were not detected.
- 2/4 infants infected intrapartum had detectable responses, one note until 11 months, one not until 42 months.
- HIV-specific CTL were not detected in ten HIV- infants that were born to HIV+ mothers.

HXB2 Location Env
Author Location
Epitope
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost *HIV component:* Env, Gag
Species (MHC) human
References Gupta *et al.* 2002

- A safety and immunogeniticity study of a vaccine dosing schedule was studied in a trial conducted in high and low risk study subjects. There was a 76% cumulative probability of detecting a Gag or Env CTL response by day 728.

HXB2 Location Env
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, responses in children
References Scott *et al.* 2001

- CTL responses before and after initiation of ART were studied in 13 HIV-1 vertically infected infants <6 months of age, and 4 that were >6 months of age.
- Before ART 2/13 infants <6 months of age showed IFNgamma Elispot CD8+ T-cell responses, one to Nef and one to Env and Nef, and these responses became undetectable after successful therapy– 3 infants were coinfected with CMV and all 3 had CMV-specific CD8+ T-cell responses.
- One older infant, at 23 months, had CTL responses against all for proteins tested, Gag, Pol, Nef and Env, and had the lowest plasma viremia of the study group. 3/4 infants older than 6 months of age responded to either Nef or Pol.
- Administration of ART over 48 weeks broadened the HIV-1-specific CTL response in 2/4 of the older children that were incomplete responders.

HXB2 Location Env
Author Location (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, supervised treatment interruptions (STI)
References Ortiz *et al.* 2001

- Immune responses in eight chronically HIV-1 infected patients undergoing HAART therapy structured treatment interruptions (STI) were studied. STI boosted HIV-1 specific CTL responses and elevated CTL responses were maintained up to 22 weeks after the last treatment interruption, but viral load rebound to pretreatment levels and CD4 T-cell count decline was observed. CD8 responses in PBMC were measured by cytokine flow cytometry with gp160, Gag p55, RT-Pol and Nef expressed in vaccinia.
- One of seven subjects with a detectable NAb response had an augmented neutralization titer in response to STI.

HXB2 Location Env
Author Location (SF2)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*2402, A*3303, B*3501, B*5101
Keywords class I down-regulation by Nef
References Tomiyama *et al.* 2002

- Nef down-regulates class I molecules, and the killing activity of HLA B*3501, A*2402, B*5101 and B*3303-restricted HIV-1-epitope specific CTL clones was inhibited by an HIV-1 strain carrying Nef, relative to a Nef-deleted virus; while Nef-induced HLA class I down-regulation inhibited lysis, it did not abolish cytokine production by HIV-1-specific CD8+ T-cells.

HXB2 Location Env
Author Location Env (gp160) (IIIB)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade NL43 *HIV component:* Env
Species (MHC) macaque
References Akahata *et al.* 2003

CTL CD8+

- Four monkeys were injected i.m. with a SHIV plasmid (SHIV-NM-3rn ZF1*) which encodes all viral proteins driven by the SIV LTR promoter. Infectivity is prevented by the introduction of mutations within the zinc-finger motifs of the nucleocapsid (NC) that prevents RNA packaging. An original NC ZF1 mutant plasmid was constructed using NL43 (Akahata 275:116-124 (2000) – the SHIV construct was made as an alternative to get improved expression in macaques using an SIV promotor. CTL were detected by lysis of HIV-1 Env IIIB or SIV Gag mac239 expressing expressing target cells, and a T cell proliferative response to Env was observed. Env-directed antibodies were detected by ELISA. All vaccinated macaques had a low peak viral loads that fell below the level of detection within 6 weeks post-challenge with autologous SHIV SHIV-NM-3rn.

HXB2 Location Env
Author Location Env (MN)
Epitope
Subtype B
Immunogen SIV infection, SHIV infection
Species (MHC) macaque
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References Calarota *et al.* 2003

- The sensitivity of gamma INF Elispot assays can be enhanced for the detection of low frequency responses, like after ART, by adding IL-15 to the assay.
- CD8+ T-cells from SHIV and SIV infected macaques with peptide pools from Gag and Env were used to test this system.

HXB2 Location Env
Author Location Env
Epitope
Subtype multiple
Immunogen
Species (MHC) human
Assay type Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Currier *et al.* 2003

- CD8-cellular immune responses from 21 HIV-1 infected patients from Kenya infected with subtype A, C, D, and unique recombinants were studied for cross-recognition of Gag, Env, and Nef vaccinia-expressed proteins representing subtypes A-H, including CRF01.
- Both subtype-specific and cross-reactive CTL were observed, with a skewing of responses towards the infecting subtype in the nine subjects with full length sequence available. The magnitude of the responses to Gag were the highest, less to Nef, and still less to Env.
- For Gag, 8/21 subjects responded to at least 7/8 different subtype proteins, 7 had a mixed response, recognizing some subtypes but not others, and 6 responded to only one or none of the different subtype proteins. For Env, 4/19 subjects responded to at least 7/8 subtypes, 8 had a mixed response, and 7 responded to one or none. For Nef, 5/19 subjects responded to at least 7/8 subtypes, 8 had a mixed response, and 6 responded to one or none.

HXB2 Location Env
Author Location Env (HIV-1 IIIB)
Epitope
Immunogen HIV-1 exposed seronegative
Species (MHC) human
Assay type Cytokine production
Keywords HIV exposed persistently seronegative (HEPS)
References Fowke *et al.* 2000

- A cohort of Nairobi sex-workers were defined as resistant to HIV-infection by virtue of remaining seronegative despite repeated high risk exposures. 24 were tested for HIV specific T-helper responses detemined by IL-2 production *in vitro* in response to gp120 peptides or soluble gp120 protein.
- 7/17 resistant women showed IL-2 stimulation which was greater than or equal to 2.0, and specific CTL responses were detected in 15/22 resistant women as compared to 0/12 of the control low-risk subjects.

HXB2 Location Env
Author Location gp160 (MN)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade MN *HIV component:* gp160 *Adjuvant:* IL-12
Species (MHC) mouse
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords adjuvant comparison
References Chattergoon *et al.* 2004

- pIL-12 used as adjuvant significantly increases the number of Ag-specific CD8+ T-cells and a sustained memory response. Also, the splenocytes from mice that received pIL-12 were shown to proliferate to a much higher extent. Mice immunized with a plasmid expressing the influenza A/PR8/34 HA gene and pIL-12 were better able to control the infection.

HXB2 Location Env
Author Location Env
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, immune dysfunction
References Trabattoni *et al.* 2004

- Reduced perforin-and granzyme- containing Env-specific CD8+ T cells were observed in ART treated individuals indicating that antiretroviral drugs might directly interfere with the production of perforin and granzymes, inhibiting CTL killing. Immunomodulants may be needed to enable CTL to become fully functional during ART.

HXB2 Location Env
Author Location gp140
Epitope
Immunogen vaccine

Vector/Type: protein, peptide in liposome *Strain:* B clade IIIB *HIV component:* gp140, gp160, oligomeric gp140 *Adjuvant:* CpG immunostimulatory sequence (ISS), liposome
Species (MHC) mouse
Donor MHC H-2d
Assay type Cytokine production, proliferation, Chromium-release assay
Keywords Th1, Th2, adjuvant comparison, vaccine antigen design
References Rao *et al.* 2004

- Administration of ogp140 in liposomes containing lipid A (LA) induces high antibody titers which are increased by adding CpG ODN. Priming and boosting of BALB/c mice with ogp140+LA induces mixed Th1/Th2 immune response, while adding CpG ODN switches the immune response to a Th1 type. Mixing ogp140 with lipomoses containing lipid A yielded excellent proliferative and CTL specific responses; CpG did not affect CTL responses. The antigen did not need to be encapsulated in the liposome to induce strong responses with LA as an adjuvant.

HXB2 Location Env
Author Location
Epitope
Subtype CRF02_AG
Immunogen vaccine
Vector/Type: virus-like particle (VLP), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* CRF02 IC0928 *HIV component:* Env, Gag, Pol
Species (MHC) macaque
Assay type T-cell Elispot, Intracellular cytokine staining
Keywords vaccine-specific epitope characteristics, vaccine antigen design
References Ellenberger *et al.* 2005

- Macaques were given a Gag-Pol-Env DNA prime followed by an MVA boost. Two DNA constructs were compared, one that resulted in mature VLPs with processed Gag (IC48) and one that had a point mutation in Gag that resulted in immature VLPs (IC1-90). IC48 DNA vaccinations, which produced mature VLPs, yielded 2-fold stronger T-cell responses with greater breadth. CD4 T-cells responded to 3-fold more peptide pools than did CD8.

HXB2 Location Env
Author Location
Epitope
Subtype CRF02_AG
Immunogen vaccine
Vector/Type: virus-like particle (VLP), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* CRF02 IC0928 *HIV component:* Env, Gag, Pol
Species (MHC) macaque
Assay type T-cell Elispot, Intracellular cytokine staining
Keywords vaccine-specific epitope characteristics, vaccine antigen design
References Ellenberger *et al.* 2005

- Macaques were given a Gag-Pol-Env DNA prime followed by an MVA boost. Two DNA constructs were compared, one that resulted in mature VLPs with processed Gag (IC48) and one that had a point mutation in Gag that resulted in immature VLPs (IC1-90). IC48 DNA vaccinations, which produced mature VLPs, yielded 2-fold stronger T-cell responses with greater breadth. CD4 T-cells responded to 3-fold more peptide pools than did CD8.

HXB2 Location Env
Author Location
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* Other *HIV component:* Env, Gag, Pol, Rev, Tat, Vif, Vpr
Species (MHC) macaque
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords vaccine-specific epitope characteristics, vaccine antigen design
References Sadagopal *et al.* 2005

- 22/23 macaques that were immunized with a DNA prime SHIV-89.6 and boosted with rMVA showed successful control of viremia, with low or undetectable viral loads and normal CD4 counts 200 weeks postchallenge. IFN-gamma producing T cells were found in unexpectedly low breadths and frequencies. T-cell responses were stable over time and maintained their production of IFN-gamma and IL-2. Long-term control was found in macaques of diverse histocompability types. The CD8 T cells seemed to have the most impact on well-contained chronic infections in the vaccinated and challenged animals.
- Both CD4 and CD8 responses were found to the SIV Gag and HIV Env proteins; 60% of CD8+ epitopes and 80% of CD4+ epitopes were in p27.

HXB2 Location Env
Author Location
Epitope
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost, DNA, Other *Strain:* Other *HIV component:* Env, Gag
Species (MHC) mouse
Assay type T-cell Elispot
Keywords vaccine-induced epitopes, vaccine antigen design
References Xu *et al.* 2006

- Sequential cross-clade vaccination strategy was tested in BALB/c and C57BL/6 mice. Vaccines used were C/B recombinant strain (CN54), B strain (RL42), A/E recombinant strain (AE2F).
- Sequential priming and boosting with heterologous HIV immunogens stimulated T cell immunity against conserved epitopes, while a single vaccine derived from one clade or the mixture of multiple vaccines from different clades raised T cells against less conservative or non-conservative epitopes.

CTL CD8+

HXB2 Location Env
Author Location
Epitope
Immunogen vaccine
Vector/Type: DNA with CMV promotor *Strain:* B clade HXB2, B clade NL43, A clade 92RW020, C clade 97ZA012 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords therapeutic vaccine
References Catanzaro *et al.* 2006

- 14 volunteers uninfected with HIV completed a set of injections with a 6-plasmid DNA vaccine encoding EnvA, EnvB, EnvC, and subtype B Gag, Pol, and Nef. CD4 and CD8 T cell responses to Env and Gag were most frequently detected.
- For EnvA, 2/14 subjects showed a positive CD8+ T cell response by ICS.

HXB2 Location Env
Author Location
Epitope
Immunogen vaccine
Vector/Type: adenovirus type 5 (Ad5) *HIV component:* Env, Gag *Adjuvant:* Cholera toxin (CT)
Species (MHC) macaque
Assay type proliferation, CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords vaccine antigen design
References Mercier *et al.* 2007

- 3 rhesus macaques were given oral immunizations with an enteric-coated mixture of adenoviral vectors expressing HIV-1 gag and a string of conserved env peptides representing broadly cross-reactive CD4+ and CD8+ epitopes. The macaques were boosted intranasally with a mixture of 6 HIV-1 envelope peptides plus cholera toxin adjuvant.
- The immunizations increased cellular immune responses, including antigen-specific IFNgamma-producing CD4+ and CD8+ effector memory T cells in the intestine. After only the oral immunization, there were no EliSpot responses to env peptides or to gag. After the intranasal boost, EliSpot responses against env peptides and against inactivated HIV were markedly increased, but gag responses were not.

HXB2 Location Env
Author Location Env
Epitope
Subtype C
Immunogen vaccine
Vector/Type: DNA *Strain:* Other, C clade consensus *HIV component:* Env
Species (MHC) guinea pig, mouse
Assay type T-cell Elispot
Keywords vaccine antigen design
References Kothe *et al.* 2006

- Ancestral and consensus subtype C sequences were tested for immunogenicity. Both AncC and ConC env genes expressed functional Env glycoproteins that were immunogenic in laboratory animals and elicited humoral and cellular immune responses of comparable breadth and magnitude.
- Mice immunized with C-ancestral, C-consensus, and 96ZM651.8-opt env plasmids all elicited IFN-g EliSpot T cell responses at similar levels.

HXB2 Location Env
Author Location Env
Epitope
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost *Strain:* B clade JRFL, A clade 92RW020, M group Consensus, C clade 96ZM651 *HIV component:* Env
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization, vaccine antigen design
References Weaver *et al.* 2006

- 3 different mouse strains were immunized with subtype A, B, C, and M-group consensus env DNA immunogens. CTL and Helper T-cell epitopes were mapped using peptide sets from heterologous A, B, and C viruses. The consensus immunogen induced a greater number and magnitude of T-cell responses than any single wild-type env.

HXB2 Location Env
Author Location
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade
Species (MHC) macaque
Assay type Intracellular cytokine staining
Keywords subtype comparisons, vaccine antigen design
References Smith *et al.* 2005

- Macaques were immunized with a clade B HIV vaccine and tested for responses to pools of clade B and A/G Env and Gag peptides. While CD4 responses were more frequent than CD8 responses, higher cross-clade responses were found for CD8 responses. The authors suggest that the better cross-clade reactivity of the CD8 responses reflects the size difference between CD8 and CD4 epitopes; the smaller CD8 epitopes provide a smaller target for mutation.
- For both B and A/G Env and Gag peptides, 3/5 pools produced CD8+ T cells, suggesting the existence of 2 or 3 cross-reactive CD8 epitopes.

HXB2 Location Env
Author Location
Epitope
Immunogen SIV infection, SHIV infection, vaccine
Species (MHC) human, macaque, mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ

Keywords review, vaccine antigen design
References Hurwitz *et al.* 2008

- St. Jude Children's Research Hospital's efforts to develop vaccines using multi-vectored, multi-envelope methods are reviewed, showing that both B- and T-cell functions (gamma-interferon ELISPOT assays using peptide pools) are elicited.
- gp140 Env cocktails were chosen based on longitudinal sequence changes in infected patients, diverse antibody-antigen binding and subtypes A-E. Immunization was performed with DNA, Vaccinia and protein vectors sequentially; and administration was not required at predicted sites of exposure for antibody generation there. Minor components of the vaccine mixture can also induce responses.

II-B-23 Nef CTL/CD8+ epitopes

HXB2 Location Nef (1–16)
Author Location Nef (1–16)
Epitope `MGGKWSKSSIVGWPAV`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location Nef (5–13)
Author Location Nef (5–13 HXB2)
Epitope `WSKSSIIGW`
Epitope name WW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2501)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Positions 4 and 6 in the epitope had potentially experienced positive selection. WSKtSIIGW and WSKSSmIGW escape variants were found.

HXB2 Location Nef (9–23)
Author Location Nef (9–23)
Epitope `SVVGWPAVRERMRRA`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A23, B62
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- SVVGWPaVRERMRRA is a previously unpublished epitope that varies from the consensus at position 7.

HXB2 Location Nef (9–23)
Author Location Nef
Epitope `SVVGWPTVRERMRRA`
Epitope name nef-5141
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A1, A19, B*3501, B44, Cw16, Cw7; A*0201, A19, B14, B44, Cw16, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
References Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than interperson sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.

- This Nef overlapping peptide, SVVGWPTVRERMRRA was mutated in the daughter D2 isolate to SiVGWPaVRdRMRRA.

HXB2 Location Nef (11–20)
Author Location Nef
Epitope `VEWPAVRERM`
Epitope name VM10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 2, VgWPAVRERM, was found not to correspond to the most polymorphic residue in the epitope. This is a novel unmapped epitope.

HXB2 Location Nef (13–20)
Author Location Nef (260–267)
Epitope `WPAIRERM`
Epitope name WM8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*08)
Donor MHC A1, A2, B49, B8, Cw7
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion
References Maurer *et al.* 2008

- The Nef HLA-B8-restricted dominant epitope FL8, FLKEKGGL, was studied both longitudinally over time as well as horizontally in a 56 subject cohort of HIV-1 infected patients to chart FL8 variants. FL8 mutants were associated with higher pVL and lower CD4 cell counts.
- Patient 01 who was studied over time accumulated a mutation in WPAIRERM to WPAIRaRM concomitant with a strong viremic increase. Original autologous and viral variant sequences were both tested for response: the original epitope elicited a CTL response but a strong decrease in recognition was seen with the variant, suggesting an escape.
- HLA restrictions in this study are previously published and correlate with the subject's HLA.

HXB2 Location Nef (13–20)
Author Location Nef (13–20)
Epitope `WPTVRERM`
Epitope name WM8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*08)
Country Australia, Canada, Germany, United States
Keywords escape, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*08-associated substitution within optimally defined epitope WPTVRERM is at position E6, WPTVReRM. WM8 has low recognition frequency and escape rate.

HXB2 Location Nef (13–20)
Author Location Nef (13–20 LAI)
Epitope `WPTVRERM`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Keywords optimal epitope
References Goulder *et al.* 1997g; Llano *et al.* 2009

- C. Brander notes this is a B*0801 epitope.

HXB2 Location Nef (13–20)
Author Location Nef (HXB2)
Epitope `WPTVRERM`
Subtype B
Immunogen HIV-1 infection
Species (MHC) (B*0801)
Keywords class I down-regulation by Nef
References Peng & Robert-Guroff 2001

- Deletion of the 19 N-terminal amino acids from Nef including the myristolation signal eliminates Nef-induced down-regulation of MHC class I and CD4 molecules. Such a construct has the potential to serve as a more potent immunogen. The known T-cell epitopes that that would be disputed by this deletion are minimal, including the HLA-B8 CTL epitope WPTVRERM.

HXB2 Location Nef (13–20)
Author Location (C consensus)
Epitope `WPAIRERM`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure

imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location Nef (13–20)
Author Location Nef
Epitope WPTVRERM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Donor MHC A*0101, B*0801
Country United Kingdom
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords escape, acute/early infection
References Milicic *et al.* 2005
- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient. In an early acute infection of the donor, the precise timing of transmission determines the viral variants transmitted.
- The recipient mounted an acute CTL response to this epitope, and the escape variant wpAvrKrm emerged in the recipient soon after.

HXB2 Location Nef (13–20)
Author Location (C consensus)
Epitope WPAIRERM
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- WPAIRERM is an optimal epitope.

HXB2 Location Nef (13–20)
Author Location Nef (13–20)
Epitope WPTVRERM
Epitope name WM8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, acute/early infection, immune evasion
References Malhotra *et al.* 2007a
- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- A CON peptide, WPTVRERMRRAEPAA contained the epitope WPTVRERM (WM8) and elicited a IFN-gamma immune response.
- HLA-B*0801 restriction for WM8 was presumed based on the subject's having the HLA allele and publication in the Los Alamos database.

HXB2 Location Nef (13–20)
Author Location Nef (13–20 LAI)
Epitope WPTVRERM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Goulder *et al.* 1997g
- Unusual epitope for HLA-B8, but compatible with crystal structure predictions.

HXB2 Location Nef (13–20)
Author Location Nef (13–20)
Epitope WPTVRERM
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords immunodominance
References Betts *et al.* 2000
- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the HLA A2+ was HLA A*0201, A31, B8, B51 and responded to this epitope as well as seven others.

HXB2 Location Nef (13–20)
Author Location Nef (13–20 SF2)
Epitope WPTVRERM
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b
- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.

CTL CD8+

- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B8+ individuals that had a CTL response to this epitope broken down by group: 1/3 group 1, 0/3 group 2, and 1/2 group 3.

HXB2 Location Nef (13–20)
Author Location Nef (13–20)
Epitope WPTVRERM
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Day *et al.* 2001

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual.

HXB2 Location Nef (13–20)
Author Location Nef (13–20)
Epitope WPTVRERM
Epitope name WM8
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A*03, A*31, B*08, B*15, Cw*04, Cw*07
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, acute/early infection, viral fitness and reversion
References Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- The variant WnTVRERM was present in 10/10 clones from a B8+ mother, was transmitted to her B8- infant, and present in 10/10 clones at months 2, 4, and 15.

HXB2 Location Nef (13–20)
Author Location Nef
Epitope WPTVRERM
Epitope name B8-WM8(Nef)
Immunogen HIV-1 infection
Species (MHC) human (B8)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (13–20)
Author Location
Epitope WPTVRERM
Immunogen
Species (MHC) (B8)
Keywords review, immunodominance, escape, vaccine antigen design
References Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection.

HXB2 Location Nef (13–20)
Author Location Nef
Epitope WPTVRERM
Epitope name WM8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- 126 days after first testing, epitope WPTVRERM showed no variation in a treated patient. Previously published HLA-restriction for WM8 is HLA-B8.

HXB2 Location Nef (13–20)
Author Location Nef (13–20)
Epitope WSMVRERM
Epitope name WM8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords rate of progression, immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-B8-restricted epitope WSMVRERM was able to elicit CTL response only by the last time point. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location Nef (13–27)
Author Location Nef
Epitope `WPTVRERMRRAEPAA`
Epitope name nef-5142
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A1, A19, B*3501, B44, Cw16, Cw7; A*0201, A19, B14, B44, Cw16, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
References Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than interperson sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, WPTVRERMRRAEPAA was mutated in the daughter D2 isolate to WPaVRdRMRRAEPAA.

HXB2 Location Nef (15–23)
Author Location
Epitope `AVRERMRRT`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B7, B8)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- Known epitope AVRERMRRT is HLA-B7 and -B8-restricted. Response to a peptide containing this epitope was detected in a rapid progressor 12 weeks post-infection.

HXB2 Location Nef (15–23)
Author Location Nef (15–23)
Epitope `TVRERMRRA`
Subtype B
Immunogen HIV-1 infection, peptide-HLA interaction
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance
References Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, TVRERMRRA, is similar to human protein Rhomboid protein, sequence TTVRsRMRRA.

HXB2 Location Nef (19–27)
Author Location Nef (19–27)
Epitope `RMRRAEPAA`
Epitope name RA9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*15)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

CTL CD8+

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*15-associated substitutions within optimally defined epitope RMRRAEPAA are at positions R3 and A5, RMrRaEPAA.

HXB2 Location Nef (19–27)
Author Location Nef
Epitope RMRRAEPAA
Epitope name RA9(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B15)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B15-restricted epitope RMRRAEPAA elicited an immune response in Chinese HIV-1 positive subjects as part of peptide PSVRERMRRAEPAADGV.
- 2 of the 21 HLA-B15 carriers responded to RMRRAEPAA-containing peptide with average magnitude of CTL response of 115 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Nef (19–27)
Author Location Nef (19–27)
Epitope RMRRAEPAA
Immunogen HIV-1 infection
Species (MHC) human (B62)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Nef (19–27)
Author Location Nef (19–27)
Epitope RMRRAEPAA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62)
Donor MHC 1261: A*0201, A29, B58, B62, Cw*0304, Cw*1601
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

HXB2 Location Nef (22–30)
Author Location Nef (22–30)
Epitope RAEPAADGV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope RAEPAADGV showed >20% conservation to subtype B and is predicted to be restricted by HLA-A*6901.

HXB2 Location Nef (29–37)
Author Location Rev (29–37)

Epitope GVGAVSRDL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, GVGAVSRDL, was detected within overlapping peptides DGVGAVSRDLEKHGAI and RRAEPAADGVGAVSRDL.

HXB2 Location Nef (29–37)
Author Location Nef (29–37)
Epitope GVGAASRDL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope GVGAASRDL showed >20% conservation to subtypes B and D. It is predicted to be restricted by HLA-A*6901.

HXB2 Location Nef (29–43)
Author Location Nef (29–43)
Epitope GVGAVSRDLEKHGAI
Epitope name GI-15 or Nef8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords rate of progression, acute/early infection, memory cells
References Sabbaj *et al.* 2007

- CD127 hi memory CTLs were correlated with different patient groups - subjects with chronic HIV-1 infection or controllers or those treated early with ART. For patients with chronic infection, CD127 hi CTL levels decrease greatly. Early ART treatment alone maintained these long-lived memory T cells.
- In response to peptide GI-15, IFN-gamma and IL-2 were produced by CD127 hi cells in patients given early ART . TNF-alpha was secreted by CD127 lo cells. Longitudinally, in one patient, IFN-gamma was secreted by both CD127 hi and lo cells before treatment but was maintained in CD127 hi cells after treatment. CD127 hi cells were responsible for producing IL-2 and TNF-alpha after ART.

HXB2 Location Nef (32–46)
Author Location Nef (32–46)
Epitope AVSRDLERHGAITSS
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A24, A3, B7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide AVSRDLErHGAITSS is a previously unpublished epitope that varies from the consensus at position 8.

HXB2 Location Nef (37–45)
Author Location Nef (37–45)
Epitope LEKHGAITS
Immunogen HIV-1 infection
Species (MHC) human (B*4001)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Nef (37–45)
Author Location Nef (37–45)

Epitope LEKHGAITS
Epitope name LS9
Immunogen HIV-1 infection
Species (MHC) human (B*4001, B50)
Donor MHC A*0201, A*2402, B*4001, B*5001, Cw03, Cw04
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords immunodominance, escape, variant cross-recognition or cross-neutralization
References Draenert *et al.* 2006

- HIV-specific cellular and humoral immune responses were examined in monozygotic male twins infected simultaneously with the same virus. 15 of 17 targeted epitopes were identical in the twins, including two immunodominant responses. 3 of 4 declining responses in the twins showed mutations at the same residue. Evolving antibody responses cross-neutralized the other twin's virus. The results were compared with a third brother, infected by the twins' virus 13 months after their seroconversion. The data show similarity in disease course in persons of identical genetic background infected with the same strain of HIV-1.
- This eptiope, LEKHGAITS (LS9) was restricted by HLA-B50/B*4001. Variants that arose were LdKHGAITS and LEKHGAvTS.

HXB2 Location Nef (37–45)
Author Location Nef
Epitope LEKHGAITS
Epitope name LS9(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B40)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Although the tested peptide SRDLEKHGAITSSNTAA contains the exact sequence of a previously described HLA-B40 optimal epitope, LEKHGAITS, none of the 20 HLA-B40 carriers responded to it (author communication and Fig.1).

HXB2 Location Nef (37–45)
Author Location Nef (37–45)
Epitope LEKHGAITS
Immunogen
Species (MHC) human (B50)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Nef (42–50)
Author Location Nef (44–52 HXB3)
Epitope ALTSSNTAA
Immunogen vaccine
Vector/Type: DNA, peptide *Strain:* B clade HXB3 *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (A*0201)
Keywords binding affinity, computational epitope prediction
References Sandberg *et al.* 2000

- Ten Nef 9-mer peptides were predicted to have a strong binding affinity with HLA-A*0201 – of these, four did bind strongly by a T2 class I stabilization assay, several others bound weakly.
- A CTL immune response to only 3/10 peptides was detected by a 51Cr-release assay after immunization of HLA-A201 transgenic mice with either nef DNA under the control of a CMV promotor, coated on gold particles delivered to abdominal skin by gene gun.
- ALTSSNTAA was also tested by subcutaneous injection of Nef peptides in Freund's adjuvant.
- ALTSSNTAA bound weakly to HLA-A2, but it had the strongest CTL response among the three elicited by the DNA vaccine and a strong response to the peptide vaccination.

HXB2 Location Nef (42–50)
Author Location Nef (42–50)
Epitope ALTSSNTAA
Epitope name Nef42-50
Immunogen HIV-1 infection
Species (MHC) human, humanized mouse (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, immunodominance, characterizing CD8+ T cells
References Chandwani *et al.* 2004

- Responses to five HLA-A2 presented epitopes in Nef were characterized in a population of 19 HIV infected adults and 21 children. The CD8 T-cell response to Nef was stronger and broader in adults than children, averaging 652 and 87 SFCs/10^6 PBMC, and 2.6 and 0.9 recognized epitopes per person, respectively.
- This is one of three novel Nef epitopes previously identified in HLA-A2 transgenic mice, shown to induce CD8 T-cell response in humans. It was not the immunodominant response.

HXB2 Location Nef (48–56)
Author Location Nef (58–66 JRFL)
Epitope TAATNADCA
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade JRFL
Species (MHC) mouse (H-2^b)
References Liang *et al.* 2002

- BALB/c, C3H/HeN and C57BL/6 mice were given intramuscular immunization with Nef DNA constructs – C57BL/6 responded to this epitope.

- The Nef mutant that lacked the myristylation site (G–>A) at position 2, and the dileucine motif (L –> A at positions 174 and 175) was impaired in terms of its ability to elicit induction of Nef-specific CD4+ and CD8+ T-cell responses. The myristylation site is critical for Nef membrane localization and function, and the di-leucine motif for the down-regulation of surface CD4 molecules, and the mutation of these regions could yield a safer vaccine.
- N-terminal addition of human tissue plasminogen activator (TPA) to Nef, enhanced CD8+ T-cell responses and could compensate for the G2A, L174A, L175A mutations – this enhanced immunogenicity correlated with enhanced levels of protein expression in transfected cells.

HXB2 Location Nef (50–58)
Author Location Nef (50–)
Epitope ATNADCAWL
Epitope name Nef50
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* Nef *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a low A2-binder that did not induce CTL or CD8+ T-cell IFN gamma responses in mice. Responses were detected in 2/17 HIV+ HLA-A2 subjects.

HXB2 Location Nef (61–75)
Author Location Nef (61–75)
Epitope QEEEEVGFPVRPQVP
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the ES. There was 65-E insertion in the Progressor.

HXB2 Location Nef (62–81)
Author Location Nef (61–80)
Epitope EEEEVGFPVTPQVPLRPMTY
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

HXB2 Location Nef (62–81)
Author Location Nef (61–80 SF2)
Epitope EEEEVGFPVTPQVPLRPMTY
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- Two of these 12 had CTL response to this peptide.
- The responding subjects were HLA-A11, A24, B8, B35, and HLA not determined.

HXB2 Location Nef (62–81)
Author Location Nef (61–80 SF2)
Epitope EEEEVGFVTPQVPLRPMTY
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

HXB2 Location Nef (62–81)
Author Location Nef (SF2)
Epitope EEEEVGFPVTPQVPLRPMTY
Immunogen HIV-1 infection
Species (MHC) human
References Altfeld *et al.* 2001a

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- Nef peptides PQVPLRRMTYKAAVDLSHFL, KAAVDLSHFLKEKGGLEGLI and EEEEVGFPVTPQVPLRPMTY were recognized and the first two share KAAVDLSHFL (a Cw8 epitope), the first and last share PQVPLRPMTY.

HXB2 Location Nef (63–73)
Author Location Nef
Epitope EEGVGFPVRPQ
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4501)
Country South Africa

CTL CD8+

Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- EEGVGFPVRPQ is a previously described HLA-B*4501-restricted epitope (part of Nef reacting peptide AWLQAQEEEEeEGVGFPVRPQ) that contains a B*4501-associated reversion at residue E (eEGVGFPVRPQ).

HXB2 Location Nef (63–77)
Author Location Nef (63–77)
Epitope `EEEVGFPVKPQVPLR`
Epitope name FL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A24, A3, B7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, EEEVGFPVkPQVPLR, varies at position 9 from the consensus.

HXB2 Location Nef (64–74)
Author Location Nef (C consensus)
Epitope `GEVGFPVRPQV`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B45)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, viral fitness and reversion
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- People who carried B45 tended to carry a variant of this epitope, while people who did not almost always carried the consensus form.
- B*4501 was one of the HLA types associated with having a high viral load.

HXB2 Location Nef (65–82)
Author Location Nef
Epitope `EVGFPVRPQVPLRPMTYK`
Epitope name NEF-10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, EVGFPVRPQVPLRPMTyK differs from the consensus C sequence EVGFPVRPQVPLRPMTfK at 1 amino acid position, i.e. by 5.6%.

HXB2 Location Nef (65–82)
Author Location Nef
Epitope `EVGFPVRPQVPLRPMTYK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The

virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- EVGFPVRPQVPLRPMTYK is the most frequently targeted across ethnicities. It is immunodominant, and had an overall frequency of recognition of 44.7% - 52.5% AA, 50% C, 34.1% H, 38.1% WI. This peptide is included in a 58 aa Nef highly reactive region to be used for vaccine design. It is also part of 'Region I', EVGFPVRPQVPLRPMTYKAAVDLSHFLKEKGGLEGLIYSQK, a 41 aa region recognized by >90% of subjects across ethnic groups.

HXB2 Location Nef (66–80)
Author Location Nef (66–80 BRU)
Epitope `VGFPVTPQVPLRMT`
Immunogen HIV-1 infection
Species (MHC) human (A1, B8)
References Hadida *et al.* 1992
- HIV-1 specific CTLs detected in lymphoid organs of HIV-1 infected patients.

HXB2 Location Nef (66–80)
Author Location Nef (64–78)
Epitope `VGFPVTPQVPLRMT`
Immunogen HIV-1 infection
Species (MHC) human (A1, B8)
References Ferrari *et al.* 2000
- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location Nef (66–97)
Author Location Nef (66–97 LAI)
Epitope `VGFPVTPQVPLRPMTYKAAVDLSHFLKEKGGL`
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide
Species (MHC) human
References Gahery-Segard *et al.* 2000
- Anti-HIV lipopeptide vaccine consisting of six long amino acid peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 5/10 reacted to this Nef peptide.
- 9/12 tested mounted a CTL response to at least one of the six peptides; each of the six peptides elicited a CTL response in at least one individual.
- 5/12 tested had an IgG response to this peptide.

HXB2 Location Nef (67–81)
Author Location Nef (67–81)
Epitope `GFPVRPQVPLRPMTY`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002
- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location Nef (68–76)
Author Location Nef (68–76)
Epitope `FPVTPQVPL`
Epitope name FL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*07)
Country Australia, Canada, Germany, United States
Keywords escape, HLA associated polymorphism
References Brumme *et al.* 2008a
- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*07-associated substitution within optimally defined epitope FPVTPQVPL is at position T4, FPVtPQVPL. FL9 has a very low recognition frequency and only 1 recorded escape.

HXB2 Location Nef (68–76)
Author Location Nef (68–76)
Epitope `FPVTPQVPL`
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Keywords optimal epitope

CTL CD8+

References Llano *et al.* 2009

HXB2 Location Nef (68–76)
Author Location Nef (103–111)
Epitope FPVRPQVPL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Assay type Other
Keywords HLA associated polymorphism
References Boutwell & Essex 2007

- Publicly available HIV-1 subtype C sequences from South Africa and Botswana were analyzed, and 94 HLA-associated amino acid polymorphisms were found. Many polymorphisms were associated with multiple HLA allele classes. 12% associations were negative: association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles accounted for 50% of associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes.
- FPVRPQVPL was a previously defined B*0702 presented epitope that encompassed a B*07 associated polymorphism, FPVrPQVPL,in the fourth position.

HXB2 Location Nef (68–76)
Author Location Nef (94–)
Epitope FPVRPQVPL
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (B*0702)
Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008

- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location Nef (68–76)
Author Location Nef (68–76)
Epitope FPVRPQVPL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Donor MHC A*03, A*24, B*35, B*40
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, variant cross-recognition or cross-neutralization, superinfection
References Yang *et al.* 2005b

- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
- This epitope FPVRPQVPL was identical in the initial and superinfecting strains, and the CTL response persisted in the patient before and after superinfection.

HXB2 Location Nef (68–76)
Author Location Nef (72–80 SF2)
Epitope FPVRPQVPL
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
References Tomiyama *et al.* 1997

- A CTL clone responsive to this epitope was obtained.
- 3/7 B35-positive individuals had a CTL response to this epitope.
- An R to T substitution at position 4 abrogates specific lysis, but not binding to B*3501.

HXB2 Location Nef (68–76)
Author Location Nef (72–80)
Epitope FPVRPQVPL
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
References Tomiyama *et al.* 2000a

- CD8+ T-cells that bound one of six HIV-specific B*3501-epitope tetramers did not express CD28 or CD45A.
- A significant increase in CD28-CD45RA- cells and a decrease of CD28+CD45RA+ cells was observed in chronically HIV-1-infected individuals relative to healthy individuals.
- CD28-CD45RA- cells are likely to be effector cells and have high levels of perforin in their cytoplasm.
- The mean percentage of total CD28- CD8+ cells in chronically infected HIV-1-infected patients was 76.6% in comparison to HIV-1-uninfected individuals (40.6%)

HXB2 Location Nef (68–76)
Author Location Nef (68–76)
Epitope FPVRPQVPL
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding

predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to published restriction above, epitope FPVRPQVPL was predicted to be restricted by HLA A*2902, B*0702, B*3501, B*5101, B*5102, B*5103, B*5301 and B*5401.

HXB2 Location Nef (68–76)
Author Location Nef (68–76)
Epitope FPVKPQVPL
Epitope name FL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B07, B35)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, acute/early infection, immune evasion
References Malhotra *et al.* 2007a
- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- A PTE-B peptide, EEEVGFPVkPQVPLR containing the epitope FPVRPQVPLR (FL10) was found in two subjects and elicited an IFN-gamma immune response.
- HLA-B35 and -B07 restriction for FL9 were presumed based on the subject's having the HLA allele and publication in the Los Alamos database.

HXB2 Location Nef (68–76)
Author Location Nef (72–80 SF2)
Epitope FPVRPQVPL
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Shiga *et al.* 1996
- Binds HLA-B*3501.

HXB2 Location Nef (68–76)
Author Location (SF2)
Epitope FPVRPQVPL
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords rate of progression
References Kawana *et al.* 1999
- HLA B35 is associated with rapid disease progression.
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals.
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals, but this was one of the six that had no B35 associated pattern of mutation.

HXB2 Location Nef (68–76)
Author Location Nef (66–74)
Epitope FPVRPQVPL
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Ferrari *et al.* 2000
- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location Nef (68–76)
Author Location Nef (68–76 BRU)
Epitope FPVTPQVPL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001
- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- FPVTPQVPL was recognized in 1/13 (8%) of individuals with HLA B7, and 1/12 (8%) of individuals with HLA B35. It was a high affinity HLA binder.

HXB2 Location Nef (68–76)
Author Location Nef (68–76)
Epitope FPVTPQVPL
Immunogen in vitro stimulation or selection
Species (MHC) human (B7)
Keywords binding affinity, dendritic cells, Th1
References Wilson *et al.* 1999b
- Dendritic cells are the most potent for priming T cell responses – DCs can stimulate autologous CTL responses from T cells cultured from HIV negative donors.
- Th1-biasing cytokines IL-12 or IFN alpha enhance CTL responses *in vitro* whether the epitope is delivered by pulsing from peptide, or expressed from within.
- B7 and A2 Nef epitopes were studied – FPVTPQVPL has a high affinity for B7.

HXB2 Location Nef (68–76)
Author Location Nef (68–76)
Epitope FPVTPQVPL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

CTL CD8+

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes.
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

HXB2 Location Nef (68–76)
Author Location Nef (68–76 BRU)
Epitope FPVTPQVPL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- FPVTPQVPL was recognized in 1/13 (8%) of individuals with HLA B7, and 1/12 of individuals with HLA B35. It was a high affinity HLA binder.

HXB2 Location Nef (68–76)
Author Location Nef (68–76)
Epitope FPVTPQVPL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. Also, none of 4 individuals had detectable responses to this epitope after STI.

HXB2 Location Nef (68–76)
Author Location Nef
Epitope FPVRPQVPL
Epitope name FL9(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope FPVRPQVPL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide EVGFPVRPQVPLRPMTYK. This epitope differs from the previously described HLA-B7-restricted epitope, FPVTPQVPL, at 1 residue, FPVrPQVPL.
- 7 of the 9 HLA-B7 carriers responded to FPVrPQVPL-containing peptide with average magnitude of CTL response of 370 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Nef (68–76)
Author Location Nef
Epitope FPVRPQVPL
Epitope name Nef1124
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Epitope FPVRPQVPL elicits IFN-gamma ELISpot responses in 5/7 subjects; and bound HLA-B7 with high affinity in cell-based assays. The authors claim previously published HLA restrictions of this epitope include B*0702, A*2902, B*5102, B*5103 (LANL database), B*3501,B*5101, B*5301, B*5401 (LANL and Immune Epitope Databases).

HXB2 Location Nef (68–76)

Author Location Nef
Epitope FPVRPQVPL
Epitope name Nef94
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.
- FPVRPQVPL is a Nef epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location Nef (68–76)
Author Location Nef (68–76)
Epitope FPVTPQVPL
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (B7 supertype)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the most frequently recognized of the 31 epitopes that the vaccinated volunteers responded to.

HXB2 Location Nef (68–76)
Author Location Nef
Epitope FPVRPQVPL
Epitope name Nef94
Subtype A, B, C, D
Immunogen HIV-1 infection
Species (MHC) human, mouse (B7 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope FPVRPQVPL of the HLA-B7 supertype bound most strongly to HLA-B*5101, -B*0702, -B*3501, -B*5401 and also to -B*5301. It was conserved 100% in subtype A, 74% in B, 88% in C and 100% in subtype D. 7/16 HLA-B7 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Nef94.

HXB2 Location Nef (68–76)
Author Location
Epitope FPVRPQVPL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*3501, B7)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression, optimal epitope
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- FPVRPQVPL is a known HLA-B7 and -B*3501 epitope that is part of peptide EVGFPVRPQVPLRPMTYKA which elicited responses in 3/9 patients.

HXB2 Location Nef (68–77)
Author Location Nef (68–77 LAI)
Epitope FPVTPQVPLR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*0702 epitope.

HXB2 Location Nef (68–77)
Author Location Nef (68–77 LAI)
Epitope FPVTPQVPLR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Haas *et al.* 1996

- There was a high degree of variation in three CTL epitopes in Nef in four slow and non-progressors, and variant specific CTLs arose over time to eliminate variants, indicating immune selection.

HXB2 Location Nef (68–77)
Author Location Nef (subtype B)
Epitope FPVTPQVPLR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords HIV exposed persistently seronegative (HEPS), escape
References Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- FPVTPQVPLR was recognized in 1 of the 6 women (ML1203), and the response was present in the last available sample prior to seroconversion, 7 months.
- 20/20 sequences of the infecting strain had no substitutions in this epitope, all were FPVTPQVPLR, so there was no evidence for escape.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 1/22 HEPS sex worker controls, ML851.

HXB2 Location Nef (68–77)
Author Location Nef (66–75)
Epitope FPVRPQVPLR
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location Nef (68–77)
Author Location Nef (68–77 SF2)
Epitope FPVTPQVPLR
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 0/4 group 1, 0/3 group 2, and 1/1 group 3.

HXB2 Location Nef (68–77)
Author Location Nef (68–77)
Epitope FPVTPQVPLR
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B7)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Subject ML 1203 started with CTL responses to A*6802 DTVLEDINL and to B7 FPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A*6802 ETAYFILKL which became dominant, B7 TPGPG(V/I)RYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV.

HXB2 Location Nef (68–77)
Author Location Nef (68–77)
Epitope FPVTPQVPLR
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes.
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

HXB2 Location Nef (68–77)
Author Location Nef (68–76)
Epitope FPVTPQVPLR
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection

References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. Also, none of 4 individuals had detectable responses to this epitope after STI.

HXB2 Location Nef (68–77)
Author Location Nef (66–75)
Epitope FPVTPQVPLR
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 7 patients recognized this epitope.

HXB2 Location Nef (68–77)
Author Location Nef (68–77)
Epitope FPVRPQVPLR
Epitope name FR10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, acute/early infection, immune evasion
References Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- A CON peptide, EVGFPVRPQVPLR contained the epitope FPVRPQVPLR (FL10) and elicited an IFN-gamma immune response.
- HLA-B07 restriction for FR10 was presumed based on the subject's having the HLA allele and publication in the Los Alamos database.

HXB2 Location Nef (68–77)
Author Location Nef
Epitope FPVRPQVPLR
Epitope name FR10(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope FPVRPQVPL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide EVGFPVRPQVPLRPMTYK. This epitope differs from the previously described HLA-B7-restricted epitope, FPVTPQVPLR, at 1 residue, FPVrPQVPLR.
- 7 of the 9 HLA-B7 carriers responded to FPVrPQVPLR-containing peptide with average magnitude of CTL response of 370 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Nef (68–77)
Author Location
Epitope FPVTPQVPLR
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A*2501, A*3002; B*0702, B*1801
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location Nef (68–81)
Author Location Nef (82–95 HXB2)
Epitope FPVTPQVPLRMTY

CTL CD8+

Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Guimaráes *et al.* 2002

- Nef sequences were obtained from Brazilians to study epitope diversity in this geographic region—the HXB2 sequence is FPVTPQVPLRMTY, but fpvRpqvplrmty was observed in most Brazilian sequences regardless of the subtype (A, C, D and F).

HXB2 Location Nef (68–82)
Author Location Nef (68–82)
Epitope FPVRPQVPLRPMTYK
Epitope name QK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A24, A3, B7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, FPVRPQVPLRPMTYK, is a variant of the consensus peptide QVPLRPMTYKAAVDL.

HXB2 Location Nef (68–82)
Author Location Nef (68–82)
Epitope FPVTPQVPLRPMTFK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A24, A3, B7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, FPVtPQVPLRPMTfK, varies at positions 4 and 14 from the consensus sequence QVPLRPMTYKAAVDL.

HXB2 Location Nef (68–82)
Author Location Nef (68–82)
Epitope FPVRPQVPLRPMTYK
Epitope name RY11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- The peptide, FPVRPQVPLRPMTYK, was found to have identity with consensus peptide PVRPQVPLRPMTYKA from aa positions 69-82.

HXB2 Location Nef (68–82)
Author Location Nef (73–82)
Epitope FPVRPOVPLRPMTYK
Subtype A, D
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0201, A*0301, B*4501, B*5802
Country Uganda
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, characterizing CD8+ T cells
References Barugahare *et al.* 2005

- T-cell immune responses were examined in HIV-1 infected Ugandans. Similar levels of cross-clade responses for Gag, Env and Nef were observed. Higher frequencies of responses in conserved regions were found for Gag within a single clade, while areas with higher viral sequence variation had fewer detectable responses. Differential interclade sequence homologies between the Gag regions did not affect the respective level of cross-clade recognition.
- This sequence contains a known epitope (RPOVPLRPMTYK). The subject recognizing the peptide carries an HLA allele (A0301) of the known restriction, and the peptide is conserved in the autologous sequence.

HXB2 Location Nef (68–84)
Author Location Nef

Epitope FPVRPQVPLRPMTYKGA
Immunogen
Species (MHC) human
Keywords subtype comparisons
References Jubier-Maurin *et al.* 1999

- 41 new HIV-1 strains describing envelope subtypes of HIV-1 A-H were genetically characterized in the nef region – 34 subtypes were classified in the same subtype in nef and env and 7 of the 41 strains were recombinants.
- This region was defined as a CTL epitope region that is conserved among HIV-1 M group subtypes.

HXB2 Location Nef (69–83)
Author Location Nef
Epitope PVRPQVPLRPMTYKA
Epitope name nef-5156
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A1, A19, B*3501, B44, Cw16, Cw7; A*0201, A19, B14, B44, Cw16, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
References Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than interperson sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, PVRPQVPLRPMTYKA was mutated in the daughter D2 isolate to PVRPQVPLRPMTfKA.

HXB2 Location Nef (70–84)
Author Location Nef (70–84 HXB2)
Epitope VTPQVPLRPMTYKAA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 34% of the study subjects, and it was the second most frequently recognized peptide.

HXB2 Location Nef (71–79)
Author Location Nef (71–79)
Epitope TPQVPLRPM
Epitope name TM9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*07)
Country Australia, Canada, Germany, United States
Keywords escape, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- Escape (and reversion) rates for B*57-restricted epitopes were highest for Gag-TW10 (TSTLQEQIGW) > RT-IW9 (IVLPEKDSW) > Nef-YY9 (YTPGPGIRY) > Nef-HW9 (HTQGYFPDW) > Gag-IW9 (ISPRTLNAW) > Gag-KF11 (KAFSPEVIPMF) .

HXB2 Location Nef (71–79)
Author Location Nef
Epitope RPQVPLRPM
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*07, B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ

Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- RPQVPLRPM is a previously described HLA-B*07 and -B*8101-restricted epitope (part of Nef reacting peptides EEEEGVGFPVrPQVPLRPMTY and VGFPVRPQVPlRPM-TYKAAFD) that contain a B*07 and B*8101-associated reversion at residues R and L (rPQVPLRPM/RPQVPlRPM).

HXB2 Location Nef (71–79)
Author Location Nef (71–79 LAI)
Epitope TPQVPLRPM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*0702 epitope.

HXB2 Location Nef (71–79)
Author Location (C consensus)
Epitope RPQVPLRPM
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- RPQVPLRPM is an optimal epitope for both B*4201 and B*4202.

HXB2 Location Nef (71–79)
Author Location
Epitope RPQVPLRPM
Epitope name RM9
Immunogen
Species (MHC) human (B*4201)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*4201 epitope.

HXB2 Location Nef (71–79)
Author Location Nef
Epitope RPQVPLRPM
Epitope name RM9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization
Keywords rate of progression
References Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naive patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer B*4201 RM9 was used to test 34 patients and gave a median ex vivo tetramer frequency of 0.22.

HXB2 Location Nef (71–79)
Author Location Nef
Epitope RPQVPLRPM
Epitope name RM9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization
Keywords rate of progression
References Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naive patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer B*4201 RM9 was used to test 34 patients and gave a median ex vivo tetramer frequency of 0.22.

HXB2 Location Nef (71–79)
Author Location
Epitope RPQVPLRPM
Epitope name RM9
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type proliferation, Tetramer binding, Intracellular cytokine staining
References Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

HXB2 Location Nef (71–79)
Author Location
Epitope RPQVPLRPM
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)

CTL CD8+

Donor MHC A*3001, A*3303, B*5301, B*8101, Cw*0401
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- RPQVPLRPM is a known HLA-B*4201-restricted epitope. Response to a peptide EVGFPVRPQVPLRPMTYKA containing this epitope is detected in an early controller (HLA alleles not determined) and an HLA-B*4201 negative rapid progressor 12 weeks post-infection.

HXB2 Location Nef (71–79)
Author Location
Epitope `RPQQVPLRPM`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201, B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- RPQQVPLRPM is a known HLA-B4201 and -B8101 epitope that is part of peptide EVGFPVRPQVPLRPMTYKA which elicited responses in 3/9 patients.

HXB2 Location Nef (71–79)
Author Location (C consensus)
Epitope `RPQVPLRPM`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4202)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- RPQVPLRPM is an optimal epitope for both B*4201 and B*4202.

HXB2 Location Nef (71–79)
Author Location Nef
Epitope `RPQVPLRPM`
Epitope name RM9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*8101)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, HLA associated polymorphism
References Frater *et al.* 2007

- To study whether CTL responses restricted by "good" HLA I molecules exert stronger immune selection than other HLA I molecules, 54 and 70 optimal epitopes within HIV-1 Gag, Pol and Nef genes for Caucasian and African cohorts were tested in patients over a mean of 14 months. "Good", advantageous HLA allele-restricted epitopes were much more polymorphic than epitopes restricted by other, non-advantageous HLA in patients, suggesting that benefits associated with HLA Class I alleles of elite controllers of disease progression are epitope-specific. Such "driver" epitopes with high polymorphism had high frequency of immune response, allowing them to be ranked for recognition and polymorphism.
- Patients with higher proportions of mutated epitopes also had lower plasma viral loads, and mean epitope variability correlated negatively with relative hazard of disease progression.
- Variant RPQVPvRPM at position 6 was the predominant polymorphism found.

HXB2 Location Nef (71–79)
Author Location
Epitope `TPQVPLRPM`
Immunogen HIV-1 infection
Species (MHC) human (B07)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B07), AN additional HLA (B42) was statistically predicted to be associated with this epitope.

HXB2 Location Nef (71–79)
Author Location Nef (71–79 BRU)
Epitope `TPQVPLRPM`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

CTL CD8+

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- TPQVPLRPM was recognized in 1/10 (10%) of individuals with HLA B7, and 1/10 (10%) of individuals with HLA B35. It was a moderate affinity HLA binder.

HXB2 Location Nef (71–79)
Author Location
Epitope RPQVPLRPM
Epitope name RM9 ?
Immunogen HIV-1 infection
Species (MHC) human (B42)
Country United States, South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords memory cells
References Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

HXB2 Location Nef (71–79)
Author Location Nef (71–79 SF2)
Epitope TPQVPLRPM
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 0/4 group 1, 0/3 group 2, and 1/1 group 3.

HXB2 Location Nef (71–79)
Author Location Nef (71–79)
Epitope TPQVPLRPM
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes.
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

HXB2 Location Nef (71–79)
Author Location Nef (71–79 BRU)
Epitope TPQVPLRPM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- TPQVPLRPM was recognized in 1/10 (10%) of individuals with HLA B7, and 1/10 (10%) individuals with HLA B35. It was a moderate affinity HLA binder.

HXB2 Location Nef (71–79)
Author Location Nef (71–79)
Epitope TPQVPLRPM
Epitope name B7-TM9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

CTL CD8+

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 2/4 individuals had detectable responses to this epitope after STI.

HXB2 Location Nef (71–79)
Author Location Nef
Epitope `TPQVPLRPM`
Epitope name B7-TM9(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A32, B14, B7; A24, B27, B7
Keywords HAART, ART, supervised treatment interruptions (STI)
References Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (`http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html`) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient A displayed the greatest response to epitope B14-EL9(gp41), a strong response to B7-TL9(p24), and responses to B7-TM9(Nef) and A32-PW10(RT). Patient C displayed the greatest response to B27-KK10(p24), and in decreasing order also responded to A24-RW8(Nef), B7-IL9(gp41), A24-RL9(gp41), A24-YL8(gp41), and B7-TM9(Nef).

HXB2 Location Nef (71–79)
Author Location Nef (180–187)
Epitope `TPQVPLRPM`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location Nef (71–79)
Author Location Nef
Epitope `TPQVPLRPM`
Epitope name B7-TM9(Nef)
Immunogen HIV-1 infection
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (71–79)
Author Location Nef
Epitope `RPQVPLRPM`
Epitope name TM9(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.

CTL CD8+

- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope RPQVPLRPM elicited an immune response in Chinese HIV-1 positive subjects as part of peptide EVGFPVRPWVPLRPMTYK. This epitope differs from the previously described HLA-B7 epitope, TPQVPLRPM, at 1 residue, rPQVPLRPM.
- 7 of the 9 HLA-B7 carriers responded to rPQVPLRPM-containing peptide with average magnitude of CTL response of >370 SFC/million PBMC.

HXB2 Location Nef (71–79)
Author Location Nef (71–79)
Epitope TPQVPLRPM
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (B7 supertype)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the most frequently recognized of the 31 epitopes that the vaccinated volunteers responded to.

HXB2 Location Nef (71–79)
Author Location Nef (C consensus)
Epitope RPQVPLRPM
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0702, B*4201, B*8101, B7, B81)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, cross-presentation by different HLA
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- People who carried either B07 or B81 tended to carry a variant of this epitope, while people who did not almost always carried the consensus form.
- B*4201 may also present this epitope, as the allele is enriched in people who react with the peptide that contains the epitope, and it is known from the database to be also presented by B*4201.

HXB2 Location Nef (71–79)
Author Location
Epitope RPQVPLRPM?
Epitope name RM9
Immunogen HIV-1 infection
Species (MHC) human (B81)
Country United States, South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords memory cells
References Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

HXB2 Location Nef (71–79)
Author Location Nef (71–79)
Epitope RPQVPLRPM
Epitope name RM9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Other
Keywords supertype, escape, cross-presentation by different HLA, TCR usage, HLA associated polymorphism
References Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alelles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope restriction.
- For this epitope, RM9, selection pressure was evidenced by studying changing epitope variants associated with HLAs of the B7 supertype.
- Higher level of sequence variation and escape mutations were associated with the B*8101 and B*0702 alleles.
- Statistically significant associations between numbers of HLA-B8101, -0702 and -B4201 expressing subjects and epitope RPQVPLRPM were found.
- In 3 B-supertype alleles studied, B*4201, B*8101 and B*0702, two RM9 variants were most common - one at the first position, kPQVPLRPM and the other at the sixth position, RPQVPvRPM. Several more variants are listed in the paper.

HXB2 Location Nef (71–81)
Author Location Nef (75–85)
Epitope RPQVPLRPMTY
Epitope name RY11
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Country Japan
Assay type Cytokine production, Tetramer binding, Intracellular cytokine staining, CTL suppression of replication, Other, HLA binding
Keywords class I down-regulation by Nef, escape
References Ueno *et al.* 2008

- The balance between Nef selective pressures to modulate HLA I or its escape mutations reducing Nef HLA I down-regulating activity is studied.
- Epitope RY11 does not share CTL with VY8 (VPLRPMTY), but is a different optimal epitope. RY11 shows less functional avidity than VY8. No subject showed an immune response to both epitopes simultaneously.
- Epitope RPQVPLRPMTY escape mutations at T75 (tPQVPLRPMTY) and F85 (RPQVPLRPMTf), are associated with HLA-B*35. Mutations tend to go from RF to TY and double mutants are rare. Only the double mutant, TF (tPQVPLRPMTf), however, diminishes Nef-mediated surface HLA-I down-regulation.
- VY-8F (VPLRPMTf) and RY-11F (RPQVPLRPMTf) do not change HLA-binding activity, but RY11-1T (tPQVPLRPMTY) does increase binding by ∼10.

HXB2 Location Nef (71–81)
Author Location Nef (75–85 SF2)
Epitope RPQVPLRPMTY
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
References Tomiyama *et al.* 1997

- A CTL clone responsive to this epitope was obtained.
- 4/7 B35-positive individuals had a strong CTL response to this epitope.
- An R to T substitution at position 1 abrogates specific lysis, but not binding to B*3501.
- An R to H substitution at position 7 did not alter reactivity.

HXB2 Location Nef (71–81)
Author Location Nef (75–85)
Epitope RPQVPLRPMTY
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
References Tomiyama *et al.* 2000a

- CD8+ T-cells that bound one of six HIV-specific B*3501-epitope tetramers did not express CD28 or CD45A.
- A significant increase in CD28-CD45RA- cells and a decrease of CD28+CD45RA+ cells was observed in chronically HIV-1-infected individuals relative to healthy individuals.
- CD28-CD45RA- cells are likely to be effector cells and have high levels of perforin in their cytoplasm.
- The mean percentage of total CD28- CD8+ cells in chronically infected HIV-1-infected patients was 76.6% in comparison to HIV-1-uninfected individuals (40.6%)

HXB2 Location Nef (71–81)
Author Location Nef (75–85 SF2)
Epitope RPQVPLRPMTY
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Shiga *et al.* 1996

- Binds HLA-B*3501.

HXB2 Location Nef (71–81)
Author Location (SF2)
Epitope RPQVPLRPMTY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords binding affinity, rate of progression, escape
References Kawana *et al.* 1999

- HLA B35 is associated with rapid disease progression.
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals.
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals – only one of these reduced the binding of the peptide to B35 and was shown to be an escape mutation.
- rpqvplrpmtF was found in 9/10 of the B35+ individuals, none of the B35- individuals—the Y–>F substituted peptide had a similar binding affinity with B35 and was recognized by a CTL clone equally with wildtype.

HXB2 Location Nef (71–81)
Author Location Nef (69–79)
Epitope RPQVPLRPMTY
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location Nef (71–81)
Author Location Nef (71–81 BRU)
Epitope TPQVPLRPMTY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- TPQVPLRPMTY was recognized in 9/12 (75%) of individuals with HLA B7, and 5/10 (50%) of individuals with HLA B35. It was a moderate affinity HLA binder, and the C-term Y readily cleaved *in vitro*.

CTL CD8+

HXB2 Location Nef (71–81)
Author Location Nef
Epitope RPQVPLRPMTY
Subtype A, B, D
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human, macaque (B51)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location Nef (71–81)
Author Location Nef (71–81 BRU)
Epitope TPQVPLRPMTY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- TPQVPLRPMTY was recognized in 9/12 (75%) of individuals with HLA B7, and 5/10 (50%) of individuals with HLA B35. It was a moderate affinity HLA binder, and the C-term Y readily cleaved *in vitro*.

HXB2 Location Nef (71–81)
Author Location Nef (71–81)
Epitope TPQVPLRPMTY
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (B7 supertype)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.
- A response was induced in one patient after immuniaation with lipopeptides alone (no adjuvant) after the third (W44) boost. A rPQVPLRPMTY variant was also recognized.

HXB2 Location Nef (71–85)
Author Location Nef (71–85)
Epitope KPQVPLRPMTYKAAV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A24, A3, B7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, KPQVPLRPMTYKAAV, is a variant of the consensus peptide QVPLRPMTYKAAVDL.

HXB2 Location Nef (72–81)
Author Location
Epitope PQVPLRPMTY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- PQVPLRPMTY is a known HLA-B35-restricted epitope that is part of peptide EVGFPVRPQVPLRPMTYKA which elicited responses in 3/9 patients.

HXB2 Location Nef (72–81)
Author Location Nef (72–82)
Epitope PQVPLRPMTY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35, B51)
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords Th1, characterizing CD8+ T cells
References Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- Three of nine patients responded to this peptide with GzB producing and IFN-gamma producing cells, and one additional with IFN-gamma producing cells.

HXB2 Location Nef (72–86)
Author Location Nef (72–86)
Epitope PQVPLRPMTYKGAFD
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location Nef (72–91)
Author Location Nef (71–90 SF2)
Epitope PQVPLRMTYKAAVDLSHFL
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- Three of these 11 had CTL response to this peptide.
- The responding subjects were HLA-A3, A32, B51, B62; HLA-A11, A24, B8, B53.

HXB2 Location Nef (72–91)
Author Location Nef (71–90 SF2)
Epitope PQVPLRPMTYKAAVDLSHFL
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

HXB2 Location Nef (72–91)
Author Location Nef (SF2)
Epitope PQVPLRRMTYKAAVDLSHFL
Immunogen HIV-1 infection
Species (MHC) human
References Altfeld *et al.* 2001a

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- Nef peptides PQVPLRRMTYKAAVDLSHFL, KAAVDLSHFLKEKGGLEGLI and EEEEVGFPVTPQVPLRPMTY were recognized and the first two share KAAVDLSHFL (a Cw8 epitope), the first and last share PQVPLRPMTY.

HXB2 Location Nef (73–81)
Author Location Nef
Epitope QVPLRPMTY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- QVPLRPMTY is a previously described HLA-B*3501-restricted epitope (part of Nef reacting peptide RPQVPLRPMTyKAAFDLSFFL) that contains a B*3501-associated reversion at residue Y (QVPLRPMTy).

HXB2 Location Nef (73–81)
Author Location Nef
Epitope QVPLRPMTY
Subtype B, C, D, AE
Immunogen HIV-1 infection
Species (MHC) human
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction
References Pérez *et al.* 2008

CTL CD8+

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- Conserved epitope QVPLRPMTY was recognized by at least 4 patients with restricting HLA supertype and infected with several HIV subtypes. Predicted HLA restriction for this epitope was to suptertype A1.

HXB2 Location Nef (73–82)
Author Location Nef
Epitope QVPLRPMTYK
Immunogen peptide-HLA interaction
Species (MHC) human (A*03)
Assay type Tetramer binding
Keywords binding affinity
References Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, QVPLRPMTYK (MHC Class I restriction, serotype Bw6) complexed with MHC A03 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C.

HXB2 Location Nef (73–82)
Author Location Nef (73–82 NL43)
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
References Koenig *et al.* 1990

- 81 Tyr is critical for binding to A3.1.
- C. Brander notes that this is an A*0301 epitope in the 1999 database.

HXB2 Location Nef (73–82)
Author Location Nef (73–82 LAI)
Epitope QVPLRPMTYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords rate of progression, escape
References Koenig *et al.* 1995

- Alanine substitutions L76A, R77A, M79A, T80A significantly decreased immunogenicity of peptide.
- Nef CTL clones (4N225) were infused into an HIV-1 infected volunteer to evaluate effects of infusion on viral load/patient health.
- Infusion led to outburst of escape variants which resulted in higher viral load/accelerated disease progression.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the A2+ individuals was A3, and responded to QVPLRPMTYK as well as two other A3.1 epitopes.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords acute/early infection
References Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B2705; and A*0201, A*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK.
- The subject with A*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705.
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

HXB2 Location Nef (73–82)
Author Location Nef (73–82 LAI)
Epitope QVPLRPMTYK
Subtype B

Immunogen
Species (MHC) human (A*0301)
Keywords optimal epitope
References Llano *et al.* 2009
- C. Brander notes this is an A*0301 epitope.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0301)
Keywords epitope processing, dendritic cells
References Andrieu *et al.* 2003
- This study demonstrates that lipopeptides carrying epitopes can be taken up by human dendritic cells, processed using different pathways, and recognized by epitope-specific CD8+ T-cells originally derived from HIV+ individuals. The RT ILKEPVHGV peptide was embedded in a longer peptide fragment in the lipopeptide, and was internalized by endocytosis and processed in the cytosol by proteasomal cleavage by following an endosome-to-cytosol pathway for processing and presentation. Administration of epoxomycin, a proteasome inhibitor, completely abrogated epitope presentation to a CD8+ T-cell line, while monensin, an inhibitor of acid-dependent endosomal enzyme activity did not.
- In contrast to the RT epitope, dendritic cell presentation of the Nef epitope QVPLRPMTYK embedded in a longer peptide in a lipopeptide was not inhibited by epoxomycin, but was inhibited by monensin, indicative of endocytolitic epitope processing.

HXB2 Location Nef (73–82)
Author Location Nef
Epitope QVPLRPMTYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Donor MHC A*0101, A*0301, B*0801, B*5101
Country United Kingdom
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords escape
References Milicic *et al.* 2005
- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient. In an early acute infection of the donor, the precise timing of transmission determines the viral variants transmitted.
- Two variants of this epitope, QVPvRPMTYK and QaPLRPMTYK, were found in 1 donor. The QaPLRPMTYK substitution reduced the binding affinity for A*0301 by 52%.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Epitope name QVP
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells
References Turnbull *et al.* 2006
- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.
- This epitope, A3-QVP (that has no assoication with accelerated or delayed progression to AIDS) and its natural variants are less efficiently cross-recognized. Its alanine-substituted variants were inconsistent between individuals showing very efficient or poor cross-reactivity. CTLs responding to this epitope expressed the same predominant TCR Vbeta family, but individuals whose CTLs predominantly used TCR Vbeta 13.6 had poor cross-recognition of alanine substituted variants.

HXB2 Location Nef (73–82)
Author Location Nef
Epitope QVPLRPMTYK
Subtype A, B, D
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human, macaque (A*0301, A11)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002
- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

CTL CD8+

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*11)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, immunodominance, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This putative epitope, QVPLRPMTYK, was detected and confirmed within overlapping peptides EVGFPVRPQVPLRPMTYK and YKAAVDLSHFLKEKGGL. It was the immunodominant HLA-A*11 restricted epitope in 10 subjects tested.

HXB2 Location Nef (73–82)
Author Location (LAI)
Epitope QVPLRPMTYK
Subtype B
Immunogen
Species (MHC) human (A*1101)
Keywords optimal epitope
References Buseyne 1999; Llano *et al.* 2009

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Subtype B, CRF01_AE
Immunogen
Species (MHC) (A*1101)
Country Thailand
Keywords HIV exposed persistently seronegative (HEPS), immunodominance, structure
References Li & Bouvier 2004

- HLA-A*1101 has been associated with resistance to acquisition of HIV-1 infection in female sex-workers in Thailand. Its crystal structure has been determined in association with two immunodominant A*1101 HIV-1 CTL epitopes. Its anchor residues are confirmed as P2(Ile/Val) and C-term (Lys). The backbone conformation of the peptides is defined as two bulges separated by a secondary anchor residue (P6 Ser or Met) that may offer various advantages in the selection and presentation of CTL epitopes by HLA-A*1101.

HXB2 Location Nef (73–82)
Author Location Nef
Epitope QVPLRPMTYK
Epitope name QK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords HAART, ART, responses in children, dendritic cells
References Zhang *et al.* 2006b

- Immune responses in HIV-1 infected children either undregoing HAART or not were analysed. HIV-specific CTLs were lower in children responding to HAART than in nonresponders and HAART-naive children. CTL frequency was correlated with myeloid DC frequency in treatment-naive patients, and inversely correlated with duration of virus supression following treatment.
- 11 of the 22 children had significant responses to SL9.

HXB2 Location Nef (73–82)
Author Location
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human (A03, A11)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- Based on a prediction of the minimum number of HLA alleles needed to cover the HLA representation in all responders to this epitope, a minimum set of 6 alleles was found: 2 alleles previously known to be associated (A03, A11) and 4 additional alleles (A02, A33, B44, Cw07).
- In addition to its known HLA associations (A03, A11), an additional HLA (A34) was statistically predicted to be associated with this epitope.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human (A11)
References Le Borgne *et al.* 2000

- Soluble factors in supernatant from both an HIV-specific cloned CTL line and an EBV (Epstein-Barr-virus) CTL line inhibit viral replication, but do not block viral entry in CD4+ T lymphocytes, by a noncytotoxic mechanism.

HXB2 Location Nef (73–82)
Author Location Nef (73–82 LAI)
Epitope QVPLRPMTYK
Subtype B

Immunogen HIV-1 infection
Species (MHC) human (A11)
References Robertson *et al.* 1993

- Development of a retroviral vector (pNeoNef) to generate autologous CTL targets.
- Hunziker *et al.* [1998] suggests that HLA-A2 does not in fact present this epitope.
- The initial assignment of HLA-A2 presentation for this epitope was based on a serological HLA typing. Subsequently, the authors revisited the issue with genetic HLA typing and found that HLA-A11 was the correct presenting molecule (Dr. Florence Buseyne, pers. comm., 2000)

HXB2 Location Nef (73–82)
Author Location Nef (73–82 LAI)
Epitope QVPLRPMTYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords review, escape
References Couillin *et al.* 1994; Goulder *et al.* 1997a

- Mutational variation in HIV epitopes in individuals with appropriate HLA types can result in evasion of CTL response.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

HXB2 Location Nef (73–82)
Author Location Nef (73–82 LAI)
Epitope QVPLRPMTYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
References Couillin *et al.* 1995

- Mutations found in this epitope in HLA-A11 positive and negative donors were characterized.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Epitope name QVP
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords HAART, ART, supervised treatment interruptions (STI), immunodominance, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- One of the 2/8 HLA-A11 study subjects recognized this CTL epitope.
- Patient SC18(HLA A2/11, B8/44, Cw06/0701, DR3/7, DR52/53, DQ2) recognizes the epitopes ACQGVGGPGHK, QVPLRPMTYK, AVDLSHFLK, and one called QIY but not fully described – he had brief therapy upon seroconversion and has had low viral load during 600 days of follow up.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A11)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human (A11)
References Appay *et al.* 2000

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α

HXB2 Location Nef (73–82)
Author Location Nef (71–80 93TH253 subtype CRF01)
Epitope QVPLRPMTYK
Epitope name N73-82
Subtype CRF01_AE
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A11)
Keywords HIV exposed persistently seronegative (HEPS)
References Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was weakly reactive in HEPS study subjects 265 who was HLA A2/A11 and 128 who was HLA A11/A33, and after a second *in vitro* stimulation, in study subject 256 who was HLA A11/33, making it the most reactive epitope tested in HLA-A11 HEPS women, with 3/4 responding.
- This epitope was strongly reactive in HIV+ study subject 053 who carried HLA-A11.

CTL CD8+

HXB2 Location Nef (73–82)
Author Location Nef (71–80 93TH253 subtype CRF01)
Epitope QVPLRPMTYK
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords subtype comparisons
References Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This epitope was predicted by the EpiMatrix method to be likely to bind to A11, and it served as an epitope in the FSWs, it was one of the six A11 epitopes that had been previously defined.
- 4/8 tested FSWs recognized this epitope.
- An HLA-A11 tetramer was made for this epitope, which was recognized by two subjects – only one subject had an expanded tetramer staining T-cell population after *in vitro* stimulation.
- This epitope was highly conserved in other subtypes, and exact matches were common.

HXB2 Location Nef (73–82)
Author Location Nef
Epitope QVPLRPMTYK
Epitope name QVP
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords HAART, ART, supervised treatment interruptions (STI)
References Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFNgamma Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

HXB2 Location Nef (73–82)
Author Location Nef
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A2, B60, B8, Bw6
Keywords HAART, ART
References Appay *et al.* 2002

- Four HIV patients with prolonged clinically successful anti-viral therapy but with ongoing evidence of replication and Nef mRNA transcription, showed specific T-cell responses by Elispot and Tetramer staining, maintained for 2-4 years after initiation of HAART.
- Nef epitope recognition was detected in all 4 subjects, gp120, Pol and Gag-specific in 1 or 2 subjects – two patients recognized this epitope, one using HLA-A3, one using HLA-A11.
- The HIV-specific CD8+ T-cells had an intermediate maturation phenotype characterized by low levels of perforin and high levels of CD27 expression.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Epitope name QK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords optimal epitope
References Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- This epitope did not vary.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location Nef (73–82)
Author Location Nef
Epitope QVPLRPMTYK
Epitope name QK9
Immunogen
Species (MHC) (A11)
Keywords review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion
References Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

HXB2 Location Nef (73–82)
Author Location Nef
Epitope QVPLRPMTYK
Epitope name A11-QK10(Nef)
Immunogen HIV-1 infection
Species (MHC) human (A11)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (73–82)
Author Location Nef (74–82)
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A24, B44, B55
Country United Kingdom
Assay type Flow cytometric T-cell cytokine assay, Other
Keywords HAART, ART, immunodominance, TCR usage, memory cells
References Weekes *et al.* 2006

- The effect of HAART on the population size, phenotype and function of HIV- and HCMV-specific CTL clones was analyzed. It was determined that the clonal composition of gag and env HIV-specific CD8 T-cells did not change after HAART. Following HAART, the size of immunodominant HIV-specific CD8 T-cell clones was found to diminish even with the relative preservation of functional memory responses. Maintainance of such strong functional responses implied the preferential loss of HIV-specific cells that have reduced cloning efficiency in vitro. HCMV-specific CTL clones had different kinetics and phenotypes than HIV-specific CTL clones in the same subject.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301, A11)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords Th1, characterizing CD8+ T cells
References Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- None of three patients responded to this peptide with GzB producing cells, while all three responded with IFN-gamma producing cells.

HXB2 Location Nef (73–82)
Author Location
Epitope QVPLRPMYTK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A11, A3)
Donor MHC A*3001, A*3303, B*5301, B*8101, Cw*0401; A*0301, A*2301, B*1503, B*5802, Cw*0210, Cw*0602
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- QVPLRPMTYK is a known HLA-A3 and -A11 epitope that is part of peptide EVGFPVRPQVPLRPMTYKA which elicited responses in 3/9 patients. HLA-A*0301-restricted response to a peptide containing this epitope was detected in an early controller and 2 rapid progressors 12 weeks post-infection.

HXB2 Location Nef (73–82)
Author Location Nef (73–81)
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human (A11, A2, A3, B35)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location Nef (73–82)
Author Location Nef (73–82 LAI)
Epitope QVPLRPMTYK
Subtype B
Immunogen HIV-1 infection

CTL CD8+

Species (MHC) human (A3)
Keywords epitope processing, escape
References Chassin *et al.* 1999

- Mutations in Nef that flank this epitope, Thr71Lys and Ala83Gly, may account for an observed loss of CTL reactivity, with escape due to the introduction of proteasome processing defects.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords subtype comparisons
References Durali *et al.* 1998

- Cross-clade CTL response was studied by determining the CTL activity in seven patients from Bangui, (6 A subtype, and 1 AG recombinant infections) and one A subtype infection from a person living in France originally from Togo, to different antigens expressed in vaccinia.
- Pol reactivity: 8/8 had CTL to A subtype, and 7/8 to B subtype, and HIV-2 Pol was not tested.
- Gag reactivity: 7/8 reacted with A or B subtype gag, 3/8 with HIV-2 Gag.
- Nef reactivity: 7/8 reacted with A subtype, and 5/8 with B subtype, none with HIV-2 Nef.
- Env reactivity: 3/8 reacted with A subtype, 1/8 with B subtype, none with HIV-2 Env.
- One of the patients was shown to react to this epitope: QVPLRPMTYK.

HXB2 Location Nef (73–82)
Author Location Nef (73–82 LAI)
Epitope QVPLRPMTYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords review, escape
References Goulder *et al.* 1997e; Goulder *et al.* 1997a

- HLA-identical siblings, twin hemophiliac brothers, were both infected with the same batch of factor VIII.
- Both had a response to this epitope. One had a response to this epitope, the other did not.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Lubaki *et al.* 1997

- Eighty two HIV-1-specific CTL clones from 5 long-term nonprogressors were isolated and analyzed for breadth of response.
- A sustained Gag, Env and Nef response was observed, and clones were restricted by multiple HLA epitopes, indicating a polyclonal response.
- An A3+ subject had a strong response to this epitope, with 10/11 CTL clones being specific for this epitope, isolated at two time points, 1 year apart.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Epitope name N1
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords HAART, ART, escape
References Samri *et al.* 2000

- The epitope was recognized by patients 252#0 and 252#4 in a study of the effects of therapy escape mutations on CTL recognition.

HXB2 Location Nef (73–82)
Author Location Nef (73–82 SF2)
Epitope QVPLRRMTYK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with preseroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A3+ individuals that had a CTL response to this epitope broken down by group: 3/7 group 1, 1/4 group 2, and 1/2 group 3.

HXB2 Location Nef (73–82)
Author Location Nef (SF2)
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.

HXB2 Location Nef (73–82)
Author Location
Epitope QVPLRPMTYK
Epitope name Nef-QK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A03, 9/20 (45%) recognized this epitope.

CTL CD8+

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Epitope name A3-QK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 3/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 5/7 individuals had detectable responses to this epitope after STI.

HXB2 Location Nef (73–82)
Author Location Nef
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A3, B44, B64, Bw4, Bw6
Keywords HAART, ART
References Appay *et al.* 2002

- Four HIV patients with prolonged clinically successful anti-viral therapy but with ongoing evidence of replication and Nef mRNA transcription, showed specific T-cell responses by Elispot and Tetramer staining, maintained for 2-4 years after initiation of HAART.
- Nef epitope recognition was detected in all 4 subjects, gp120, Pol and Gag-specific in 1 or 2 subjects – two patients recognized this epitope, one using HLA-A3, one using HLA-A11.
- The HIV-specific CD8+ T-cells had an intermediate maturation phenotype characterized by low levels of perforin and high levels of CD27 expression.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A1, A3, B14, B7, Cw*0702, Cw*0802
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these eptiopes, but this increased over time.

HXB2 Location Nef (73–82)
Author Location Nef
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords HIV exposed persistently seronegative (HEPS)
References Koning *et al.* 2004

CTL CD8+

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A*11, A*31 and Cw*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
- 3/5 HLA A3+ infection-resistant men, compared to 1/3 pre-seroconversion men who went on to become infected, reacted to this epitope.

HXB2 Location Nef (73–82)
Author Location Nef (71–80)
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong T-helper cell responses. Only patients starting with moderately high viral load (VL) were able to reduce the VL set point. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up.
- 9/14 patients recognized this epitope, it was the most recognized of six A*03 epitopes.

HXB2 Location Nef (73–82)
Author Location (B consensus)
Epitope QVPLRPMTYK
Epitope name QK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A03, B14, B60, Cw3, Cw7; A01, A03, B08, B14, Cw7, Cw8
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 2/9 individuals recognized this epitope, presented by HLA-A3.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A2, A3, B44, B7
Country United States
Assay type Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, escape, variant cross-recognition or cross-neutralization
References Casazza *et al.* 2005

- Evidence of continued viral evolution during HAART therapy despite low viral load was found in 1/5 patients studied.
- The epitope QVPLRPMTYK was invariant (18/18 sequences) prior to therapy in the patient that recognized it.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A*0301, A*7401, B*1510, B*3501, Cw*0401; A*0301, A*68, B*0702, B*1510, Cw*0401, Cw*0702
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, acute/early infection
References Pillay *et al.* 2005

- HIV-specific CTLs in infants were shown to be able to select for viral escape variants early in life, despite a lack of escape with the same CTL specificity in the mother. Infant CTL responses may be compromised by transmission of escape variants that arose in the mother and also those that arose in the father, if the father was the source of the mother's infection.
- QVPLRPMTYK is the C subtype consensus form of an epitope recognized in a mother, who carried this autologous variant: QVPLRPMTfK. QVPLRPMTfK was the dominant form in her infant at 2 weeks of age, but new variants rapidly emerged: QVPLkPMTfK, QVPLRPMnYK, QVPvRPMTfK, QVPLRPMsYr, QVPLRPMsYK.

HXB2 Location Nef (73–82)
Author Location Nef
Epitope QVPLRPMTYK
Epitope name A3-QK10(Nef)
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.

- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRRMTYK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A*0101, A*0301, B*0801
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimates of escape rate for this epitope, QVPLRRMTYK, were found to be 0.022 and 0.003/day (upper bound on rate of escape = 0.05 and 0.011), with SEs of 0.013 and 0.003 respectively, in 2 subjects.
- In the first subject, a number of mutations arose in Nef 73-82; all but one of these (V74A) elicited a very weak ELISpot response compared to the wild type. In the second subject, large epitope deletions and a V74I substitution in the recognized epitope were selected for.

HXB2 Location Nef (73–82)
Author Location
Epitope QVPLRPMTYK
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location Nef (73–82)
Author Location Nef (73–82 LAI)
Epitope QVPLRPMTYK
Epitope name N1
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3 supertype)
Keywords HAART, ART, supertype
References Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNgamma production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

HXB2 Location Nef (73–82)
Author Location Nef (94–103)
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human (A3 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A*0301, A*1101, A*3101, A*3301 and A*6801).

HXB2 Location Nef (73–82)
Author Location Nef (73–82 BRU)
Epitope QVPLRPMTYK
Subtype B, CRF02_AG
Immunogen HIV-1 infection

CTL CD8+

Species (MHC) human (A11, A3)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 0/9 CRF02_AG-infected Ivorians, and 2/9 B-infected French subjects.
- 3/8 Ivorians carried a substitution in this epitope, while only 1/5 B clade infected French people did, QVPvRPMTYK, and the substitution was found in one of the people that recognized the peptide.

HXB2 Location Nef (73–82)
Author Location Nef
Epitope `QVPLRPMTYK`
Epitope name QK10(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11, A3)
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- HLA-A3- and -A11-restricted epitope QVPLRPMTYK elicited an immune response in Chinese HIV-1 positive subjects as part of peptides EVGFPVRPQVPLRPMTYK and QVPLRPMTYKGALDLSHF.
- 1 of the 3 HLA-A3 carriers responded to a QVPLRPMTYK-containing peptide with average magnitude of CTL response of 230 SFC/million PBMC (author communication and Fig.1). 13 of the 28 HLA-A11 carriers responded to QVPLRPMTYK-containing peptide EVGFPVRPQVPLRPMTYK with average magnitude of CTL response of 263 SFC/million PBMC; and 5 of the 28 HLA-A11 carriers responded to QVPLRPMTYK-containing peptide QVPLRPMTYKGALDLSHF with average magnitude of CTL response of 133 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope `QVPLRPMTYK`
Immunogen peptide-HLA interaction
Species (MHC) (A11, A3, A30)
Assay type HLA binding
Keywords binding affinity, immunodominance
References Racape *et al.* 2006

- Interaction between purified HLA-A3 molecules and several dominant CD8 epitopes was characterized. Amplitude, stability, and kinetic parameters of the interaction between HLA-A3, peptides, and anti-HLA mAbs were tested.
- Epitopes tested bound strongly to HLA-A3 and formed very stable complexes.
- Gag epitope RLRPGGKKK and Nef epitope RLAFHHVAR complexes with HLA-A3 were not recognized by the A11.1 mAb specific to HLA-A3 alleles. The proposed explanation was that Arg at position P1 of the peptide may push the α2 helix residue and affect mAb recognition.

HXB2 Location Nef (73–82)
Author Location Nef (73–82 BRU)
Epitope `QVPLRPMTYK`
Immunogen HIV-1 infection
Species (MHC) human (A11, A3, B35)
References Culmann *et al.* 1991

- Nef CTL clones from HIV+ donors.

HXB2 Location Nef (73–82)
Author Location Nef (73–82 LAI)
Epitope `QVPLRPMTYK`
Subtype B
Immunogen
Species (MHC) human (B27)
References Culmann 1998

- Optimal epitope mapped by peptide titration.

HXB2 Location Nef (73–82)
Author Location Nef (73–82 LAI)
Epitope `SVPLRPMTYK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35, Cw4)
References Buseyne *et al.* 1993a

- Vertical transmission of HIV ranges from 13% to 39%.
- Primary assays showed that cytotoxic activity against at least one HIV protein was detected in 70% of infected children.
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
- Patient EM13, who had a CTL response to three epitopes in Nef, was infected via blood transfusion after birth and went from CDC stage P2A to P2E during the study.

HXB2 Location Nef (73–82)
Author Location
Epitope `QVPLRPMTYK`
Epitope name QK10
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country United States
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords immunodominance, acute/early infection, characterizing CD8+ T cells, immune dysfunction
References Lichterfeld *et al.* 2004a

- HIV-1 specific CD8+ T-cells in acute and long-term nonprogressive HIV-1 infection show strong ex-vivo proliferative capacities which are rapidly lost in chronic HIV-1 infection. The loss of CD8+ T-cell function is closely linked with the loss of HIV-1 specific, IL2 secreting CD4+ T-cells. The function can be rescued in vitro and in vivo by restoring the specific CD4+ T-cell help.
- Full CD8+ T-cell responses to this epitope were dependent on co-stimulation with a CD4+ T cell dependent epitope from T-cells harvested during acute infection. The CD8+ T-cell response to this epitope was immunodominant in one study individual.

HXB2 Location Nef (73–82)
Author Location Nef (73–82)
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human
References Garcia *et al.* 1997

- The anti-Nef CTL line P1 specific for this epitope is able to kill target cells via two mechanisms.
- First: Ca^{2+}-dependent, perforin-dependent Nef-specific lysis.
- Second: Ca^{2+}-independent, CD95-dependent apoptosis that could also kill non-specific targets.
- Findings indicate that the two mechanisms are not mutually exclusive in human CTL, as they are in mice.
- CTL mediated CD95-dependent apoptosis may play a role in pathogenesis.

HXB2 Location Nef (73–82)
Author Location
Epitope QVPLRPMTYK
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords binding affinity, acute/early infection
References Lichterfeld *et al.* 2007b

- Differences in early versus chronic AIDS include a decline in CTL number accompanied by a reducing viremia. Comparative analysis of such CTLs in this study show that early infection is characterized by a different clonotypic composition and higher functional avidity of CTLs followed by their selective depletion during transition to chronic disease. The total magnitude of CTL cytokine production is lower in early infection. Intraindividual, early CTLs' functional avidity for the same epitope decreases concomitantly with a reduction in clonotypic TCR repertoire especially of strongly activated and CD127lo, CD38+, Ki-67hi CTLs while progressing to chronic infection states.
- None of the target epitopes, including this epitope QVPLRPMTYK seen in 1 patient, underwent sequence changes.

HXB2 Location Nef (73–83)
Author Location Nef (73–82 BRU)
Epitope QVPLRPMTYKA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- QVPLRPMTYKA was recognized in 9/15 (60%) of individuals with HLA A3. It was a high affinity HLA-A3 binder.

HXB2 Location Nef (73–87)
Author Location Nef
Epitope QVPLRPMTYKAAVDL
Epitope name nef-5157
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A1, A19, B*3501, B44, Cw16, Cw7; A*0201, A19, B14, B44, Cw16, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
References Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, QVPLRPMTYKAAVDL was mutated in the daughter D2 isolate to QVPLRPMTfKAAVDL.

HXB2 Location Nef (73–90)
Author Location Nef
Epitope QVPLRPMTYKAAVDLSHF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States

CTL CD8+

Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, QVPLRPMTYKAAVDLSHF, had an overall frequency of recognition of 34% - 40.7% AA, 38.5% C, 29.5% H, 19% WI. This peptide is included in a 58 aa Nef highly reactive region to be used for vaccine design. It is also part of 'Region I', EVGFPVRPQVPLRPMTYKAAVDLSHFLKEKGGLEGLIYSQK, a 41 aa region recognized by >90% of subjects across ethnic groups.

HXB2 Location Nef (74–81)
Author Location Nef (74–82)
Epitope `VPLRPMTY`
Immunogen
Species (MHC) human (A3)
References Carreno *et al.* 1992

- Included in HLA-A3 binding peptide competition study.

HXB2 Location Nef (74–81)
Author Location Nef (75–85)
Epitope `VPLRPMTY`
Epitope name VY8
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Country Japan
Assay type Cytokine production, Tetramer binding, Intracellular cytokine staining, CTL suppression of replication, Other, HLA binding
Keywords class I down-regulation by Nef
References Ueno *et al.* 2008

- The balance between Nef selective pressures to modulate HLA I or its escape mutations reducing Nef HLA I down-regulating activity is studied.
- Epitope VY8, VPLRPMTY, does not share CTL with RY11, RPQVPLRPMTY, but is a different optimal epitope. VY8 shows more functional avidity and cytolytic activity than RY11. No subject showed an immune response to both epitopes simultaneously.

HXB2 Location Nef (74–81)
Author Location Nef (74–81)
Epitope `VPLRPMTY`
Epitope name VY8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*35-associated substitution within optimally defined epitope VPLRPMTY is at position Y8, VPLRPMTy.

HXB2 Location Nef (74–81)
Author Location Nef (73–82 LAI)
Epitope `VPLRPMTY`
Subtype B
Immunogen HIV-1 or HIV-2 infection
Species (MHC) human (B*3501)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*3501 epitope.

HXB2 Location Nef (74–81)
Author Location Nef (75–82)
Epitope `VPLRPMTY`
Immunogen peptide-HLA interaction
Species (MHC) human (B*3501)
References Smith *et al.* 1996

- Crystal structure of VPLRPMTY-class I B allele HLA-B*3501 complex.

HXB2 Location Nef (74–81)
Author Location Nef
Epitope `VPLRPMTY`
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Keywords dendritic cells
References Ostrowski *et al.* 2000

- The role of CD4+ T-cell help in expansion of virus-specific memory CTL was studied through co-culture *ex vivo*
- Optimal expansion of HIV-1-specific memory CTL depended on CD4+ T cell help in 9 of 10 patients – CD40 ligand trimer (CD40LT) could enhance CTL in the absence of CD4+ T cell help to a variable degree in most of patients.
- Those CTL that didn't respond to CD40LT could expand with IL2 present, and IL15 produced by dendritic cells also contributes.
- The T-helper epitope used for CD4+ T cell stimulation was the universal tetanus helper epitope TET830-843 (QYIKANSKFIGITE)

HXB2 Location Nef (74–81)
Author Location Nef (74–81)
Epitope VPLRPMTY
Epitope name VY8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Donor MHC A*0201, A*0301, B*3501, B*51, Cw*04, Cw*06
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords escape, acute/early infection
References Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- Point mutation of epitope at position 8 (Y to F,VPLRPMTf) was detected at a chronic infection timepoint. The CTL response was strong in early infection, but diminished by month 13. This mutation had reduced avidity.

HXB2 Location Nef (74–81)
Author Location Nef (subtype B)
Epitope VPLRPMTY
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B35)
References Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T cell epitopes: DTVLEDINL (3 individuals), SLYNTVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

HXB2 Location Nef (74–81)
Author Location Nef
Epitope VPLRPMTY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords acute/early infection
References Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B2705; and A*0201, A*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK.
- The subject with A*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705.
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

HXB2 Location Nef (74–81)
Author Location Nef (73–82 LAI)
Epitope VPLRPMTY
Subtype B
Immunogen HIV-1 or HIV-2 infection
Species (MHC) human (B35)
Keywords review
References Culmann *et al.* 1991; McMichael & Walker 1994

- Review of HIV CTL epitopes – defined by B35 motif found within a larger peptide.

HXB2 Location Nef (74–81)
Author Location Nef (75–82 LAI)
Epitope VPLRPMTY
Subtype B, HIV-2
Immunogen HIV-1 or HIV-2 infection
Species (MHC) human (B35)
Country Gambia
Keywords HIV exposed persistently seronegative (HEPS), HIV-2
References Rowland-Jones *et al.* 1995

- VPLRPMTY was recognized by CTL from HIV-1-infected and HIV-2-infected B35+ subjects; epitope is conserved between HIV-1 and HIV-2.

HXB2 Location Nef (74–81)
Author Location Nef
Epitope VPLRPMTY
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B35)

CTL CD8+

Keywords subtype comparisons, HIV exposed persistently seronegative (HEPS)
References Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A and D subtype consensus are identical to the B clade epitope.

HXB2 Location Nef (74–81)
Author Location Nef (75–82)
Epitope VPLRPMTY
Immunogen in vitro stimulation or selection
Species (MHC) human (B35)
References Lalvani *et al.* 1997

- A peptide-based protocol was optimized for restimulation of CTLp using optimized peptide and IL-7 concentrations – importantly this protocol does not stimulate a primary response, only secondary – peptide-specific CTLp counts could be obtained via staining with peptide-Class I tetramers.
- This peptide was one of the B35 presented test peptides used in control experiments showing that the assay gave no activity using lymphocytes from 21 healthy B35 seronegative donors.

HXB2 Location Nef (74–81)
Author Location Nef (subtype B)
Epitope VPLRPMTY
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B35)
Keywords subtype comparisons
References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among A, B, and D clade viruses.

HXB2 Location Nef (74–81)
Author Location Nef
Epitope VPLRPMTY
Immunogen
Species (MHC) human (B35)
References Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive,
- HIV-2 version of this epitope is conserved: VPLRPMTY, and CTLs are cross-reactive – one of five B35 CTL epitopes that are cross-reactive, see also Rowland-Jones *et al.* [1995]

HXB2 Location Nef (74–81)
Author Location Nef (74–81)
Epitope VPLRPMTY
Epitope name VPL
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords HAART, ART, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- One of two HLA B35+ among the eight study subjects recognized this epitope.
- Patient SC15 (HLA A1/68, B8/35, Bw4/6, Cw4/0704) was given acute and sustained therapy and recognized epitopes PPIPVGDIY and VPLRPMTY during 331 days of HAART treatment.

HXB2 Location Nef (74–81)
Author Location Nef (75–82)
Epitope VPLRPMTY
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B35)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Subject ML 857 shifted from a A*6802 DTVLEDINL and B35 (H/N)PDIVIYQY response prior to seroconversion to a B35 PPIPVGDIY and B35 VPLRPMTY response post-seroconversion.

HXB2 Location Nef (74–81)
Author Location
Epitope VPLRPMTY
Epitope name Nef-VY8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B35, 12/22 (55%) recognized this epitope.

- Among HIV+ individuals who carried HLA B*5301, 0/11 (0%) recognized this epitope.

HXB2 Location Nef (74–81)
Author Location Nef (74–81 BRU)
Epitope VPLRPMTY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- VPLRPMTY was recognized in 5/16 (31%) of individuals with HLA B35, and it was a moderate affinity HLA binder. Cleavage at the C-term Y was frequent *in vitro*.

HXB2 Location Nef (74–81)
Author Location
Epitope VPLRPMTY
Subtype A, B, D
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human, macaque (B35)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location Nef (74–81)
Author Location Nef (74–81)
Epitope VPLRPMTY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC A1, A3, B35, B8
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, early treatment
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. SubjectBroadcast message from root Thu May 27 21:34:36 2004...n of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma vBattery Low Notification from APM BIOS (8% 0:12)or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

HXB2 Location Nef (74–81)
Author Location Nef (72–79)
Epitope VPLRPMTY
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 9 patients recognized this epitope.

HXB2 Location Nef (74–81)
Author Location Nef (C consensus)
Epitope VPLRPMTY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Kiepiela *et al.* 2004

CTL CD8+

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- People who carried B35 carried a variant of this epitope, while people who did not almost always carried the consensus form.

HXB2 Location Nef (74–81)
Author Location Nef (72–79)
Epitope VPLRPMTY
Epitope name VPL
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC A2, A68.1, B*07, B*3503, Cw*0401, Cw*0702, DQ2, DQ6, DR15, DR17, DR51, DR52
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, escape
References Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses,and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relatively efficiency of the variant eptiopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- VPL epitope was one of six that were largely or completely replaced by escape variants, with the two escape forms coming up between days 172 and 635, vplrpmSy and vplrmptF.

HXB2 Location Nef (74–81)
Author Location Nef
Epitope VPLRPMTY
Epitope name B35-VY8(Nef)
Immunogen HIV-1 infection
Species (MHC) human (B35)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (74–81)
Author Location Nef (74–81)
Epitope VPLRPMTY
Epitope name VY8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, acute/early infection, immune evasion
References Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- 2 PTE-B peptides, IPLRPMTYKgAlDLS and VPLRPMTYrAArDLS contained the epitope VPLRPMTY (VY8) and elicited IFN-gamma immune responses.
- HLA-B35 restriction for VY8 was presumed based on the subject's having the HLA allele and publication in the Los Alamos database.

HXB2 Location Nef (74–81)
Author Location Nef
Epitope VPLRPMTY
Epitope name VY8(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B35-restricted epitope VPLRPMTY elicited an immune response in Chinese HIV-1 positive subjects as part of peptides EVGFPVRPQVPLRPMTYK and QVPLRPMTYKGALDLSHF.

- 9 of the 12 HLA-B35 carriers responded to VPLRPMTY-containing peptide EVGFPVRPQVPLRPMTYK with average magnitude of CTL response of >654 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Nef (74–81)
Author Location
Epitope VPLRPMTY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B35, B42)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- VPLRPMTY is a known HLA-B35 and -B42-restricted epitope that is part of peptide EVGFPVRPQVPLRPMTYKA which elicited responses in 3/9 patients.

HXB2 Location Nef (74–81)
Author Location Nef
Epitope VPLRPMTY
Immunogen HIV-1 infection
Species (MHC) human
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons, cross-presentation by different HLA, variant cross-recognition or cross-neutralization
References Currier *et al.* 2006

- The pattern of immunodominance and epitope clustering within Gag and Nef proteins in subtype A infected individuals was similar to that seen in subtype B and C infections. An immunodominant HLA-C restricted epitope, YVDRFFKTL (YL9 from Gag protein) was observed and restricted to Cw0304.
- The sequence fpvrpqVPLRPMTYk is associated with HLA-B*4201/02 and HLA-B*5301 and contains the epitope VPLRPMTY that has previously published restriction to HLA-B*3501.

HXB2 Location Nef (74–82)
Author Location Nef (73–82)
Epitope VPLRPMTYK
Immunogen peptide-HLA interaction
Species (MHC) human (A11)
References Zhang *et al.* 1993

- Exploration of A11 binding motif.

HXB2 Location Nef (74–83)
Author Location Nef
Epitope VPLRPMTYKA
Epitope name Nef1163
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Epitope VPLRPMTYKA elicits IFN-gamma ELISpot responses in 4/7 subjects; and bound HLA-B7 with high affinity in cell-based assays. The authors claim previously published HLA restrictions of this epitope include B61 and a questionable B60 (LANL database).

HXB2 Location Nef (74–88)
Author Location Nef (74–88)
Epitope IPLRPMTYKGALDLS
Epitope name FL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7 supertype)
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This epitope, IPLRPMTYKgAlDLS, varies from the consensus peptide at positions 10 and 12.

HXB2 Location Nef (75–82)
Author Location Nef (75–82 LAI)
Epitope PLRPMTYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Keywords review
References McMichael & Walker 1994

- Review of HIV CTL epitopes.
- C. Brander notes that this is an A*1101 epitope in the 1999 database.

CTL CD8+

HXB2 Location Nef (75–82)
Author Location Nef (75–82 LAI)
Epitope PLRPMTYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*1101 epitope.

HXB2 Location Nef (75–82)
Author Location Nef
Epitope PLRPMTYK
Epitope name PK8(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A11-restricted epitope PLRPMTYK elicited an immune response in Chinese HIV-1 positive subjects as part of peptide QVPLRPMTYKGALDLSHF.
- 5 of the 28 HLA-A11 carriers responded to a PLRPMTYK-containing peptide QVPLRPMTYKGALDLSHF with average magnitude of CTL response of 133 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Nef (75–82)
Author Location
Epitope PLRPMYTK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- PLRPMYTK is a known HLA-A11-restricted epitope that is part of peptide EVGFPVRPQVPLRPMTYKA which elicited responses in 3/9 patients.

HXB2 Location Nef (77–85)
Author Location Nef (77–85)
Epitope RPMTYKAAL
Epitope name RL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*07)
Country Australia, Canada, Germany, United States
Keywords escape, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*07-associated substitutions within optimally defined epitope RPMTYKAAL are at positions T4, Y5 and L9, RPMtyKAAl. RL9 has very low recognition frequency and escape.

HXB2 Location Nef (77–85)
Author Location Nef (77–85 LAI)
Epitope RPMTYKAAL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Keywords escape
References Bauer *et al.* 1997

- Structural constraints on the Nef protein may prevent escape.
- Noted in Brander 1999, this database, to be B*0702.

HXB2 Location Nef (77–85)
Author Location Nef (77–85 LAI)
Epitope RPMTYKAAL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*0702 epitope.

HXB2 Location Nef (77–85)
Author Location Nef (75–83 IIIB)
Epitope RPMTYKAAL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords binding affinity, TCR usage
References Oxenius *et al.* 2001b

- Study of tetramer staining of B7 around RPMTYKAAL gave quantitative results that were very different than functional measurements based on an ELISPOT assay.

- Autologous clones were checked and 39/40 clones from two time points had the variant sequence RPMTYKGAL – tetramers based on RPMTYKGAL gave a more intense and uniform staining and bound with higher affinity to the RPMTYKGAL Vβ14 TCR.

HXB2 Location Nef (77–85)
Author Location Nef (77–85 SF2)
Epitope RPMTYKAAL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 1/4 group 1, 0/3 group 2, and 1/1 group 3.

HXB2 Location Nef (77–85)
Author Location Nef (77–85)
Epitope RPMTYKAAL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes.
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

HXB2 Location Nef (77–85)
Author Location Nef (77–85)
Epitope RPMTYKAAV
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
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- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

HXB2 Location Nef (77–85)
Author Location Nef (77–85 BRU)
Epitope RPMTYKAAV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- RPMTYKAAV was recognized in 7/10 (70%) of individuals with HLA B7, and 0/3 (0%) of individuals with HLA B35. It was a moderate affinity HLA binder.

HXB2 Location Nef (77–85)
Author Location Nef (77–85)
Epitope RPMTYKAAL
Epitope name B7-RL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.

CTL CD8+

- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 3/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 2/4 individuals had detectable responses to this epitope after STI.

HXB2 Location Nef (77–85)
Author Location Nef (77–85)
Epitope RPMTYKAAV
Epitope name B7-RV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 2/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 3/4 individuals had detectable responses to this epitope after STI.

HXB2 Location Nef (77–85)
Author Location Nef (75–83)
Epitope RPMTYKAAL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 3/7 patients recognized this epitope.

HXB2 Location Nef (77–85)
Author Location Nef (75–83)
Epitope RPMTYKGAL
Epitope name RPM
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A2, A68.1, B*07, B*3503, Cw*0401, Cw*0702, DQ2, DQ6, DR15, DR17, DR51, DR52
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, CD4 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, escape
References Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses,and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relatively efficiency of the variant eptiopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- This epitope was one of six epitopes found to be under positive selection for escape mutations and was completely replaced by escape variants between days 172 and 635 (rpmtFkgal, rpmSykAal, rpmtykgaV, rpmtykAal). The first two were the most common at day 635, and experimentally shown to be escape.

HXB2 Location Nef (77–85)
Author Location Nef
Epitope RPMTYKGAL
Epitope name RL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 4, RPMnYKGAL, was found not to correspond to the most polymorphic residue in the epitope.

HXB2 Location Nef (77–85)
Author Location Nef (77–85 BRU)
Epitope RPMTYKAAV
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons

References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 0/9 CRF02_AG-infected Ivorians, and 2/9 B-infected French subjects.
- One of the B-clade infected subjects that recognized this peptide was not sequenced, the other had one amino acid change: RPMTYKAAl. A variant form was in 3/5 B clade infection sequences. 8/8 CRF01 infected individuals had a variant of this peptide.

HXB2 Location Nef (77–85)
Author Location Nef (77–85)
Epitope RPMTYKAAL
Epitope name RW9
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A*24, A*30, B*07, B*39, Cw*12, Cw*17
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, characterizing CD8+ T cells, viral fitness and reversion
References Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- The variant RPMThqAAw was present in 10/10 clones from a B7- mother, was transmitted to her B7+ infant,and present in 29/30 clones at months 2, 6, and 152.

HXB2 Location Nef (77–85)
Author Location Nef
Epitope RPMTYKAAV
Epitope name RV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords superinfection
References Streeck *et al.* 2008b

- Loss of viral replication control by an elite controller after superinfection was found to coincide with rapid recombination events in 2, ∼50 residue regions of Gag and Env that include immunodominant epitopes KK10 (KRWIILGLNK) and CL9 (CAPAGFAIL). Viral escape was seen at both epitopes and consequent CTL responses against the epitope-variants.
- CTL responses to previously described, HLA-B7-restricted RPMTYKAAV were seen post-superinfection and -recombination.

HXB2 Location Nef (77–85)
Author Location Nef
Epitope RPMTYKAAL
Epitope name RL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords superinfection
References Streeck *et al.* 2008b

- Loss of viral replication control by an elite controller after superinfection was found to coincide with rapid recombination events in 2, ∼50 residue regions of Gag and Env that include immunodominant epitopes KK10 (KRWIILGLNK) and CL9 (CAPAGFAIL). Viral escape was seen at both epitopes and consequent CTL responses against the epitope-variants.
- CTL responses to previously described, HLA-B7-restricted RPMTYKAAL were seen post-superinfection and -recombination.

HXB2 Location Nef (77–85)
Author Location Nef (75–83)
Epitope RPMTYKAAL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Switzerland
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords HAART, ART
References Rehr *et al.* 2008

- By following T-cell function in ART-regimented patients over time, it was shown that ART resulted in reduced viral replication and the restoration of CTLs to polyfunctionality. It is concluded that in vivo antigenic exposure during declining viremia has a positive influence on CTL function.
- Epitope RPMTYKAAL was used to interrogate CTL function in 37 chronically infected HIV-1 positive subjects, with respect to cytokine production.

HXB2 Location Nef (77–85)
Author Location Nef
Epitope RPMTYKGAL
Epitope name RL9(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

CTL CD8+

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined HLA-B7-restricted epitope RPMTYKGAL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide QVPLRPMTYKGALDLSHF. This epitope differs from the previously described HLA-B7-restricted epitopes RPMTYKAAL and RPMTYKAAV, at 1 or 2 residues, RPMTYKgAL and RPMTYKgAl.

HXB2 Location Nef (77–85)
Author Location Nef
Epitope `RPMTYKAAV`
Epitope name RL9(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B7-restricted epitope RPMTYKAAV elicited an immune response in Chinese HIV-1 positive subjects as part of peptide QVPLRPMTYKGALDLSHF.

HXB2 Location Nef (77–85)
Author Location Nef (77–85)
Epitope `RPMTYKGAL`
Epitope name RL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, acute/early infection, immune evasion
References Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- 2 PTE-B peptide sequences were identified, IPLRPMTYKgAlDLS and VPLRPMTYrAArDLS, containing variants of this consensus epitope sequence RL9, viz. RPMTYKgAL and RPMTYrAAr, both of which elicited IFN-gamma immune responses.
- RL9 restriction to HLA-B7 supertype was inferred based on the subject's known HLA type and published MHC Class I restricted CTL epitopes.

HXB2 Location Nef (77–85)
Author Location Nef (79–85)
Epitope `RPMTYKAAV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A3, A33, B14, B35, Cw*0401, Cw*0802
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, early treatment
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

HXB2 Location Nef (77–91)
Author Location Nef (77–91)
Epitope `RPMTYKAALDLSHFL`
Epitope name AL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62)
Donor MHC A23, B62
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, RPMTYKAAlDLSHFL, varies at position 9 from the consensus peptide RPMTYKAAVDLSHFL.

HXB2 Location Nef (77–91)
Author Location Nef (77–91)
Epitope `RPMTYKGAVDLSHFL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62)
Donor MHC A23, B62
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, RPMTYKgAVDLSHFL varies at position 7 (glycine) from the consensus peptide YKAAVDLSHFLKEKG.

HXB2 Location Nef (77–91)
Author Location Nef (77–91)
Epitope `RPMTYKGAFDLSFFL`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location Nef (77–91)
Author Location Nef
Epitope `RPMTYKAAVDLSHFL`
Epitope name nef-5158
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A1, A19, B*3501, B44, Cw16, Cw7; A*0201, A19, B14, B44, Cw16, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
References Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than interperson sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, RPMTYKAAVDLSHFL was mutated in the daughter D2 isolate to RPMTfKAAVDLSHFL.

HXB2 Location Nef (78–92)
Author Location Nef (78–92)
Epitope `PMTYKAAVDLSHFLK`
Epitope name AK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A24, A3, B7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.

CTL CD8+

- This epitope, PMTYKAAVDLSHFLK, has identity with the consensus peptide YKAAVDLSHFLKEKG from positions 81-92.

HXB2 Location Nef (78–92)
Author Location Nef (78–92)
Epitope PMTYKAAVDLSHFLK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62)
Donor MHC A23, B62
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, PMTYKAAVDLSHFLK has identity with the consensus peptide YKAAVDLSHFLKEKG from positions 81-92.

HXB2 Location Nef (78–92)
Author Location Nef (78–92)
Epitope PMTYKGAFDLSHFLK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62)
Donor MHC A23, B62
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, PMTYKgAfDLSHFLK, varies at positions 6 and 8 from the consensus peptide YKAAVDLSHFLKEKG.

HXB2 Location Nef (79–87)
Author Location Nef (81–89 HXB3)
Epitope MTYKAALDL
Immunogen vaccine
Vector/Type: DNA, peptide *Strain:* B clade HXB3 *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (A*0201)
Keywords binding affinity, computational epitope prediction
References Sandberg *et al.* 2000

- Ten Nef 9-mer peptides were predicted to have a strong binding affinity with HLA-A*0201 – of these, four did bind strongly by a T2 class I stabilization assay, several others bound weakly.
- A CTL immune response to only 3/10 peptides was detected by a 51Cr-release assay after immunization of HLA-A201 transgenic mice with either nef DNA under the control of a CMV promotor coated on, gold particles delivered to abdominal skin by gene gun.
- MTYKAALDL bound weakly to HLA-A2, but the DNA nef vaccine elicited a good CTL response.

HXB2 Location Nef (79–87)
Author Location Nef (79–87)
Epitope MTYKAALDL
Epitope name Nef79-87
Immunogen HIV-1 infection
Species (MHC) human, humanized mouse (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, immunodominance, characterizing CD8+ T cells
References Chandwani *et al.* 2004

- Responses to five HLA-A2 presented epitopes in Nef were characterized in a population of 19 HIV infected adults and 21 children. The CD8 T-cell response to Nef was stronger and broader in adults than children, averaging 652 and 87 SFCs/10^6 PBMC, and 2.6 and 0.9 recognized epitopes per person, respectively.
- This is one of three novel Nef epitopes previously identified in HLA-A2 transgenic mice, shown to induce CD8 T-cell response in humans. It was not the immunodominant response.

HXB2 Location Nef (79–87)
Author Location Nef
Epitope MTYKAAVDL
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B63)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, cross-presentation by different HLA
References Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.

- This is a putative HLA-B63/57/58 epitope containing the B58 supertype binding motif. There is no evidence for B57/B58 cross-presentation of this epitope.

HXB2 Location Nef (79–93)
Author Location Nef
Epitope MTYKGAFDLSHFLKE
Subtype A, D
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*6601, A*6801, B*5301, B*5802; A*0202, A*3002, B*5703, B*5802
Country Uganda
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, characterizing CD8+ T cells
References Barugahare *et al.* 2005

- T-cell immune responses were examined in HIV-1 infected Ugandans. Similar levels of cross-clade responses for Gag, Env and Nef were observed. Higher frequencies of responses in conserved regions were found for Gag within a single clade, while areas with higher viral sequence variation had fewer detectable responses. Differential interclade sequence homologies between the Gag regions did not affect the respective level of cross-clade recognition.
- Novel unmapped epitope, this test peptide was conserved in the people that recognized it.

HXB2 Location Nef (80–87)
Author Location Nef (80–87)
Epitope TYKAAVDL
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (A24)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

HXB2 Location Nef (80–87)
Author Location Nef (80–87 BRU)
Epitope TYKAAVDL
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (A24)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 1/9 CRF02_AG-infected Ivorians, and 0/9 B-infected French subjects.
- This epitope was highly variable in Ivorians; 8/9 had amino acid substitutions. The only one that reacted carried the sequence TYKgAfDL. 3/5 of the B clade French subjects carried variants, which tended to have only 1 amino acid substitution.

HXB2 Location Nef (80–94)
Author Location Nef (80–94 HXB2)
Epitope TYKAAVDLSHFLKEK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 47% of the study subjects, and it was the most frequently recognized peptide.

HXB2 Location Nef (81–91)
Author Location Nef (81–91)
Epitope YKGALDLSHFL
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008

- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.
- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.
- CTL immune response to consensus sequence YKGALDLSHFL was elicited in subject 00015. Consensus epitope of both subjects was YKGAvDLSHFL.

HXB2 Location Nef (81–95)
Author Location Nef (81–95)
Epitope `YKAAVDLSHFLKEKG`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the ES. Both the ES and the Progressor had A83G, V85L substitutions.

HXB2 Location Nef (81–97)
Author Location Nef
Epitope `YKGALDLSHFLKEKGGL`
Epitope name NEF-12
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, yKGAlDLShFLKEKGGL differs from the consensus C sequence fKGAfDLSfFLKEKGGL at 3 amino acid positions, i.e. by 17.6%.

HXB2 Location Nef (81–97)
Author Location Nef
Epitope `YKAAVDLSHFLKEKGGL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, YKAAVDLSHFLKEKGGL, had an overall frequency of recognition of 30% - 33.9% AA, 30.8% C, 31.8% H,

14.3% WI. This peptide is included in a 58 aa Nef highly reactive region to be used for vaccine design. It is also part of 'Region I', EVGFPVRPQVPLRPMTYKAAVDLSH-FLKEKGGLEGLIYSQK, a 41 aa region recognized by >90% of subjects across ethnic groups.

HXB2 Location Nef (82–90)
Author Location (C consensus)
Epitope KGAFDLSFF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location Nef (82–90)
Author Location Nef (82–90)
Epitope KAAVDLSHF
Epitope name KF9
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*57, B*5801)
Country Australia
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords subtype comparisons, computational epitope prediction, mother-to-infant transmission, escape, viral fitness and reversion, optimal epitope
References Leslie *et al.* 2005

- KAAVDLSHF is the susceptible optimal form of the epitope, and KgAVDLSHF an escape variant. The KgAVDLSHF form of the epitope was shown to be an escape mutation by virtue of an increased off-rate; however Elispot reactions to both forms are positive. The escape form was shown to be transmitted, and the most common form of the epitope in a B clade infected population in Perth, Australia (52%).

HXB2 Location Nef (82–90)
Author Location Nef
Epitope KAAFDLSFF
Epitope name KF9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*57, B*5801)
Country Botswana, Ethiopia, Tanzania, South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, HLA associated polymorphism
References Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore et al., Science 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- There are two variant forms of this B57/B5801 epitope at the second position KaAFDLSFF and KgAFDLSFF. Leslie et al., J Exp Med. 2005 201:891 suggest that the escape form KgAFDLSFF may have come to dominate the C clade lineage over time due to higher HLA B57/B5801 frequencies in southern Africa. Bhattacharya suggests lineage effects are also playing an important role in the observed amino acid frequencies, and note that the ratio of G/A has not change over time, and that the frequency of G/A in different epidemic populations does not correlate with HLA B57/B5801 allele frequency.

HXB2 Location Nef (82–90)
Author Location
Epitope KAAFDLSFF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5701, B*5801)
Donor MHC A*0301, A*2301, B*1503, B*5802, Cw*0210, Cw*0602
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- KAAFDLSFF is a known HLA-B5701 and -B5801-restricted epitope that is part of peptide RPMTYKAAFDLSFFLKEKG which elicited responses in 9/25 patients, and which belongs to peptide pool 3 that accounted for over 70% of Nef responses. Response to a peptide containing this epitope was detected in 1 rapid progressor at 12 weeks post-infection.

HXB2 Location Nef (82–90)
Author Location Nef
Epitope KAAFDLSFF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5801)

CTL CD8+

Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- KAAFDLSFF is a previously described HLA-B*5801-restricted epitope (part of Nef reacting peptide QVPLRPM-TYKaAFDLSFFLKE) that contains a B*5801-associated reversion at residue A (KaAFDLSFF).

HXB2 Location Nef (82–90)
Author Location Nef (82–90)
Epitope KGALDLSHF
Epitope name KF9
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Navis *et al.* 2008

- HLA-B57/5801 progressing and long term non-progressing HIV-1-infected individuals were compared to observe the reason for the difference in their clinical outcomes. LTNP non-progression to AIDS was associated with protective HLA-alleles B57/5801 and preserved CTL IFN-gamma response against the WT Nef epitope HW9. Progressing HIV-1 positive subjects expressed the inhibitory receptor PD-1 which reflects an exhausted CTL phenotype.
- Epitope KGALDLSHF had various potential escape variations in progressors - KGAfDLSHF, KGAhDLSHF, KaAhDf-SHF, KGAvDLSHF, KaAiDmSHF, KGAfDLSfF, KaAfDL-SHF, KaALDLSHF, raAvDLSHF and KGgvvdisF.
- Epitope KGALDLSHF variants in LTNPs were - KaALDL-SHF, saAvDLSHF, KGALnLSHF, KaAvDLSHF, KGAvDL-SHF, KaAfDLSHF and KaAmfLSHF.
- Nef KF9 is previously known to be restricted by HLA-B57/5801.

HXB2 Location Nef (82–90)
Author Location Nef (C consensus)
Epitope KAAFDLSFF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, viral fitness and reversion
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- People who carried B57 all carried a variant of this epitope, while about half of the people who did not carry B57 carried the susceptible form, suggesting there is not a high fitness cost and revision rate in this case.
- HLA-B57 was associated with a low viral load.

HXB2 Location Nef (82–90)
Author Location Nef (82–90)
Epitope KAAFDLSFF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A*3001, A*66, B*4201, B*5802, Cw*0602, Cw*1701; A*66, A*68, B*57, B*5802, Cw*0602, Cw*0701
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, acute/early infection
References Pillay *et al.* 2005

- HIV-specific CTLs in infants were shown to be able to select for viral escape variants early in life, despite a lack of escape with the same CTL specificity in the mother. Infant CTL responses may be compromised by transmission of escape variants that arose in the mother and also those that arose in the father, if the father was the source of the mother's infection.
- KAAFDLSFF is the C consensus form of the epitope; the autologous form in the mother was KAAFDLgFF, and this was transmitted to her infant. By 33 weeks a new dominant form of the epitope had emerged in the infant: gAAFDLgFF.

HXB2 Location Nef (82–90)
Author Location
Epitope KAAVDLSHF
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location Nef (82–91)
Author Location Nef (82–91)
Epitope KAALDLSHFL
Subtype B

Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (A2)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of 31 that the vaccinated volunteers responded to.
- A KAAvDLSHFL variant was cross-recognized after the last boost.

HXB2 Location Nef (82–91)
Author Location Nef (82–91 LAI)
Epitope KAAVDLSHFL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*0802)
Keywords HAART, ART
References Nixon *et al.* 1999

- A patient who made a mono-specific CTL response to this Nef specific epitope was given effective anti-retroviral therapy within 90 days of infection, reducing the antigenic stimulous.
- Within 7 days of therapy, his CTLp frequency dropped from 60 to 4 per million PBMC, as his viremia dropped.
- The patient went from having an activated effector population (detected by CTLp and clone specific RNA) to a non-activated quiescent population (detected by the CTL-clone specific DNA)

HXB2 Location Nef (82–91)
Author Location
Epitope KAAVDLSHFL
Immunogen HIV-1 infection
Species (MHC) human (Cw08)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope KAAVDLSHFL elicited a magnitude of response of 540 SFC with a functional avidity of 0.01nM.

HXB2 Location Nef (82–91)
Author Location
Epitope KAAVDLSHFL
Immunogen HIV-1 infection
Species (MHC) human (Cw08)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (Cw08), an additional HLA (Cw03) was statistically predicted to be associated with this epitope.

HXB2 Location Nef (82–91)
Author Location Nef (82–91 SF2)
Epitope KAAVDLSHFL
Immunogen HIV-1 infection
Species (MHC) human (Cw8)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-Cw8+ individuals that had a CTL response to this epitope broken down by group: 1/3 group 1, 0/0 group 2, and 0/1 group 3.

HXB2 Location Nef (82–91)
Author Location Nef (SF2)
Epitope KAAVDLSHFL
Immunogen HIV-1 infection
Species (MHC) human (Cw8)
References Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.

HXB2 Location Nef (82–91)

CTL CD8+

Author Location (B consensus)
Epitope KAAVDLSHFL
Epitope name KL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw8)
Donor MHC A25, A32, B08, B14, Cw7, Cw8
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location Nef (82–91)
Author Location Nef
Epitope KAAVDLSHFL
Epitope name KL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw8)
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 6, KAAVDmSHFL, was found not to correspond to the most polymorphic residue in the epitope.

HXB2 Location Nef (82–91)
Author Location
Epitope KAAVDLSHFL
Epitope name KL10
Immunogen
Species (MHC) human (Cw8)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a Cw08 epitope.

HXB2 Location Nef (82–96)
Author Location Nef (82–96)
Epitope KGAFDLSFFLKEKGG
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 8 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location Nef (82–101)
Author Location Nef (81–100 SF2)
Epitope KAAVDLSHFLKEKGGLEGLI
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- Three of these 11 had CTL response to this peptide.
- The responding subjects were HLA-A1, A2, B8, B14; HLA-A11, A24, B8, B53.

HXB2 Location Nef (82–101)
Author Location Nef (SF2)
Epitope KAAVDLSHFLKEKGGLEGLI
Immunogen HIV-1 infection
Species (MHC) human
References Altfeld *et al.* 2001a

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- Nef peptides PQVPLRRMTYKAAVDLSHFL, KAAVDLSHFLKEKGGLEGLI and EEEEVGFPVTPQVPLRPMTY were recognized and the first two share KAAVDLSHFL (a Cw8 epitope), the first and last share PQVPLRPMTY.

HXB2 Location Nef (83–90)
Author Location Nef (83–90 HXB2)
Epitope AAVDLSHF
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (B62)
Country Viet Nam
Assay type HLA binding
Keywords subtype comparisons, computational epitope prediction, escape, variant cross-recognition or cross-neutralization, vaccine antigen design
References Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- CRF01_AE variant GaFdlsFf had a higher HLA-B62 binding score than the HXB2 epitope.

HXB2 Location Nef (83–91)
Author Location Nef (83–91)
Epitope AAVDLSHFL
Epitope name AL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- The AL9 epitope AAVDLSHFL elicited a potent CTL response while its minor variant AAVDiSHFL containing substitution L87I at position 5 elicited a less intense response, resulting in the L87I variant later dominating the viral population. This is a novel viral adaptation to an HLA-A2 restricted immune response discovered in Nef epitope AL9. In later longitudinal studies, more variants were seen either linked - AAVDirHFL - or not linked with the L87I mutant. Two new mutants seen were the A83G at position 1, gAlDLSHFL and gArDLSHFL; and the V85L at position 3, AAlDLSHFL, AAlDiSHFL, AAlDiSHlL. Amino acid positions 83, 85, 97 and 91 were under positive selection pressure.
- Responses to AL9 were seen in early chronic infection.

HXB2 Location Nef (83–91)
Author Location Nef (85–93 HXB3)
Epitope AALDLSHFL
Immunogen vaccine
Vector/Type: DNA, peptide *Strain:* B clade HXB3 *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (A*0201)
Keywords binding affinity, computational epitope prediction
References Sandberg *et al.* 2000

- Ten Nef 9-mer peptides were predicted to have strong binding affinity for HLA-A*0201 – of these, four did bind strongly by a T2 class I stabilization assay, several others bound weakly.
- A CTL immune response to only 3/10 peptides was detected by a 51Cr-release assay after immunization of HLA-A201 transgenic mice with nef DNA under the control of a CMV promotor, coated on gold particles delivered to abdominal skin by gene gun.
- AALDLSHFL was predicted to have a strong binding capacity for HLA-A2, and did, but it was the only one of the peptides recognized that was a strong binder, the other two recognized peptides were weak binders.
- AALDLSHFL was also tested by subcutaneous injection of Nef peptides in Freund's adjuvant and gave a strong response to the peptide.

HXB2 Location Nef (83–91)
Author Location (C consensus)
Epitope GAFDLSFFL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0205)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- GAFDLSFFL is an optimal epitope.

HXB2 Location Nef (83–91)
Author Location Nef (83–91)
Epitope GAFDLSFFL
Epitope name GL9
Immunogen HIV-1 infection
Species (MHC) human (A*0205)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a A*0205 epitope.

HXB2 Location Nef (83–91)
Author Location Nef
Epitope GAFDLSFFL
Epitope name GL9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*0205)
Country South Africa
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization
Keywords rate of progression

CTL CD8+

References Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naive patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer A*0205 GL9 was used to test 11 patients and gave a median ex vivo tetramer frequency of 0.48.

HXB2 Location Nef (83–91)
Author Location
Epitope GAFDLSFFL?
Epitope name GL9
Immunogen HIV-1 infection
Species (MHC) human (A*0205)
Country United States, South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords memory cells
References Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

HXB2 Location Nef (83–91)
Author Location Nef (83–91)
Epitope GAFDLSFFL
Epitope name GL9
Immunogen HIV-1 infection
Species (MHC) human (A*0205)
Country South Africa
Assay type proliferation, Tetramer binding, Intracellular cytokine staining
References Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

HXB2 Location Nef (83–91)
Author Location Nef (83–91)
Epitope GAFDLSFFL
Epitope name GL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*03)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLAs-A*03-associated substitution within optimally defined epitope GAFDLSFFL is at position F3, GAfDLSFFL.

HXB2 Location Nef (83–91)
Author Location Nef (83–91 BRU)
Epitope AAVDLSHFL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- AAVDLSHFL was recognized in 3/18 (17%) of individuals with HLA A2. It was a low affinity HLA binder.

HXB2 Location Nef (83–91)
Author Location Nef (83–91)
Epitope AAVDLSHFL
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (A2)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of 31 that the vaccinated volunteers responded to.

HXB2 Location Nef (83–91)
Author Location Nef (83–91)
Epitope AALDLSHFL
Epitope name Nef83-91
Immunogen HIV-1 infection
Species (MHC) human, humanized mouse (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, immunodominance, characterizing CD8+ T cells
References Chandwani *et al.* 2004

- Responses to five HLA-A2 presented epitopes in Nef were characterized in a population of 19 HIV infected adults and 21 children. The CD8 T-cell response to Nef was stronger and broader in adults than children, averaging 652 and 87 SFCs/10^6 PBMC, and 2.6 and 0.9 recognized epitopes per person, respectively.
- The novel AALDLSHFL Nef epitope was the most frequently and most strongly recognized epitope in this study, making it a possible immunodominant epitope.
- This is one of three novel Nef epitopes previously identified in HLA-A2 transgenic mice, shown to induce CD8 T-cell response in humans.

HXB2 Location Nef (83–91)
Author Location Nef (83–91 BRU)
Epitope AAVDLSHFL
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 1/9 CRF02_AG-infected patients, and by 1/9 B-infected patients. Variants were present in 6/8 Ivorians, and in 3/5 French subjects.
- The Ivorian who recognized the B clade peptide carried the substitutions gAfDLSHFL.

HXB2 Location Nef (83–91)
Author Location Nef (83–91 HXB2)
Epitope AAVDLSHFL
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Viet Nam
Assay type HLA binding
Keywords subtype comparisons, computational epitope prediction, escape, variant cross-recognition or cross-neutralization, vaccine antigen design
References Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- The CRF01_AE variant GaFdlsFfl had a higher HLA-A2 binding score than the HXB2 epitope.

HXB2 Location Nef (83–91)
Author Location Nef (83–91)
Epitope AAVDLSHFL
Epitope name AL9
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A*02, A*30, B*13, B*18, Cw*01, Cw*05; A*02, A*32, B*07, B*40, Cw*03, Cw*07
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, characterizing CD8+ T cells, viral fitness and reversion
References Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- An escape form of the A2 epitope, AAVDmSHFL, was transmitted from an A2- mother to her A2+ infant, where it persisted in 29/29 sequences sampled over 11 months.
- Another form of this A2 epitope, gAlDLSHFL, was transmitted by an A2+ mother to an A2- infant, where it persisted in 30/30 sequences sampled over 15 months.
- AAVDmSHFL was shown to have lower responder cell frequencies than AAVDLSHFL.

HXB2 Location Nef (83–91)
Author Location Nef
Epitope GALDLSHFL
Subtype AG, B, C, A1
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization
References Pérez *et al.* 2008

CTL CD8+

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- Epitope GALDLSHFL and its variant aAvDLSHFL were cross-recognized by 5 subjects, however 1 subtype C infected patient only recognized GALDLSHFL.
- The well identified, immunogenic HLA-A2-restricted epitope GALDLSHFL of HIV-Nef was used in a peptide pool to stimulate PBMCs from 31 HIV-1 + subjects by ELISpot assay. Patients were infected with several HIV subtypes.

HXB2 Location Nef (83–91)
Author Location Nef
Epitope AAVDLSHFL
Subtype AG, B, A1
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- Epitope AAVDLSHFL and its variant gAlDLSHFL were cross-recognized by 5 subjects.
- The well identified, immunogenic HLA-A2-restricted epitope AAVDLSHFL of HIV-Nef was used in a peptide pool to stimulate PBMCs from 31 HIV-1 + subjects by ELISpot assay.

HXB2 Location Nef (83–91)
Author Location Nef
Epitope AAVDLSHFL
Epitope name A68-AL(Nef)
Immunogen HIV-1 infection
Species (MHC) human (A68)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (83–91)
Author Location
Epitope AAFDLSFFL
Epitope name AL9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5703)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression, optimal epitope
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- AAFDLSFFL is a known, optimal HLA-B*5703-restricted epitope that is part of peptide RPMTYKAAFDLSFFLKEKG which elicited responses in 9/25 patients, and which belongs to peptide pool 3 that accounted for over 70% of Nef responses. Epitope AL9 was experimentally verified as optimal.

HXB2 Location Nef (83–91)
Author Location
Epitope AAFDLSFFL
Epitope name AL9
Immunogen
Species (MHC) human (B*5703)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*5703 epitope.

HXB2 Location Nef (83–91)
Author Location Nef (83–91)
Epitope AAVDLSHFL
Immunogen HIV-1 infection
Species (MHC) human (B60, B62, Cw*0802, Cw8)
Donor MHC A*0201, A23, B44, B62, Cw3, Cw4; A1, A3, B14, B7, Cw*0702, Cw*0802; A*0201, A31, B44, B60, Cw16, Cw3; A1A1, B14, B8, Cw7, Cw8
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, early treatment
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- Four different individuals recognized this epitope during a primary infection, and it was shown to be presented by HLA B60, B62, C2*0802, and Cw8.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

HXB2 Location Nef (83–91)
Author Location Nef (83–91)
Epitope AAVDLSHFL
Epitope name AL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62, Cw8)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, acute/early infection, immune evasion
References Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- 5 additional variants of this epitope, AAVDLSHFL, were seen - gAVDLSHFL, AAiDLSHFL, AAlDLSHFL, gAlDLSHFL and gAfDLSHFL. The last 3 variants show lower avidity than responses to the consensus epitope do.
- HLA-restriction to epitope AL9 in two different subjects were -B62 and -Cw08.

HXB2 Location Nef (83–91)
Author Location Nef (83–91)
Epitope AAVDLSHFL
Epitope name AL9
Immunogen HIV-1 infection
Species (MHC) human (Cw*03)
Assay type CTL suppression of replication
Keywords class I down-regulation by Nef
References Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Nef epitope AAVDLSHFL-recognizing HLA-C restricted CTLs were unaffected by Nef.

HXB2 Location Nef (83–91)
Author Location Nef (83–91 LAI)
Epitope AAVDLSHFL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*0802)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a C*0802(Cw8) epitope. Variant gAfDLSfFL also noted.

HXB2 Location Nef (83–91)
Author Location Nef (83–91)
Epitope AALDLSHFL
Immunogen
Species (MHC) human (Cw3)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Nef (83–91)
Author Location Nef (83–91)
Epitope AALDMSHFL
Epitope name AL9
Immunogen HIV-1 infection
Species (MHC) human (Cw3)
Donor MHC A*0201, A*2402, B*4001, B*5001, Cw03, Cw04
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords immunodominance, escape, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells
References Draenert *et al.* 2006

CTL CD8+

- HIV-specific cellular and humoral immune responses were examined in monozygotic male twins infected simultaneously with the same virus. 15 of 17 targeted epitopes were identical in the twins, including two immunodominant responses. 3 of 4 declining responses in the twins showed mutations at the same residue. Evolving antibody responses cross-neutralized the other twin's virus. The results were compared with a third brother, infected by the twins' virus 13 months after their seroconversion. The data show similarity in disease course in persons of identical genetic background infected with the same strain of HIV-1.
- This epitope, AALDMSHFL (AL9), is restricted by HLA-Cw3. Variants that arose were AALDiSHFL and gALDMSHFL.

HXB2 Location Nef (83–91)
Author Location Nef (83–91)
Epitope AALDLSHFL
Epitope name AL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw3)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-Cw*03-associated substitutions within optimally defined epitope AALDLSHFL are at positions A1 and L3, aAlDLSHFL.

HXB2 Location Nef (83–91)
Author Location Nef (83–91)
Epitope AAVDLSHFL
Epitope name AL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw8)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-Cw*08-associated substitutions within optimally defined epitope AAVDLSHFL are at positions V3 and D4, AAvdLSHFL.

HXB2 Location Nef (83–91)
Author Location
Epitope AAVDLSHFL
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101; B*0801, B*1401
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- AAVDLSHFL was recognized by a placebo patient after infection.

HXB2 Location Nef (83–91)
Author Location Nef
Epitope GALDLSFFL
Epitope name GL9(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope GALDLSFFL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide YKGALDLSHFLKEKGGL. This epitope differs from the previously described HLA-A2-restricted epitope, GAFDLSFFL, at 1 residue, GAlDLSFFL.

- 21 of the 55 HLA-A2 carriers responded to GAlDLSFFL-containing peptide with average magnitude of CTL response of 226 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Nef (83–92)
Author Location Nef (81–90 93TH253 subtype CRF01)
Epitope `GAFDLSFFLK`
Epitope name N83-92
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords HIV exposed persistently seronegative (HEPS)
References Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was strongly reactive in HIV+ study subjects 053 and 184 who carried HLA-A11.

HXB2 Location Nef (83–92)
Author Location Nef (81–90 93TH253 subtype CRF01)
Epitope `GAFDLSFFLK`
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords subtype comparisons
References Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This epitope was predicted by the EpiMatrix method to be likely to bind to A11, and it served as an epitope in the FSWs, it was one of the six A11 epitopes that had been previously defined.
- 4/8 tested FSWs recognized this epitope.
- This epitope was only conserved in CRF01 and subtype C, and exact matches were uncommon.

HXB2 Location Nef (83–92)
Author Location Nef (83–92)
Epitope `AAVDLSHFLK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A*0201, A11, B51, B61, Cw*14, Cw2
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, early treatment
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.

HXB2 Location Nef (83–92)
Author Location Nef (83–92)
Epitope `AAVDLSHFLK`
Epitope name AK10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, acute/early infection, immune evasion
References Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- 2 PTE-B peptide sequences were identified, PMTYKAAVDLSHFLK and GAlDLSHFLKEKGGL, containing variants of this consensus epitope sequence AK10, viz. AAVDLSHFLK and GAlDLSHFLK, both of which elicited IFN-gamma immune responses.
- HLA-A11 restriction for AK10 was presumed based on the subject's having the HLA allele and publication in the Los Alamos database.

HXB2 Location Nef (83–94)
Author Location Nef (83–94 BRU)
Epitope `AAVDLSHFLKEK`
Immunogen HIV-1 infection
Species (MHC) human (A11)
References Culmann *et al.* 1991

- Epitope defined by boundaries of overlapping peptides that stimulate Nef CTL clones.

HXB2 Location Nef (83–97)

CTL CD8+

Author Location Nef (83–97)
Epitope GALDLSHFLKEKGGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A24, A3, B7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide GAlDLSHFLKEKGGL varies at position 3 (leucine)from the consensus peptide YKAAVDLSHFLKEKG .

HXB2 Location Nef (84–91)
Author Location Nef (84–91)
Epitope AVDLSHFL
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (A2)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of 31 that the vaccinated volunteers responded to.

HXB2 Location Nef (84–91)
Author Location Nef (84–91)
Epitope ALDLSHFL
Epitope name AL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, acute/early infection, immune evasion
References Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- A PTE-B peptide, GAlDLSHFLKEKGGL contained the epitope ALDLSHFL (AL8) and elicited an IFN-gamma immune response.
- HLA-A02 restriction for AL8 was presumed based on the subject's having the HLA allele and publication in the Los Alamos database.

HXB2 Location Nef (84–91)
Author Location Nef (84–91 LAI)
Epitope AVDLSHFL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62)
References Culmann-Penciolelli *et al.* 1994

HXB2 Location Nef (84–91)
Author Location Nef (84–91)
Epitope AVDLSHFL
Immunogen HIV-1 infection
Species (MHC) human (B62)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the A2+ individuals that didn't respond to SLYNTVATL reacted with seven other epitopes including this epitope.

HXB2 Location Nef (84–91)
Author Location Nef (84–91 BRU)
Epitope AVDLSHFL
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (B62)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 2/9 CRF02_AG-infected Ivorians, and 0/9 B-infected French subjects.
- The 2 CRF02 infected subjects that recognized this peptide carried a form with one amino acid change: AfDLSHFL. Variant forms were in 4/8 CRF02 infection sequences. 3/5 B clade infected individuals had a variant of this peptide.

HXB2 Location Nef (84–92)
Author Location Nef (84–92)
Epitope AVDLSHFLK
Epitope name AK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*03, A*11)
Country Australia, Canada, Germany, United States
Keywords escape, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-A*03-associated substitution within optimally defined epitope AVDLSHFLK is at position V2, AvDLSHFLK and HLA-A*11 substitutions are at V2 and K9, AvDLSHFLk. With > 40% recognition frequency, AK9 has a high rate of escapes at months 5, 7 and earlier, post-infection.

HXB2 Location Nef (84–92)
Author Location Nef (84–92)
Epitope AVDLSHFLK
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Nef (84–92)
Author Location Nef (84–92)
Epitope AVDLSHFLK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*11)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This putative epitope, AVDLSHFLK, was detected and confirmed within overlapping peptides SHFLKEKGGLEGLIYSQK and YKAAVDLSHFLKEKGGL.

HXB2 Location Nef (84–92)
Author Location Nef (84–92 LAI)
Epitope AVDLSHFLK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*1101 epitope.

HXB2 Location Nef (84–92)
Author Location Nef (84–92)
Epitope AVDLSHFLK
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A*1101)
Keywords subtype comparisons
References Fukada *et al.* 2002

- Counterparts for eight known clade B HLA A*1101 epitopes were generated for clade E (CRF01). Three epitopes, identical among clade A-E, were cross-reactive and recognized by clade E infected individuals. The clade E and B analogs to three more HLA A*1101 epitopes was recognized in a clade specific manner. Two other HLA A*1101 clade B defined epitopes were found not to have stimulated a response in clade E infected individuals.
- AVDLSHFLK was found to elicit clade-specific responses in clade B (AVDLSHFLK is most common, aLdlshflk is a common variant also found in clade A) and clade E (aFdlsFflk is most common and is also common in clade C). AVDLSHFLK was strongly recognized by CTL from 2/5 B clade infected Japanese subjects, as was aLdlshflk, and aFdlsFflk by CTL from 5/7 E clade infected Thai subjects.
- The binding of aFdlsFflk to HLA A*1101 was 10-50 times lower than the other variants, and bulk CTL generated from individuals did not cross-react with the cross-clade peptides.

HXB2 Location Nef (84–92)
Author Location Nef
Epitope AVDLSHFLK
Immunogen HIV-1 infection
Species (MHC) human (A03, A11)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.

CTL CD8+

- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope AVDLSHFLK when restricted by HLA-A03 elicited a magnitude of response of 620 SFC with a functional avidity of 0.5nM and binding affinity of 0.65nM. When restricted by HLA-A11, it elicited a magnitude of response of 50 SFC with a functional avidity of 0.5nM and binding affinity of 5.9nM.

HXB2 Location Nef (84–92)
Author Location
Epitope AVDLSHFLK
Immunogen HIV-1 infection
Species (MHC) human (A03, A11)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- Based on a prediction of the minimum number of HLA alleles needed to cover the HLA representation in all responders to this epitope, a minimum set of 6 alleles was found: 2 alleles previously known to be associated (A03 and A11) and 4 additional alleles (A02, A23, A30, B44).

HXB2 Location Nef (84–92)
Author Location Nef (84–92 LAI)
Epitope AVDLSHFLK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords review
References McMichael & Walker 1994

- Review of HIV CTL epitopes.
- C. Brander notes that this is an A*1101 epitope in the 1999 database.

HXB2 Location Nef (84–92)
Author Location Nef (84–92)
Epitope AVDLSHFLK
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the A2+ individuals that didn't respond to SLYNTVATL reacted with seven other epitopes including this epitope.

HXB2 Location Nef (84–92)
Author Location Nef (84–92 LAI)
Epitope AVDLSHFLK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords review, escape
References Couillin *et al.* 1994; Goulder *et al.* 1997a

- Mutational variation in HIV epitopes in individuals with appropriate HLA types can result in evasion of CTL response.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

HXB2 Location Nef (84–92)
Author Location Nef (84–92 LAI)
Epitope AVDLSHFLK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
References Couillin *et al.* 1995

- Mutations found in this epitope in HLA-A11 positive and negative donors were characterized.

HXB2 Location Nef (84–92)
Author Location Nef (84–92)
Epitope AVDLSHFLK
Epitope name AVD
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords HAART, ART, supervised treatment interruptions (STI), immunodominance, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- Both of the 2/8 HLA-A11 study subjects recognized this CTL epitope.
- Patient SC19(HLA A11/12, B8/44, Cw06/0701, DR3/7, DR52/53, DQ 2/8) had a CTL response to epitopes FLKEKGGL, GEIYKRWII, ACQGVGGPGHK, AVDLSHFLK, and FNCGGEFFY that declined during therapy initiated at day 197.
- Patient SC18(HLA A2/11, B8/44, Cw06/0701, DR3/7, DR52/53, DQ2) recognizes the epitopes ACQGVGGPGHK, QVPLRPMTYK, AVDLSHFLK, and one called QIY but not fully described – he had brief therapy upon seroconversion and has had low viral load during 600 days of follow up.

HXB2 Location Nef (84–92)
Author Location Nef (82–90)
Epitope AVDLSHFLK
Immunogen HIV-1 infection
Species (MHC) human (A11)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location Nef (84–92)
Author Location Nef (84–92 SF2)
Epitope AVDLSHFLK
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A11+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 0/0 group 2, and 2/2 group 3.

HXB2 Location Nef (84–92)
Author Location Nef (84–92)
Epitope AVDLSHFLK
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A11)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location Nef (84–92)
Author Location Nef
Epitope AVDLSHFLK
Epitope name AVD
Immunogen HIV-1 infection
Species (MHC) human (A11)
Keywords HAART, ART, supervised treatment interruptions (STI)
References Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFNgamma Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

HXB2 Location Nef (84–92)
Author Location Nef
Epitope AVDLSHFLK
Subtype A, B, D, F
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human, macaque (A11)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location Nef (84–92)
Author Location Nef (84–92)
Epitope AVDLSHFLK
Epitope name AK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords optimal epitope
References Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- This epitope did not vary.

HXB2 Location Nef (84–92)
Author Location Nef (84–92)
Epitope AVDLSHFLK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)

CTL CD8+

Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location Nef (84–92)
Author Location Nef
Epitope `AVDLSHFLK`
Epitope name A11-AK9(Nef)
Immunogen HIV-1 infection
Species (MHC) human (A11)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (84–92)
Author Location Nef
Epitope `AVDLSHFLK`
Epitope name AK9(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A11-restricted epitope AVDLSHFLK elicited an immune response in Chinese HIV-1 positive subjects as part of peptide YKGALDLSHFLKEKGGL.
- 11 of the 28 HLA-A11 carriers responded to FLGKIWPShK-containing peptide with average magnitude of CTL response of 196 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Nef (84–92)
Author Location Nef (B consensus)
Epitope `AVDLSHFLK`
Epitope name AK9
Immunogen HIV-1 infection
Species (MHC) human (A11, A3)
Donor MHC A02, A11, B18, B44, Cw12, Cw5; A03, B14, B60, Cw3, Cw7
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, cross-presentation by different HLA, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 2/9 individuals recognized this epitope, each in the context of a different HLA-presenting molecule.

HXB2 Location Nef (84–92)
Author Location Nef
Epitope `AVDLSHFLK`
Epitope name AL9, ALK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A11, Cw8)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127, a marker whose down-modulation indicates lack of memory T cell formation, however, is not impacted by viral escape. Both markers are linked to CTL functional exhaustion.

- 409 days after first testing, epitope AVDLSHFLK showed no variation in an untreated patient. 511 days after first testing, an untreated patient's epitope, AAVDLSHFL, varied to AAfDLSyFL and AAlDLSyFL. Previously published HLA-restriction for AL9 is HLA-A11, -Cw8.

HXB2 Location Nef (84–92)
Author Location Nef (84–92 BRU)
Epitope AVDLSHFLK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- AVDLSHFLK was recognized in 4/12 (33%) of individuals with HLA A3. It was a high affinity HLA-A3 binder.

HXB2 Location Nef (84–92)
Author Location Nef (84–94)
Epitope AVDLSHFLK
Epitope name A3-ALK9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 1/7 individuals began to have detectable responses to this epitope after STI.

HXB2 Location Nef (84–92)
Author Location Nef (84–92)
Epitope AVDLSHFLK
Epitope name AK9
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A*03, A*31, B*08, B*15, Cw*04, Cw*07; A*24, A*31, B*15, B*47, Cw*04, Cw*07
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, characterizing CD8+ T cells, viral fitness and reversion
References Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- Variant sequence aMdlshflk was present in 7/10 clones from A3+ mother, was transmitted and present in 10/10 clones at months 2 and 4, but dropped to 0/10 clones by 15 months of age in her A3- child.

HXB2 Location Nef (84–92)
Author Location Nef
Epitope AVDLSHFLK
Epitope name A3-AK9(Nef)
Immunogen HIV-1 infection
Species (MHC) human (A3)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (84–92)
Author Location Nef (84–92)
Epitope AVDLSHFLK
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (A11, A3)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay

CTL CD8+

Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the most frequently recognized of the 31 epitopes that the vaccinated volunteers responded to.

HXB2 Location Nef (84–92)
Author Location Nef (84–92 BRU)
Epitope AVDLSHFLK
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (A11, A3)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 0/9 CRF02_AG-infected Ivorians, and 2/9 B-infected French subjects.
- One of the B-clade infected subjects that recognized this peptide carried the identical form, the other had one amino acid change: AlDLSHFLK. This variant form was in 3/5 B clade infection sequences. 4/8 CRF01 infected individuals had a variant of this peptide.

HXB2 Location Nef (84–92)
Author Location
Epitope AVDLSHFLK
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A*0201, A*1101; B*4002, B*5101
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it both before and after infection.

HXB2 Location Nef (84–92)
Author Location Nef
Epitope AVDLSHFLK
Subtype B, D, A1
Immunogen HIV-1 infection
Species (MHC) human
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- Subtype A- B- and D-infected subjects cross-recognized epitopes AVDLSHFLK and AlDLSHFLK. The predicted HLA restriction for this epitope was supertype A3. It was recognized by at least 4 patients with restricting HLA supertype who were infected with several different HIV subtypes.

HXB2 Location Nef (84–92)
Author Location Nef
Epitope ALDLSHFLK
Subtype B, D, A1
Immunogen HIV-1 infection
Species (MHC) human
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
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- Subtype A- B- and D-infected subjects cross-recognized epitopes ALDLSHFLK and AvDLSHFLK. The predicted HLA restriction for this epitope was supertype A3. It was recognized by at least 4 patients with restricting HLA supertype who were infected with several different HIV subtypes.

HXB2 Location Nef (84–92)
Author Location Nef
Epitope `AFDLSHFLK`
Subtype B, C, AE
Immunogen HIV-1 infection
Species (MHC) human
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- Variant epitope AFDLSHFLK was recognized exclusively by subtype-C and CRF01_AE infected patients. The predicted HLA restriction for this epitope was supertype A3.

HXB2 Location Nef (84–92)
Author Location Nef
Epitope `ALDLSHFLK`
Epitope name AK10(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope ALDLSHFLK elicited an immune response in Chinese HIV-1 positive subjects as part of peptide YKGALGLSHFLKEKGGL. This epitope differs from the previously published HLA-A3- and -A11-restricted epitope AVDLSHFLK, at 1 residue, AlDLSHFLK.
- 1 of the 3 HLA-A3 carriers responded to AlDLSHFLK-containing peptide with average magnitude of CTL response of 80 SFC/million PBMC and 11 of the 28 HLA-A11 carriers responded with an average magnitude of CTL response of 196 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Nef (86–94)
Author Location Nef (84–92 LAI)
Epitope `DLSHFLKEK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301)
Keywords review
References McMichael & Walker 1994

- Review of HIV CTL epitopes.

HXB2 Location Nef (86–94)
Author Location Nef
Epitope `DLSHFLKEK`
Subtype A, B, D, F
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human, macaque (A*0301)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location Nef (86–94)

CTL CD8+

Author Location Nef (86–94)
Epitope DLSHFLKEK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0301, A11)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords Th1, characterizing CD8+ T cells
References Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- Two of nine patients responded to this peptide with GzB producing cells, while three of the patients responded with IFN-gamma producing cells. Only one patient had both GzB and IFN-gamma responses.

HXB2 Location Nef (86–94)
Author Location
Epitope DLSFLKEK
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A11, A3)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- DLSFLKEK is a known HLA-A3 and -A11-restricted epitope that is part of peptide RPMTYKAAFDLSFFLKEKG which elicited responses in 9/25 patients, and which belongs to peptide pool 3 that accounted for over 70% of Nef responses.

HXB2 Location Nef (86–94)
Author Location Nef (86–94)
Epitope DLSHFLKEK
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A3)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location Nef (86–94)
Author Location Nef (86–94 HXB2)
Epitope DLSHFLKEK
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A11, A3)
Country Viet Nam
Assay type HLA binding
Keywords subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization, vaccine antigen design
References Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- The CRF01_AE variant dlsFflkek had same HLA-binding score as the HXB2 epitope.

HXB2 Location Nef (86–100)
Author Location Nef (86–100 LAI)
Epitope DLSHFLKEKGGLEGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Robertson *et al.* 1993

- Development of a retroviral vector (pNeoNef) to generate autologous targets.

HXB2 Location Nef (86–100)
Author Location Nef (86–100 LAI)
Epitope DLSHFLKEKGGLEGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Buseyne *et al.* 1993b

HXB2 Location Nef (86–100)
Author Location Nef (86–100 LAI)
Epitope DLSHFLKEKGGLEGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35, Cw4)
References Buseyne *et al.* 1993a

- Vertical transmission of HIV ranges from 13% to 39%
- Primary assays showed that cytotoxic activity against at least one HIV protein was detected in 70% of infected children.
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
- Patient EM13, who had a CTL response to three epitopes in Nef, was infected via blood transfusion after birth and went from CDC stage P2A to P2E during the study.

HXB2 Location Nef (87–99)
Author Location Nef
Epitope LSHFLKEKGGLEG
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human

Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Garrison *et al.* 2007

- The study examined the influence of HIV-1 infection on human endogenous retroviruses (HERVs) activity and explored T cells cross-reactivity in regions of HIV-1/HERV similarity.
- T cell responses to HERV peptides were identified in HIV-1 positive individuals. There was an inverse correlation between anti-HERV T cell responses and HIV-1 viral load.
- HIV-1 epitope LSHFLKEKGGLEG has a corresponding HERV peptide LDLLTAEKGGLCI. These 2 peptides were used in measuring IFN-γ ELISPOT responses in HIV-1-positive and -negative individuals.
- HIV-1 LSHFLKEKGGLEG and HERV LDLLTAEKGGLCI share 5 amino acids and there was parallel dynamics of T cell responses for these peptides in HIV-1 infected individuals.

HXB2 Location Nef (87–102)
Author Location Nef
Epitope `FSHFLKEKGGLEGLIY`
Immunogen
Species (MHC) human
Keywords subtype comparisons
References Jubier-Maurin *et al.* 1999

- 41 new HIV-1 strains describing envelope subtypes of HIV-1 A-H were genetically characterized in the nef region – 34 subtypes were classified in the same subtype in nef and env and 7 of the 41 strains were recombinants.
- This region was defined as a CTL epitope region that is conserved among HIV-1 M group subtypes.

HXB2 Location Nef (88–100)
Author Location Nef (103–116)
Epitope `SHFLKEKGGLEGL`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Guimaráes *et al.* 2002

- Nef sequences were obtained from Brazilians to study epitope diversity in this geographic region—most B subtype sequences are SHFLKEKGGLEGL, but sFflkekgglegl is found in most subtype C samples.

HXB2 Location Nef (88–105)
Author Location Nef
Epitope `SHFLKEKGGLEGLIYSQK`
Epitope name NEF-13
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, ShFLKEKGGLEGLIYSqK differs from the consensus C sequence SfFLKEKGGLEGLIYSkK at 2 amino acid positions, i.e. by 11.1%.

HXB2 Location Nef (88–105)
Author Location Nef
Epitope `SHFLKEKGGLEGLIYSQK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.

CTL CD8+

- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, SHFLKEKGGLEGLIYSQK, had an overall frequency of recognition of 18% - 20.3% AA, 30.8% C, 15.9% H, 0% WI. This peptide is included in a 58 aa Nef highly reactive region to be used for vaccine design. It is also part of 'Region I', EVGFPVRPQVPLRPMTYKAAVDLSHFLKEKGGLEGLIYSQK, a 41 aa region recognized by >90% of subjects across ethnic groups.

HXB2 Location Nef (90–97)
Author Location Nef (90–97)
Epitope FLKEKGGL
Epitope name BRU
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (A2, B8)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 1/9 CRF02_AG-infected Ivorians, and 2/9 B-infected French subjects.

HXB2 Location Nef (90–97)
Author Location Nef
Epitope FLKEKGGL
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords dendritic cells
References Ostrowski *et al.* 2000

- The role of CD4+ T-cell help in expansion of virus-specific memory CTL was studied through co-culture *ex vivo*
- Optimal expansion of HIV-1-specific memory CTL depended on CD4+ T cell help in 9 of 10 patients – CD40 ligand trimer (CD40LT) could enhance CTL in the absence of CD4+ T cell help to a variable degree in most of patients.
- Those CTL that didn't respond to CD40LT could expand with IL2 present, and IL15 produced by dendritic cells also contributes.
- The T-helper epitope used for CD4+ T cell stimulation was the universal tetanus helper epitope TET830-843 (QYIKANSKFIGITE)

HXB2 Location Nef (90–97)
Author Location
Epitope FLKEKGGL
Epitope name Nef-FL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*08)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B*08, 1/3 (33%) recognized this epitope.

HXB2 Location Nef (90–97)
Author Location Nef (SF2)
Epitope FLKEKGGL
Epitope name FL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*08)
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining
Keywords TCR usage
References Meyer-Olson *et al.* 2006

HXB2 Location Nef (90–97)
Author Location
Epitope FLKEKGGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*08)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Addo *et al.* 2007

- Maturation phenotypes of CTLs were compared between HIV-1 Controller and Progressor subjects. Controllers were found to recognize a median of 18 epitopes compared to 15 by Progressors. While Controllers certainly had higher frequencies of terminally differentiated effector CTLs (CD45RA+/CCR7-), Progressors had higher mean frequencies of CD45RA-/CCR7- effector memory, CD45RA-/CCR7+ central memory (statistically significant) and CD45RA+/CCR7+ naive CTLs. No correlation was seen between CTL effector phenotype and either HLA-type or epitope.
- B*08-restricted epitope FLKEKGGL does not correlate with any particular CTL maturation phenotype.

HXB2 Location Nef (90–97)
Author Location Nef (89–96)
Epitope FLKEKGGL
Epitope name FL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*08)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords rate of progression, acute/early infection, memory cells
References Sabbaj *et al.* 2007

- CD127 hi memory CTLs were correlated with different patient groups - subjects with chronic HIV-1 infection or controllers or those treated early with ART. For patients with chronic infection, CD127 hi CTL levels decrease greatly. Early ART treatment alone maintained these long-lived memory T cells.

- In response to epitope FL8, FLKEKGGL, IFN-gamma and TNF-alpha were produced by CD127 lo cells in chronic patients with viremia. IL-2 was produced by both CD127 hi and lo cells. HLA-restriction was to -B*8.

HXB2 Location Nef (90–97)
Author Location Nef (90–97)
Epitope FLKEKGGL
Epitope name FL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*08)
Donor MHC A1, A2, B49, B8, Cw7
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords immune evasion
References Maurer *et al.* 2008

- The Nef HLA-B8-restricted dominant epitope FL8, FLKEKGGL, was studied both longitudinally over time as well as horizontally in a 56 subject cohort of HIV-1 infected patients to chart FL8 variants and . FL8 mutants were associated with higher pVL and lower CD4 cell counts.
- Mutations in FL8 seen in B8-positive patients were FLKEqGGL, FLKEnGGL, FLKEmGGL, FLKEtGGL, FLKEeGGL, FLrEKGGL, FLrdKGGL and FLrkeGGL.
- Mutations in FL8 seen in B8-negative patients were FLrEKGGL, FLrkeGGL, FLrkKGGL, FLqEqGGL, FLiaKGGL and lLKEKGGL.
- HLA restrictions in this study are previously published and correlate with the subject's HLA. All variants except for FL8-V2 (FLrdKGGL) were recognized though to a lower degree than wild type FL8, by Patient 01.

HXB2 Location Nef (90–97)
Author Location Nef (90–97)
Epitope FLKEKGGL
Epitope name FL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*08)
Country Australia, Canada, Germany, United States
Keywords escape, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*08-associated substitutions within optimally defined epitope FLKEKGGL are at positions L2, E4 and K5, FlKekGGL. FL8 has a high (>70%) recognition frequency and robust escape rate.

HXB2 Location Nef (90–97)
Author Location Nef (89–97 LAI)
Epitope FLKEKGGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*0801 epitope.

HXB2 Location Nef (90–97)
Author Location Nef (90–97)
Epitope FLKEKGGL
Epitope name FL8
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Donor MHC A*0201, A*2402, B*0801, B*5701, Cw*0602, Cw*0701; A*0101, A*0201, B*0801, B*5701, Cw*0602, Cw*0701; A*2402, A2, B*0801, B15, Cw12, Cw7; A*0101, A*0201, B*0801, B*5701, Cw*0602, Cw*0701
Country United Kingdom
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape, TCR usage, characterizing CD8+ T cells
References Dong *et al.* 2004

- In 4 donors with delayed disease progression, the response to the FL8 Nef epitope was dominated by V-beta-13.2 TCR expressing CTLs with an unusually long CDR3 region. These CTLs were shown to be resistant to apoptosis and able to recognize escape variants of the FL8 Nef epitope. Thus, selection of these CTLs may be related to better clinical outcome.
- The Q5 variant flkeQggl was rapidly selected in a donor that responded to the FLKEKGGL epitope. The FLKEKGGL peptide and the variant flkeQggl HLA-B8 complexes bound to the Vbeta13.2 FLKEKGGL TCR with equal affinity, while the Vbeta6 FLKEKGGL TCR had reduced affinity for the FLKEKGGL form and did not recognize the Q5 variant. Other variants (T5, N5, and M5 as well as Q5) were recognized by Vbeta13.2 clones from all 4 donors. One clone from donor 046 that was not Vbeta13.2 could only recognize the index variant.

HXB2 Location Nef (90–97)
Author Location (C consensus)
Epitope FLKEKGGL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

CTL CD8+

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location Nef (90–97)
Author Location Nef
Epitope FLKEKGGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Donor MHC A*0101, B*0801
Country United Kingdom
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords escape, acute/early infection
References Milicic *et al.* 2005

- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient. In an early acute infection of the donor, the precise timing of transmission determines the viral variants transmitted.
- The recipient mounted an acute CTL response to this epitope, and the escape variant flkeQggl emerged soon after.

HXB2 Location Nef (90–97)
Author Location (C consensus)
Epitope FLKEKGGL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- FLKEKGGL is an optimal epitope.

HXB2 Location Nef (90–97)
Author Location Nef
Epitope FLKEKGGL
Epitope name FL8
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Country South Africa
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization
Keywords rate of progression
References Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naive patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer B*0801 FL8 was used to test 26 patients and gave a median ex vivo tetramer frequency of 0.40.

HXB2 Location Nef (90–97)
Author Location Nef
Epitope FLKEKGGL
Immunogen peptide-HLA interaction
Species (MHC) human (B*0801)
Assay type Tetramer binding
Keywords binding affinity
References Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, FLKEKGGL (MHC Class I restriction, serotype Bw6) complexed with MHC B*0801 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C.

HXB2 Location Nef (90–97)
Author Location Nef (90–97)
Epitope FLKEKGGL
Epitope name FLK
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells
References Turnbull *et al.* 2006

- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.

- This epitope, B8-FLK that is associated with more rapid progression to AIDS and its natural as well as alanine-substituted variants were quite weakly cross-recognized. CTLs responding to this epitope expressed the same predominant TCR Vbeta family.

HXB2 Location Nef (90–97)
Author Location
Epitope FLKEKGGL
Epitope name FL8
Immunogen HIV-1 infection
Species (MHC) human (B*0801)
Country South Africa
Assay type proliferation, Tetramer binding, Intracellular cytokine staining
References Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

HXB2 Location Nef (90–97)
Author Location
Epitope FLKEKGGL
Epitope name FL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B08)
Country United States
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Chromium-release assay
Keywords TCR usage, characterizing CD8+ T cells
References Alter *et al.* 2008

- By studying HIV-1 dysregulation of CTLs at different infection stages induced by inhibitory KIRs (Killer Immunoglobulin-like receptors), it was determined that KIR surface expression on memory T cells correlates with HIV replication. It results in reduced activation, proliferation, cytokine secretion, and killing following TCR stimulation. Since non-TCR-dependent CTL stimulation was unaffected, TCR-mediated stimulation appears to be defective. KIR induced suppression of CTL function was found to be KIR-ligand-independent.
- FL8-specific CTLs had heterogeneous surface expression of KIR. Of these tetramer positive B08-CTLs, only KIR- cells were able to secrete IFN-gamma upon stimulation.

HXB2 Location Nef (90–97)
Author Location Nef (89–97 LAI)
Epitope FLKEKGGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords review, escape
References Price *et al.* 1997

- CTL escape variants appeared over time in HLA-B8 HIV-1 + individual, providing evidence of immune escape.
- Most variants appear at position 5, an anchor residue.
- FLKE(E,N or Q)GGL showed reduced binding efficiency and recognition.
- Double mutants (FIKENGGL, FLEENGGL, and FLKGNGGL) completely escaped recognition.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study in the context of CTL escape to fixation.

HXB2 Location Nef (90–97)
Author Location Nef (90–97 IIIB)
Epitope FLKEKGGL
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART, responses in children
References Spiegel *et al.* 1999

- Study examines the effect of highly active antiretroviral therapy (HAART) on HIV-1 plasma viral load, CTLp and CTLe frequencies in 8 infected children.
- CTLp (precursors) were measured by stimulating in culture and assaying using 51Cr release, against vaccina expressed IIIB Env, Gag, Pol, Nef.
- B7-FLKEKGGL tetramer complex was used for one of the children that was HLA-B7, and this infant showed a vigorous response (> 4% of CD8+ T cells) at 9 months of age.
- HIV-1 specific CTL responses initially increased in children with complete viral suppression, but then decreased, suggesting viral replication is needed to maintain CTL responses.

HXB2 Location Nef (90–97)
Author Location Nef
Epitope FLKEKGGL
Immunogen vaccine
Vector/Type: vaccinia
Species (MHC) human (B8)
References Hanke *et al.* 1998a; Hanke *et al.* 1998b

- This epitope was shown to be processed and presented to appropriate CTL clones upon infection of human target cells with vaccinia virus Ankara (VVA) carrying 20 HIV-1 epitopes recognized by humans.

HXB2 Location Nef (90–97)
Author Location Nef (88–95)
Epitope FLKEKGGL
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Goulder *et al.* 1997g

- Natural variants for this epitope have been observed in several donors.
- Substitutions Q5, N5, E5 that alter anchor position 5 are not well recognized.
- Substitution I2 binds well to B8 and is recognized.

HXB2 Location Nef (90–97)
Author Location Nef (90–97)
Epitope FLKEKGGL
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Dyer *et al.* 1999

- CTL specific responses were measured over a 1.3 to 1.5 year period in members of the Sydney Blood Bank Cohort (SBBC) who had been infected with a natural attenuated strain of HIV-1 which was Nef-defective.
- Some of these patients had prolonged high levels of CTL effector and memory cells despite low viral load.

HXB2 Location Nef (90–97)
Author Location Nef (SF2)
Epitope FLKEKGGL
Epitope name FL8
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Goulder *et al.* 2001a

- This peptide elicited a weak CTL response during acute HIV-1 infection in patient PI004.
- Three CTL responses, to epitopes TSTLQEQIGW, ISPRTLNAW, and KAFSPEVIPMF, were evident early after infection; CTL responses to SLYNTVATL, QASQEVKNW, EIYKRWII, and FLKEKGGL were detectable at 5 months post-infection and beyond.
- FL8 was recognized in an additional patient, AC29, in chronic infection.

HXB2 Location Nef (90–97)
Author Location Nef (92–99)
Epitope FLKEKGGL
Epitope name FLK
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART
References Oxenius *et al.* 2001a

- Characterization of specific CTL phenotype patterns in response to variation of the virus load in response to antiviral therapy in 3 patients with chronic HIV-1 infection.
- CTL activation in response to increasing viral load sequential, and co-segregated with apoptosis only during later stages of the response, suggesting antigen-specific cell-death is restricted to distinct CTL sub-populations.

HXB2 Location Nef (90–97)
Author Location Nef (92–99)
Epitope FLKEKGGL
Epitope name FLK
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART, supervised treatment interruptions (STI), immunodominance, escape, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- Six of the 7/8 study subjects that were HLA B8 recognized this early dominant CTL epitope.
- Patient SC2 (HLA A1, B7/8, Cw0701/0702, DR4/53, DQ7) had CTL responsiveness against epitopes FLKEKGGL, GPKVKQWPL, and GEIYKRWII peptides – FLKEKGGL tetramer staining steadily declined and at day 1340 the FLKEKGGL stained cells were no longer detected and the escape mutant FLKENGGI was found in 8/10 clones.
- Patient SC9 (HLA A1/2, B8/13, Cw0/0701, DR2/11, DQ6/7) had a CTL response against epitopes FLKEKGGL, ILKEPVHGV, SQRRQDILDLWIYHTQGYFPDWQNY, and GEIYKRWII peptides and all responses declined during therapy initiated at day 390 but were restored when therapy become intermittent.
- Patient SC19(HLA A11/12, B8/44, Cw06/0701, DR3/7, DR52/53, DQ 2/8) had a CTL response to epitopes FLKEKGGL, GEIYKRWII, ACQGVGGPGHK, AVDLSHFLK, and FNCGGEFFY that declined during therapy initiated at day 197.
- Patient SC10(HLA A1/3, B8/35, DR1/8, DQ 4/5) had sustained therapy started during acute infection and maintained an immunodominant response to FLKEKGGL and a response to GEIYKRWII through day 1088.
- Patient SC12(HLA A1, B8/39, Cw0701/0702, DR2/3, DR51/52, DQ2/6) had sustained therapy started during acute infection and maintained an immunodominant response to FLKEKGGL throughout and minor responses to GEIYKRWII, DCKTILKAL, GGKKKYKLK – GEIYKRWII and GGKKKYKLK responses were stimulated by a brief period off therapy.
- Patient SC11(HLA A1, B8, Cw0201, DR3/11, DR52, DQ2/7) started therapy early, remained on therapy for 40 days, then reinitiated HAART at day 640 had a CTL response to FLKEKGGL, GPKVKQWPL, and GEIYKRWII throughout and received a benefit from the early limited course therapy.

HXB2 Location Nef (90–97)
Author Location Nef
Epitope FLKEKGGL
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Kostense *et al.* 2001

- HLA tetramers to six epitopes were used to study HLA-A2, B8 and B57 CTL in 54 patients – HIV-specific tetramer positive cells were inversely correlated with viral load in patients with high CD4, but in patients with CD4 T-cells below 400 high tetramer frequencies were found despite high viral load.
- Most patients have high levels of HIV-specific T-cell expansions, but many of these cells aren't functional.
- In 15 of the patients, the proportion of IFN gamma producing tetramer cells correlated with AIDS-free survival.
- Stimulation with HLA-B8 p24 and Nef epitopes significantly increased Nef-specific T-cell numbers in 2 patients (748 and 1113)
- There were more functional IFN-gamma producing Nef-specific T-cells within the T-cell population than there were active p24 Gag-specific T-cells.
- No correlation between elevated numbers of Nef-specific CTL cells and plasma viral load was observed.

HXB2 Location Nef (90–97)
Author Location Nef (88–95)

Epitope FLKEKGGL
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

HXB2 Location Nef (90–97)
Author Location Nef (88–95 SF2)
Epitope FLKEKGGL
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B8+ individuals that had a CTL response to this epitope broken down by group: 3/3 group 1, 1/3 group 2, and 1/2 group 3.

HXB2 Location Nef (90–97)
Author Location Nef (89–97)
Epitope FLKEKGGL
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Appay *et al.* 2000

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α

HXB2 Location Nef (90–97)
Author Location Nef (90–97)
Epitope FLKEKGGL
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Day *et al.* 2001

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual.
- The response to FLKEKGGL was the second highest response in magnitude compared to all the HLA class I A- and B-restricted epitopes tested in this individual.

HXB2 Location Nef (90–97)
Author Location Nef
Epitope FLKEKGGL
Immunogen HIV-1 infection
Species (MHC) human (B8)
References Goulder *et al.* 2000b

- Tetramer assays were compared with three functional assays in 42 people with chronic HIV infection: ELISPOT, intracellular cytokine staining, and precursor frequency (limiting dilution assay [LDA])
- HIV-specific tetramer staining CTLs appeared to be active, and inert CTL were not found to play a significant role in chronic pediatric or adult HIV infection.

HXB2 Location Nef (90–97)
Author Location Nef (90–97 BRU)
Epitope FLKEKGGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- FLKEKGGL was recognized in 12/14 (86%) of individuals with HLA B8, and it was a high affinity HLA binder.

HXB2 Location Nef (90–97)
Author Location Nef
Epitope FLKEKGGL
Epitope name FLK
Immunogen HIV-1 infection
Species (MHC) human (B8)
Keywords HAART, ART, supervised treatment interruptions (STI)
References Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFNgamma Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

HXB2 Location Nef (90–97)
Author Location Nef
Epitope FLKEKGGL
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A11, A2, B60, B8, Bw6
Keywords HAART, ART

CTL CD8+

References Appay *et al.* 2002

- Four HIV patients with prolonged clinically successful anti-viral therapy but with ongoing evidence of replication and Nef mRNA transcription, showed specific T-cell responses by Elispot and Tetramer staining, maintained for 2-4 years after initiation of HAART.
- Nef epitope recognition was detected in all 4 subjects, gp120, Pol and Gag-specific in 1 or 2 subjects – two patients recognized FLKEKGGL.
- The HIV-specific CD8+ T-cells had an intermediate maturation phenotype characterized by low levels of perforin and high levels of CD27 expression.

HXB2 Location Nef (90–97)
Author Location Nef
Epitope FLKEKGGL
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A1, A3, B65, B8, Bw6
Keywords HAART, ART
References Appay *et al.* 2002

- Four HIV patients with prolonged clinically successful anti-viral therapy but with ongoing evidence of replication and Nef mRNA transcription, showed specific T-cell responses by Elispot and Tetramer staining, maintained for 2-4 years after initiation of HAART.
- Nef epitope recognition was detected in all 4 subjects, gp120, Pol and Gag-specific in 1 or 2 subjects – two patients recognized FLKEKGGL.
- The HIV-specific CD8+ T-cells had an intermediate maturation phenotype characterized by low levels of perforin and high levels of CD27 expression.

HXB2 Location Nef (90–97)
Author Location Nef
Epitope FLKEKGGL
Subtype A, B, C, D
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human, macaque (B8)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location Nef (90–97)
Author Location Nef (90–97)
Epitope FLKEKGGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A1, A3, B62, B8, Cw3, Cw7
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

HXB2 Location Nef (90–97)
Author Location Nef (90–97 B consensus)
Epitope FLKEKGGL
Epitope name FL8
Subtype B
Immunogen vaccine
Vector/Type: adeno-associated virus (AAV) *HIV component:* gp120
Species (MHC) human (B8)
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords dynamics, immune evasion
References Brainard *et al.* 2004

- HIV-1 gp120 is shown to suppress the ability of antigen-specific CTLs to migrate or remain at sites of high viral replication by concentration-dependent chemotaxis and fugetaxis. Directional T-cell movement is shown to depend on the interaction of the V2 and V3 loops with the CXCR4 receptor. X4

HIV-1 gp120 causes the migration of T-cells, including HIV-1 specific CTL, away from infected target cells, another potential mechanism for immune evasion.

HXB2 Location Nef (90–97)
Author Location Nef (87–95)
Epitope FLKEKGGL
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A03, A28, B07, B08
Assay type proliferation, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, memory cells, immune dysfunction
References Gamberg *et al.* 2004a

- HAART restores HIV specific immunity after advanced infection by increase of CD4+ and CD8+ T cell numbers after supression of viral replication. However, HIV specific CTLs emerged only with detectable viral replication breakthroughs and were short-lived while CD4+ T-cell responses remained compromised, suggesting failure of generating stable CD8+ memory T-cells in the absence of HIV-specific T-helper responses.

HXB2 Location Nef (90–97)
Author Location Nef
Epitope FLKEKGGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) (B8)
Keywords binding affinity, review, escape, characterizing CD8+ T cells
References da Silva 2003

- Evidence of the evolutionary adaptation of HIV-1 to the specific neutralizing antibody response and CTL detection is reviewed. Both SIV and HIV epitopes are discussed, with a detailed summary of one patient's response and CTL escape in the FLKEKGGL epitope. The three C-terminal amino acids were left unchanged, and it may be due to high fitness costs as these are putatively invloved in CD4 down-regulation and formation of a hydrophobic pocket in Nef. The N terminal residue is involved in binding to protein tyrosine kinases.
- Immediately after infection the susceptible eptiope FLKEKGGL was found in 20/20 viral sequences. Six months later, it was only found in 4/44 sequences. The flkeNggL form was most common, 24/44 cases; it bound poorly to HLA B08 and was poorly recognized by CTL. Two minor variants were found 3/44 times, flkeEggl and flkeQggl; both bound poorly to B08, but the K->Q substitution was still well recognized. A variant flkDkggl was found in 4/44 sequences; it bound B08 moderately well, but was poorly recognized. 3 double mutants were found once each, and were not recognized by CTL: fIkeNggL, flEeNggL, and flkGNggL.

HXB2 Location Nef (90–97)
Author Location Nef (89–97)
Epitope FLKEKGGL
Immunogen HIV-1 infection
Species (MHC) human (B8)
Assay type Cytokine production, proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, memory cells, characterizing CD8+ T cells
References Daniel *et al.* 2004

- CD4+ and CD8+ responses in chronically HIV-1 infected patients on HAART were weak with decreased polyclonality. Only 33% of patients had CD4+ T-cells that could proliferate, and only 22% had HIV-specific CD8+ T-cells T-cell responses, and those rare responses showed low perforin levels and persistent expression of CD27, indicating incomplete differentiation and loss of lytic function.

HXB2 Location Nef (90–97)
Author Location Nef
Epitope FLKEKGGL
Epitope name FL8
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country United States
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords immunodominance, acute/early infection, characterizing CD8+ T cells, immune dysfunction
References Lichterfeld *et al.* 2004a

- HIV-1 specific CD8+ T-cells in acute and long-term nonprogressive HIV-1 infection show strong ex-vivo proliferative capacities which are rapidly lost in chronic HIV-1 infection. The loss of CD8+ T-cell function is closely linked with the loss of HIV-1 specific, IL2 secreting CD4+ T-cells. The function can be rescued in vitro and in vivo by restoring the specific CD4+ T-cell help.
- Full CD8+ T-cell responses to this epitope were dependent on co-stimulation with a CD4+ T cell dependent epitope from T-cells harvested during acute infection. The CD8+ T-cell response to this epitope was immunodominant in one study individual.

HXB2 Location Nef (90–97)
Author Location (B consensus)
Epitope FLKEKGGL
Epitope name FL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A02, A03, B08, B62, Cw10, Cw7; A11, A29, B08, B44, Cw4, Cw7; A25, A32, B08, B14, Cw7, Cw8; A01, A03, B08, B14, Cw7, Cw8
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

CTL CD8+

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 4/9 individuals recognized this epitope, presented by HLA-B8.

HXB2 Location Nef (90–97)
Author Location Nef
Epitope FLKEKGGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country United Kingdom
Assay type Tetramer binding, T-cell Elispot, Intracellular cytokine staining
Keywords rate of progression, acute/early infection, characterizing CD8+ T cells, immune dysfunction
References Papagno *et al.* 2004

- Acute HIV-1 infection induces massive activation of HIV-specific and non-HIV-specific CD8+ T-cells resulting in differentiation of these cells. High differentiation of CD8+ T-cells is correlated with disease progression. Differentiation is a natural process but it can be driven by elevated immune activation, such as in HIV infection.

HXB2 Location Nef (90–97)
Author Location Nef
Epitope FLKEKGGL
Epitope name FL8
Immunogen HIV-1 infection
Species (MHC) human (B8)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 5, FLKEnGGL, was found not to correspond to the most polymorphic residue in the epitope.

HXB2 Location Nef (90–97)
Author Location Nef
Epitope FLKEKGGL
Epitope name FL8
Immunogen
Species (MHC) (B8)
Keywords review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion
References Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

HXB2 Location Nef (90–97)
Author Location Nef (90–97 HXB2)
Epitope FLKEKGGL
Epitope name FL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A*0101, A*0201, B*0801, B*50, Cw*0602, Cw*0701
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, viral fitness and reversion, optimal epitope
References Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- A Nef epitope FLKEeGGL (Nef-94E) presumed escape variant was transmitted from a B8 positive donor to a B8 negative recipient. FLKEgGGL, FLKgeGGL variants as well as FLKEkGGL reversions were found in the recipient subject.

HXB2 Location Nef (90–97)
Author Location Nef
Epitope FLKEKGGL
Epitope name B8-FL8(Nef)
Immunogen HIV-1 infection
Species (MHC) human (B8)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (90–97)
Author Location
Epitope FLKEKGGL
Immunogen
Species (MHC) (B8)
Keywords review, immunodominance, escape, vaccine antigen design
References Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection (recognized by >70% of subjects).

HXB2 Location Nef (90–97)
Author Location
Epitope FLKEKGGL?
Epitope name FL8
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country United States, South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding
Keywords memory cells
References Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

HXB2 Location Nef (90–97)
Author Location Nef
Epitope FLKEKGGL
Epitope name FL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- 163 days after first testing, this epitope, FLKEKGGL, went from dual- and triple-functional to monofunctional in the response it was able to elicit.
- Epitope FLKEKGGL showed no variation in a treated patient. 163 and 364 days after first testing, epitope FLKEKGGL showed no variations in untreated patients; 409 days after first testing, epitope FLKEKGGL showed variations in untreated patients to FLrKEGGL, and to FLKEqGGL. Previously published HLA-restriction for FL8 is HLA-B8.

HXB2 Location Nef (90–97)
Author Location Nef (90–97)
Epitope FLKEMGGL
Epitope name FL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-B8-restricted autologous epitope FLKEMGGL elicited decreasing CTL responses at the last 2 time points. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location Nef (90–97)
Author Location Nef (90–97)
Epitope FLKEKGGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country Switzerland
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords HAART, ART
References Rehr *et al.* 2008

- By following T-cell function in ART-regimented patients over time, it was shown that ART resulted in reduced viral replication and the restoration of CTLs to polyfunctionality. It is concluded that in vivo antigenic exposure during declining viremia has a positive influence on CTL function.
- Epitope FLKEKGGL was used to interrogate CTL function in 37 chronically-infected HIV-1 positive subjects, with respect to cytokine production.

HXB2 Location Nef (90–97)
Author Location Nef (89–97)
Epitope FLKEKGGL
Immunogen HIV-1 infection
Species (MHC) human
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the A2+ individuals that responded to SLYNTVATL reacted with seven other epitopes including this epitope previously described as presented by B8.

HXB2 Location Nef (90–97)
Author Location Nef (90–97)
Epitope FLKEKGGL
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A1, B7, B8
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, FLKEKGGL, was found to be 0.049/day, with SE of 0.012.
- In the subject studied, a number of variants arose in the Nef epitope 90-97 (including complete epitope deletion) that were poorly recognized by CTL or escaped recognition completely.

HXB2 Location Nef (90–97)
Author Location
Epitope FLKEKGGL
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101; B*0801, B*1401
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- FLKEKGGL was recognized by a placebo patient after infection.

HXB2 Location Nef (90–97)
Author Location
Epitope FLKEKGGL
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A1, A10 (26); B17 (57), B8
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes
References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location Nef (90–97)
Author Location
Epitope FLKEKGGL
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords binding affinity, acute/early infection
References Lichterfeld *et al.* 2007b

- Differences in early versus chronic AIDS include a decline in CTL number accompanied by a reducing viremia. Comparative analysis of such CTLs in this study show that early infection is characterized by a different clonotypic composition and higher functional avidity of CTLs followed by their selective depletion during transition to chronic disease. The total magnitude of CTL cytokine production is lower in early infection. Intraindividual, early CTLs' functional avidity for the same epitope decreases concomitantly with a reduction in clonotypic TCR repertoire especially of strongly activated and

CD127lo, CD38+, Ki-67hi CTLs while progressing to chronic infection states.
- None of the target epitopes, including this epitope FLKEKGGL seen in 4 patients, underwent sequence changes.

HXB2 Location Nef (90–100)
Author Location Nef (90–100 BRU)
Epitope FLKEKGGLEGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001
- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- FLKEKGGLEGL was recognized in 8/12 (67%) of individuals with HLA A2. It was a low affinity HLA A2 binder.

HXB2 Location Nef (90–104)
Author Location Nef (90–105 HXB2)
Epitope FLKEKGGLEGLIHSQ
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003
- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- Responses to this peptide were detected in 16% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location Nef (92–100)
Author Location Nef (92–100)
Epitope KEKGGLEGL
Epitope name KL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*40)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007
- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- A minor response was detected against an E98D variant of this epitope, KEKGGLdGL.

HXB2 Location Nef (92–100)
Author Location Nef (92–100)
Epitope KEKGGLEGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*40)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords assay standardization/improvement, optimal epitope
References Wang *et al.* 2007c
- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A*11-restricted epitopes were recognized less frequently than other epitopes, and A*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, KEKGGLEGL, was detected within overlapping peptide SHFLKEKGGLEGLIYSQK.

HXB2 Location Nef (92–100)
Author Location Nef (92–100)
Epitope KEKGGLEGL

Epitope name KL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*40)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*40-associated substitutions within optimally defined epitope KEKGGLEGL are at positions E2, E7 and L9, KeKGGLeGl.

HXB2 Location Nef (92–100)
Author Location (LAI)
Epitope KEKGGLEGL
Subtype B
Immunogen
Species (MHC) human (B*4001)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*4001,B60 epitope.

HXB2 Location Nef (92–100)
Author Location Nef
Epitope KEKGGLEGL
Epitope name KL9
Immunogen
Species (MHC) (B*4001)
Keywords review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion
References Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

HXB2 Location Nef (92–100)
Author Location Nef
Epitope KEKGGLEGL
Epitope name KL9
Immunogen HIV-1 infection
Species (MHC) human (B*4001)
Donor MHC A*0201, A*2402, B*4001, B*5001, Cw03, Cw04
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords immunodominance, escape, variant cross-recognition or cross-neutralization
References Draenert *et al.* 2006

- HIV-specific cellular and humoral immune responses were examined in monozygotic male twins infected simultaneously with the same virus. 15 of 17 targeted epitopes were identical in the twins, including two immunodominant responses. 3 of 4 declining responses in the twins showed mutations at the same residue. Evolving antibody responses cross-neutralized the other twin's virus. The results were compared with a third brother, infected by the twins' virus 13 months after their seroconversion. The data show similarity in disease course in persons of identical genetic background infected with the same strain of HIV-1.
- This epitope, KEKGGLEGL (KL9) restricted by HLA-B*4001, was one of two immunodominant responses.

HXB2 Location Nef (92–100)
Author Location
Epitope KEKGGLEGL
Epitope name Nef-KL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*4002)
Donor MHC A*0201, A*3201, B*4002, B*5301, Cw*0202, Cw*0401
Keywords HAART, ART
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Patient 01RCH59 was Hispanic, not on HAART, and had a viral load of 5100 and CD4 count of 349 – she also recognized TERQANFL, p2p7p1p6(64-70), HLA-B*4002 and AEWDRVHPV, p24(78-86), HLA-B*4002.
- Among HIV+ individuals who carried HLA B40, 3/5 (60%) recognized this epitope.

HXB2 Location Nef (92–100)
Author Location Nef (92–100)
Epitope KEKGGLEGL
Immunogen
Species (MHC) human (B*4002)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Nef (92–100)
Author Location Nef
Epitope KEKGGLEGL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4403)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ

CTL CD8+

Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- RPQVPLRPM is a previously described HLA-B*4403-restricted epitope (part of Nef reacting peptides AAFDLSF-FLKeKGGLEGLIYS and KEKGGLEGLIySKKRQEILDL) that contain a B*4403-associated reversion at residue E (KeKGGLEGL).

HXB2 Location Nef (92–100)
Author Location Nef
Epitope KEKGGLEGL
Epitope name B40-KL9(Nef)
Immunogen HIV-1 infection
Species (MHC) human (B40)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (92–100)
Author Location Nef
Epitope KEKGGLEGL
Epitope name KL-9
Immunogen HIV-1 infection
Species (MHC) human (B40)
Keywords escape, TCR usage, immune evasion
References Yu *et al.* 2007b

- The dependence of TCR clonotype recruitment on genetic background was determined by studying monozygotic twins infected with the same HIV-1 strain. After an early, initial correlation in the magnitude, specificity and immunodominance of CTL response [Draenert et al. J. Exp. Med. 203:529-539(2006)], subsequent disease was mixed with respect to CTL epitopes' mutational escape. TCR alpha and beta chain repertoires were analyzed and it was found that their clonotypes in HIV-specific CTLs were broadly heterogeneous for both concordant and discordant epitope sequence evolution between the twins. Therefore initial TCR recruitment appears to be an entirely random process independent of genetic background of the infected individual.
- This epitope, KL9, showed concordant epitope evolution between the twins, but both alpha and beta TCR chains recruited were entirely different between them.

HXB2 Location Nef (92–100)
Author Location
Epitope KEKGGLEGL
Immunogen HIV-1 infection
Species (MHC) human (B40)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B40), an additional HLA (B49) was statistically predicted to be associated with this epitope.

HXB2 Location Nef (92–100)
Author Location Nef
Epitope KEKGGLEGL
Epitope name KL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B40)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- Epitope KEKGGLEGL varied to rEKGGLEGL in an untreated patient. Previously published HLA-restriction for KL9 is HLA-B40.

HXB2 Location Nef (92–100)
Author Location Nef
Epitope KEKGGLEGL
Epitope name KL9(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B40)

CTL CD8+

Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- HLA-B40-restricted epitope KEKGGLEGL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide SHFLKEKGGLEGLIYSQK.
- 11 of the 20 HLA-B40 carriers responded to KEKGGLEGL-containing peptide with average magnitude of CTL response of 321 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Nef (92–100)
Author Location Nef (90–98 SF2)
Epitope `KEKGGLEGL`
Immunogen HIV-1 infection
Species (MHC) human (B60)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B60+ individuals that had a CTL response to this epitope broken down by group: 2/2 group 1, 1/1 group 2, and 0/0 group 3.

HXB2 Location Nef (92–100)
Author Location Nef (SF2)
Epitope `KEKGGLEGL`
Immunogen HIV-1 infection
Species (MHC) human (B60)
References Altfeld *et al.* 2000

- This epitope was the dominant B60 (encoded by B*4001) response in 6/8 HLA-B60 individuals, and recognized in all eight.
- This epitope was also recognized two expressing HLA-B61 individuals (B61 is usually encoded by B*4002, but this study did not distinguish between B*4002, B*4003, B*4004, B*4006, and B*4008)
- ELISPOT was a rapid an effective method that was used to define five novel B60 epitopes.
- HLA-B60 is present in 10-20% of the Caucasoid population and B60/B61 are very common in Asian populations.

HXB2 Location Nef (92–100)
Author Location Nef
Epitope `KEKGGLEGL`
Immunogen HIV-1 infection
Species (MHC) human (B60)
Keywords epitope processing
References Cao *et al.* 2002

- KM is a B60 restricted CTL clone that recognizes KEKGGLEGL.
- CTL could be activated by a fusion protein of an HIV protein and anthrax lethal factor (LFn-HIV) that promotes antigen presenting cell uptake of exogenous protein and allows processing through the MHC class I pathway. This strategy for CTL detection could allow antigen presentation without generation of cells by the standard methods of using live viral vectors carrying a protein, or by loading the cells with peptides and by-passing processing.

HXB2 Location Nef (92–100)
Author Location Nef (92–100 NL-43)
Epitope `KEKGGLEGL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B60)
Keywords class I down-regulation by Nef, escape
References Ali *et al.* 2003

- NL43 was passaged in the presence of Nef KEKGGLEGL-specific CTL clones STD11 and KM3, giving rise to rapid selection of escape mutations, including E93G, E93K, K94N+G99R, G95R+G99R, E98K, E98D, G99R, G99E, L100P, and L100I; insertions, deletions, frameshifts and an early stop codon. 34/36 (94%) of sequences carried mutations in the epitope by seven days, 36/36 (100%) by 14 days.
- NL43 was also passaged in the presence of a Nef TQGYFPDWQNY-specific CTL clone. 7/15 clones had a frameshifting or stop codon introduced by one week; F121T was also observed. The most common escape mutation for both Nef epitopes was an early stop codon at position 91.
- Several mutations selected by KEKGGLEGL-specific CTL were shown to impair the down regulation of class I MHC by Nef, in particular E93G, E93K, and a truncation mutation at position 51.
- Nef deletion mutants increased 100-fold NL-43 susceptibility to inhibition by CTL specific for epitopes in other proteins, the A2 epitopes ILKEPVHGV in RT and SLYNTVATL in p17 Gag.

HXB2 Location Nef (92–100)
Author Location Nef
Epitope `KEKGGLEGL`
Epitope name KL9
Immunogen HIV-1 infection
Species (MHC) human (B60)
Donor MHC A2, A24, B38, B60, Cw12, Cw2
Assay type CD8 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), early treatment
References Montefiori *et al.* 2003

- HIV-1 + patient AC10 underwent early HAART treatment, which was discontinued 1.5 years later. At this timepoint potent NAb responses against autologous virus were detected. Treatment interruption initially induced weak CD8+ responses directed against 5 epitopes. By days 873d and 923d the CTL response had broadened to target 22 epitopes; of these six were fully characterized. Eventually the virus escaped the NAb response, but escape was not accompanied by a rise in viral load, and the authors suggest the virus was contained by the CTL response.

HXB2 Location Nef (92–100)
Author Location Nef (92–100 NL43)
Epitope KEKGGLEGL
Epitope name KL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B60)
Assay type Chromium-release assay, CTL suppression of replication
Keywords escape
References Yang *et al.* 2003a

- Virus was cultured in the presence of CTL lines specific for 5 different epitopes (SLYNTVATL, ILKEPVHGV, IEIKDTKEAL, SEGATPQDL, and KEKGGLEGL) to study the emergence of escape mutations. Escape varied between clones for the same epitope, and between different epitopes. Gag and RT epitope escape, if it occurred at all, tended to be monoclonal and within the epitope, indicating strong fitness constraints, while the Nef epitope escape was rapid, polyconal, and sometimes the result of upstream frameshifts.
- Two cloned CTL lines recongized KEKGGEGL, STD11 and KM3. Highly resistant clones emerged after a single round of passage with both CTL clones, and multiple substitutions accrued including frameshits and stop codons, reflecting the dispensability of Nef in viral culture.
- The following epitope variants were observed after passaging with clone STD11 for one week: kekggegI, kKkggegl, and 12/20 frameshifts and 1 early stop. By two weeks, a more complex polyclonal mixture was observed including: kekggegI, kKkggegl kekggegP, kekggeEl, kekggeRl, kekRgeRl, keNggeRl, and 11/22 framshifts.

HXB2 Location Nef (92–100)
Author Location Nef (92–100)
Epitope KEKGGLEGL
Epitope name Nef KL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B60)
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, TCR usage, characterizing CD8+ T cells
References Yang *et al.* 2003b

- Killing efficiency of CTLs and their ability to suppress viral replication is shown to depend more on epitope specificity than to antigenic avidity. Different clones recognizing the same epitope had similar killing efficiency despite their variation in avidity. Nef specific CTL clones tended to be most inhibitory, followed by Gag, then by RT specific clones, regardless of avidity.
- 2/14 CTL T-cell clones tested were specific for Nef KL9. Under conditions of excess peptide (100ug/ml), there was no difference in their lytic potential; all possessed similar effector capacity. Avidity was measured as the sensitizing dose of peptide required for 50% of maximal killing (SD50), which varied from 20 pg/ml to 100 ng/ml, over four orders of magnitude for all 14 epitopes. The SD50 range for Nef KL9 was 20-30 pg/ml, both high avidity. These clones were among the most efficient at inhibiting viral replication in the set tested, but because of the general lack of correlation between avidity and viral inhibition efficiency in this study, the authors attribute other reasons to Nefs ability to inhibit viral replication that pertain to presentation like kinetics and expression levels.

HXB2 Location Nef (92–100)
Author Location (B consensus)
Epitope KEKGGLEGL
Epitope name KL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B60)
Donor MHC A03, B14, B60, Cw3, Cw7
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope; the authors write that it is presented by HLA-B40 in their Table 1, but the subject that recognizes it, AC05, is HLA-B60, so we assume they meant B60.

HXB2 Location Nef (92–100)
Author Location Nef (92–100)
Epitope KEKGGLEGL
Immunogen HIV-1 infection
Species (MHC) human (B60, B61)
Keywords immunodominance
References Day *et al.* 2001

- No immunodominant responses were detected to five B61-restricted epitopes tested.
- All five B60-restricted epitopes were reactive in another subject, and the B60-restricted responses together contributed over one-third of the total CTL response.

HXB2 Location Nef (92–105)
Author Location Nef
Epitope KEKGGLEGLVYSQK
Subtype B

CTL CD8+

Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Novel unmapped epitope.There was a V->A change KEKGGLEGLaYSQK over time in an individual that reacted with this peptide.

HXB2 Location Nef (92–112)
Author Location Nef (SF2)
Epitope `KEKGGLEGLIHSQRRQDILDL`
Immunogen HIV-1 infection
Species (MHC) human
References Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined.

HXB2 Location Nef (92–112)
Author Location Nef (SF2)
Epitope `KEKGGLEGLIHSQRRQDILDL`
Immunogen HIV-1 infection
Species (MHC) human
References Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined.

HXB2 Location Nef (93–106)
Author Location Nef (93–106 BRU)
Epitope `EKGGLEGLIHSQRR`
Immunogen HIV-1 infection
Species (MHC) human (A1, B8)
References Hadida *et al.* 1992

- HIV-1 specific CTLs detected in lymphoid organs of HIV-1 infected patients.

HXB2 Location Nef (93–106)
Author Location Nef (93–106)
Epitope `EM/KGGLEGLV/IYSQKR`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A1, B8)
Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-A1 and B8-restricted autologous epitope EM/KGGLEGLV/IYSQKR failed to generate CTL response. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location Nef (96–113)
Author Location Nef
Epitope `GLEGLIYSQKRQDILDLW`
Epitope name NEF-14
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, GLEGLIYSqKRQdILDLW differs from the consensus C sequence GLEGLIYSkKRQeILDLW at 2 amino acid positions, i.e. by 11.1%.

CTL CD8+

HXB2 Location Nef (97–111)
Author Location Nef (97–111)
Epitope LEGLIYSKKRQEILD
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location Nef (101–109)
Author Location Nef (101–109 SF2, HXBc2/Bal R5)
Epitope IHSQRRQDI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A24)
Donor MHC A24, A25, B18, B7, Cw12, Cw7
Country United States
Assay type Cytokine production, Flow cytometric T-cell cytokine assay, Degranulation, CD107a and b cell surface mobilization
Keywords supervised treatment interruptions (STI), immunodominance, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells, drug resistance
References Daucher *et al.* 2008

- A detailed analysis of 6 chronically infected patients' CTL responses to autologous virus was performed after ART and SIT (structured interruption of therapy). Qualitative responses including degranulation and production of IFN-gamma, MIP-1beta, TNF-alpha, IL-2, but not memory CD27, CD45RO and CD57 T cells correlated with extended low plasma viremia. Frequency and breadth of CTL response as well as immune escape did not influence virological outcome.
- One patient exhibited drug resistance mutations K170R (to NNRTI efavirenz) and D76N, K70R (to NRTIs).
- Data confirmed that autologous epitopes were preferentially recognized over optimal, consensus sequences.
- Patients with favorable virological outcomes demonstrated CTL recognition within multiple, conserved regions of Gag and Nef.
- Patients with poor virological outcomes recognized optimal epitopes with much lower frequencies, though this was not significant.
- HLA-A24-restricted epitope, IHSQRRQDI, elicited a response in 1 patient and is found in Nef immunodominant region IHSQRRQDILDLWIYGTQG. Patient autologous sequence was IySQkRQDI.

HXB2 Location Nef (101–109)
Author Location Nef (101–109)
Epitope IYSQKRQDI
Subtype B
Immunogen HIV-1 infection, peptide-HLA interaction
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords immunodominance
References Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, IYSQKRQDI, is similar to human protein Ig heavy chain variable region, sequence tYSQKfQDI.

HXB2 Location Nef (101–115)
Author Location Nef (101–115)
Epitope IYSQKRQDILDLWIY
Epitope name KY11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw07)
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- The peptide, IYSQKRQDILDLWiY, is a variant of the consensus peptide IYSQKRQDILDLWVY.

HXB2 Location Nef (101–115)
Author Location
Epitope IHSQRRQDILDLWIY
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
Species (MHC) human
Donor MHC A1, A2; B38, B8
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes

CTL CD8+

References Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromized by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

HXB2 Location Nef (102–110)
Author Location Nef (102–110)
Epitope `HSQRRQDIL`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope HSQRRQDIL showed some conservation to subtype B. It's HLA-restriction is predicted to be either to HLA-A*24, -B*37, Cw*0602 or Cw*0401.

HXB2 Location Nef (102–110)
Author Location Nef
Epitope `HSQRRQDIL`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords HLA associated polymorphism
References Rousseau *et al.* 2008

- 3 phylogenetic correction methods—MLL (maximum likelihood character state analysis followed by likelihood ratio test), MLF (maximum likelihood character state analysis followed by Fisher test), and parsimony character state analysis were used to identify points in the HIV-1 subtype C proteome that conferred susceptibility or resistance to CTLs. Associations of HLA-epitope combinations that were inferred to be susceptible or resistant were organized into immunological sets that would help identify the best residues and genes as candidates for vaccines. While all proteins were interrogated, Gag, Pol, Env and Nef were focused upon. Amino acid changes were evaluated for association with plasma viral load.
- Proteome maps may be seen at `http://www.hiv.lanl.gov/content/immunology/hlatem/study5/index.html` with information showing single or multiple sites involving escape and reversion.
- HLA- B and -C alleles associated more with aa changes than HLA-A, suggesting that the former two are more important in driving viral evolution.
- The ratio of susceptible to resistant residues in HIV proteins was in descending order, Vpr>Gag>Rev>Pol>Nef>Vif>Tat>Env>Vpu, showing that epitopes from the earlier proteins are more conserved owing to viral fitness cost upon mutation.
- This Nef HLA-Cw*0404-restricted epitope, HSQRRQDIL, lies within a set of 6 immunological associations, experiencing conflicting selective pressures.

HXB2 Location Nef (102–115)
Author Location Nef (102–115 LAI)
Epitope `HSQRRQDILDLWIY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords review, escape
References Goulder *et al.* 1997e; Goulder *et al.* 1997a

- HLA identical sibling hemophiliac brothers were both infected with the same batch of factor VIII.
- They were tested 6-8 years after infection; one had a strong response to this peptide, the other did not.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

HXB2 Location Nef (102–115)
Author Location Nef (100–113)
Epitope `HSQRRQDILDLWIY`
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.

- 5/7 patients recognized this epitope.

HXB2 Location Nef (102–121)
Author Location Nef (101–120 SF2)
Epitope HSQRRQDILDLQIYHTQGYF
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- Two of these 11 had CTL response to this peptide.
- The responding subjects were HLA-A2, A3, B8, B62 and HLA-A2, B21.

HXB2 Location Nef (103–117)
Author Location Nef (103–117)
Epitope SQRRQDILDLWVYHT
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw07)
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This epitope, SQRRQDILDLWVYHT, varies at position 3 from the consensus peptide KRQDILDLWVYHTQG.

HXB2 Location Nef (103–117)
Author Location Nef
Epitope SKKRQEILDLWVYHT
Subtype A, D
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0202, A*3002, B*5703, B*5802; A*6801, A*7401, B*0702, B*3501
Country Uganda
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, variant cross-recognition or cross-neutralization
References Barugahare *et al.* 2005

- T-cell immune responses were examined in HIV-1 infected Ugandans. Similar levels of cross-clade responses for Gag, Env and Nef were observed. Higher frequencies of responses in conserved regions were found for Gag within a single clade, while areas with higher viral sequence variation had fewer detectable responses. Differential interclade sequence homologies between the Gag regions did not affect the respective level of cross-clade recognition.
- The sequence contains a previously-defined epitope (KRQEILDLWVY) of unknown HLA restriction. The viral sequence from the subjects that recognized the peptide was skkrqKildlwvyNt.

HXB2 Location Nef (103–127)
Author Location Nef (103–127 PV22)
Epitope SQRRQDILDLWIYHTQGYFPDWQNY
Immunogen HIV-1 infection
Species (MHC) human (B13)
References Jassoy *et al.* 1993

- HIV-1 specific CTLs release γ-IFN, and α- and β-TNF.

HXB2 Location Nef (103–127)
Author Location Nef (103–127)
Epitope SQRRQDILDLWIYHTQGYFPDWQNY
Epitope name SQR
Immunogen HIV-1 infection
Species (MHC) human (B13)
Keywords HAART, ART, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- The only study subject out of eight that was HLA B13+ recognized this epitope.
- Patient SC9 (HLA A1/2, B8/13, Cw0/0701, DR2/11, DQ6/7) had a CTL response against epitopes FLKEKGGL, ILKEPVHGV, SQRRQDILDLWIYHTQGYFPDWQNY, and GEIYKRWII peptides and all responses declined during therapy initiated at day 390 but were restored when therapy become intermittent.

HXB2 Location Nef (104–112)
Author Location Nef (104–112)
Epitope QRRQDILDL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

CTL CD8+

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope QRRQDILDL showed some conservation to subtypes A and B. It is predicted to be restricted by HLA-B*37 or -Cw*0602.

HXB2 Location Nef (104–121)
Author Location Nef
Epitope QKRQDILDLWVYHTQGYF
Epitope name NEF-15
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, qKRQdILDLWVYHTQGYF differs from the consensus C sequence kKRQeILDLWVYHTQGYF at 2 amino acid positions, i.e. by 11.1%.

HXB2 Location Nef (104–121)
Author Location Nef
Epitope QKRQDILDLWVYHTQGYF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, QKRQDILDLWVYHTQGYF, had an overall frequency of recognition of 26% - 28.8% AA, 26.9% C, 25% H, 19% WI. This peptide is included in a 54 aa Nef highly reactive region to be used for vaccine design. It is also part of 'Region II', QKRQDILDLWVYHTQGYFPDWQNYTPGPGIRYPLTFGWCFKLVPVEPEKVEEAN, a 54 aa region recognized by >90% of subjects across ethnic groups.

HXB2 Location Nef (105–113)
Author Location Nef
Epitope KRQEILDLW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords HLA associated polymorphism
References Rousseau *et al.* 2008

- 3 phylogenetic correction methods—MLL (maximum likelihood character state analysis followed by likelihood ratio test), MLF (maximum likelihood character state analysis followed by Fisher test), and parsimony character state analysis were used to identify points in the HIV-1 subtype C proteome that conferred susceptibility or resistance to CTLs. Associations of HLA-epitope combinations that were inferred to be susceptible or resistant were organized into immunological sets that would help identify the best residues and genes as candidates for vaccines. While all proteins were interrogated, Gag, Pol, Env and Nef were focused upon. Amino acid changes were evaluated for association with plasma viral load.

- Proteome maps may be seen at `http://www.hiv.lanl.gov/content/immunology/hlatem/study5/index.html` with information showing single or multiple sites involving escape and reversion.
- HLA- B and -C alleles associated more with aa changes than HLA-A, suggesting that the former two are more important in driving viral evolution.
- The ratio of susceptible to resistant residues in HIV proteins was in descending order, Vpr>Gag>Rev>Pol>Nef>Vif>Tat>Env>Vpu, showing that epitopes from the earlier proteins are more conserved owing to viral fitness cost upon mutation.
- This Nef HLA-B*44-restricted epitope, KRQEILDLW, lies within a set of 7 immunological associations, experiencing the most conflicting selective pressures.

HXB2 Location Nef (105–114)
Author Location Nef (105–114 LAI)
Epitope `RRQDILDLWI`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*2705)
Keywords rate of progression
References Goulder *et al.* 1997c

- Defined as optimal epitope from within reactive peptide HSQRRQDILDLWIYHTQGYF [Nef(102-121 LAI)]
- HLA-B*2705 is associated with slow HIV disease progression.
- The HLA-B*2705 binding motif includes R at position 2, and L in the C-term position.

HXB2 Location Nef (105–114)
Author Location Nef (105–114 LAI)
Epitope `RRQDILDLWI`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*2705)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*2705 epitope.

HXB2 Location Nef (105–114)
Author Location Nef (105–114 SF2)
Epitope `RRQDILDLWI`
Immunogen HIV-1 infection
Species (MHC) human (B27)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B27+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/0 group 2, and 1/1 group 3.

HXB2 Location Nef (105–114)
Author Location Nef (105–114)
Epitope `RRQDILDLWI`
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Day *et al.* 2001

- B27-restricted CTL response was strongest to this epitope in one individual.

HXB2 Location Nef (105–114)
Author Location
Epitope `RRQDILDLWI`
Epitope name Nef-RI10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B27, 1/2 (50%) recognized this epitope.

HXB2 Location Nef (105–114)
Author Location Nef
Epitope `RRQDILDLWI`
Epitope name RI10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- RI10, RRQDILDLWI, is a known HLA-B27-restricted epitope used as a positive control for eliciting CTL IFN-gamma response.

HXB2 Location Nef (105–115)

Author Location Nef (105–115)
Epitope RRQDILDLWVY
Epitope name RY11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*18)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*18-associated substitution within optimally defined epitope RRQDILDLWVY is at position D4, RRQdILDLWVY.

HXB2 Location Nef (105–115)
Author Location Nef
Epitope KRQEILDLWVY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1801, B*4403)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008

- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- KRQEILDLWVY is a previously described HLA-B*4403 and -B*18(01)-restricted epitope (part of Nef reacting peptide EGLIYSKKRQeILDLWVYHTQ) that contains a B*4403 and B*18(01)-associated reversion at residue e (KRQeILDLWVY).

HXB2 Location Nef (105–115)
Author Location
Epitope RRQDILDLWVY
Epitope name RY11
Immunogen
Species (MHC) human (B18)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B18 epitope.

HXB2 Location Nef (105–115)
Author Location Nef (105–115)
Epitope RRQDILDLWVY
Epitope name RY11
Immunogen HIV-1 infection
Species (MHC) human (Cw*07)
Assay type CTL suppression of replication
Keywords class I down-regulation by Nef
References Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Nef epitope RRQDILDLWVY-recognizing HLA-C restricted CTLs were unaffected by Nef.

HXB2 Location Nef (105–115)
Author Location (C consensus)
Epitope KRQDILDLWIY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0701)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the R2 residue of KRQDILDLWIY are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location Nef (105–115)
Author Location Nef
Epitope KRQEILDLWVY
Immunogen HIV-1 infection
Species (MHC) human (Cw*0701)
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons, cross-presentation by different HLA, variant cross-recognition or cross-neutralization
References Currier *et al.* 2006

- The pattern of immunodominance and epitope clustering within Gag and Nef proteins in subtype A infected individuals was similar to that seen in subtype B and C infections. An immunodominant HLA-C restricted epitope, YVDRFFKTL (YL9 from Gag protein) was observed and restricted to Cw0304.
- The sequence kKRQEILDLWVYhtq is associated with HLA-Cw*0701 and contains the epitope KRQEILDLWVY.

HXB2 Location Nef (105–115)
Author Location
Epitope KRQDILDLWVY

Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0701)
Donor MHC A*2301, B*0801, B*1510, Cw*0701, Cw*1601
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- Known epitope KRQDILDLWVY is HLA-Cw*0701-restricted. Response to a peptide containing this epitope was detected in a rapid progressor 12 weeks post-infection.

HXB2 Location Nef (105–115)
Author Location (C consensus)
Epitope KRQEILDLWVY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0701, Cw*0702)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords cross-presentation by different HLA, characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location Nef (105–115)
Author Location (C consensus)
Epitope KRQDILDLWIY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw*0702)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Optimal epitope.

HXB2 Location Nef (105–115)
Author Location
Epitope RRQDILDLWIY
Immunogen HIV-1 infection
Species (MHC) human (Cw07)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope RRQDILDLWIY elicited a magnitude of response of 460 SFC with a functional avidity of 0.0005nM.

HXB2 Location Nef (105–115)
Author Location Nef (105–115)
Epitope RRQDILDLWIY
Epitope name Cw7-RY11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw7)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- AC-06 was homozygous at all three class I alleles (A3, B7, Cw7), and was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 response to RRQDILDLWIY restricted by HLA-Cw7.

HXB2 Location Nef (105–115)
Author Location Nef (105–115)
Epitope KRQEILDLWVY
Immunogen
Species (MHC) human (Cw7)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this as a Cw7 epitope. Variant rRQdILDLWiY also noted.

HXB2 Location Nef (105–115)
Author Location Nef (C consensus)
Epitope KKQEILDLWVY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (Cw7)

CTL CD8+

Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- People who carried Cw07 often carried a variant of this epitope, while the susceptible form of the epitope was highly conserved among those who did not.

HXB2 Location Nef (105–115)
Author Location Nef (105–115)
Epitope KRQDILDLWVY
Epitope name KY11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, acute/early infection, immune evasion
References Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- 4 additional variants of this epitope, KRQDILDLWVY, were determined using PTE-B - rRQDILDLWVY, KRQeILDLWVY, rRQeILDLWiY, and KRQDILDLWiY. Only the consensus and last variant, KRQDILDLWiY, were found as patient autologous sequences.
- HLA-Cw07 restriction for KY11 was presumed based on the subject having the HLA allele and publication in the Los Alamos database.

HXB2 Location Nef (105–115)
Author Location Nef
Epitope RRQDILDLWIY
Epitope name RY11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords superinfection
References Streeck *et al.* 2008b

- Loss of viral replication control by an elite controller after superinfection was found to coincide with rapid recombination events in 2, ∼50 residue regions of Gag and Env that include immunodominant epitopes KK10 (KRWIILGLNK) and CL9 (CAPAGFAIL). Viral escape was seen at both epitopes and consequent CTL responses against the epitope-variants.
- CTL responses to previously described, HLA-Cw7-restricted RRQDILDLWIY were seen post-superinfection and -recombination.

HXB2 Location Nef (105–115)
Author Location Nef
Epitope KRQDILDLWVY
Epitope name KY11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- This epitope, KRQDILDLWVY, went from polyfunctional to monofunctional in the response it was able to elicit, without epitope variations. Previously published HLA-restriction for KY11 is HLA-Cw7.

HXB2 Location Nef (105–115)
Author Location Nef (105–115)
Epitope KRQEILDLWVY
Epitope name KY11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw7)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-Cw*07-associated substitutions within optimally defined epitope KRQEILDLWVY are at positions K1 and V10, kRQEILDLWvY.

HXB2 Location Nef (105–115)
Author Location Nef (105–115)

Epitope KRQDILDLWVY
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* Gag *Adjuvant:* aluminum phosphate
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
References Balamurugan *et al.* 2008

- To check whether unsuccessful vaccines may interfere with normal patient immune response,2 subjects were followed. The first, 00015, was seronegative while receiving vaccination, but later contracted infection. The second, 00016, had temporary sexual contact with subject 00015 and showed symptoms of disease 2 weeks before him. Without treatment, both reached low chronic viremic levels, and showed similar magnitude of immune response.
- Similar immune pressure was seen on viral sequences in both patients, over time in Gag, Pol, Nef.
- Data suggest that the vaccine failed to prime subject 00015 against HIV infection, but it did not impair ability to naturally contain viremia in comparison with infecting subject 00016.
- CTL immune response to consensus sequence KRQDILDL-WVY was elicited in subject 00016. Consensus epitope of both subjects was KRQeILDLWVY.

HXB2 Location Nef (105–119)
Author Location Nef (105–119 HXB2)
Epitope RRQDILDLWIYHTQG
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 19% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location Nef (106–114)
Author Location Nef (106–114)
Epitope RQDILDLWV
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*13)
Donor MHC A*0301, A*3001, B*1301, B*1402, Cw*0602, Cw*0802
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords epitope processing, immune evasion, viral fitness and reversion, HLA associated polymorphism
References Honeyborne *et al.* 2007

- To determine whether HLA-B*13-restricted CTL responses could partially explain low viremic loads in patients, a cohort of chronic C-clade infected subjects was studied. 6 novel B*13-restricted CTL epitopes were defined from both C- and B-clade viruses, 3 of which were within Gag. B*13-restricted CTL responses correlated with lower viremia, with most immunity targeted against Gag epitopes (p15, p17, p24). Gag epitope escape variants may exact a high viral fitness cost, mutations being seen within and around the optimal epitope.

HXB2 Location Nef (106–114)
Author Location Nef (106–114)
Epitope RQDILDLWV
Epitope name RV9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*13)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*13-associated substitution within optimally defined epitope RQDILDLWV is at position Q2, RqDILDLWV.

HXB2 Location Nef (106–114)
Author Location
Epitope RQDILDLWV
Epitope name RV9
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*1302)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay

Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- RQDILDLWV is a known HLA-B*1302-restricted epitope that is part of peptide IHSKRRQDILDLWVYYHTQG which elicited responses in 6/25 patients, and which belongs to peptide pool 3 that accounted for over 70% of Nef responses. Epitope RV9 was experimentally verified as optimal.

HXB2 Location Nef (106–114)
Author Location
Epitope `RQDILDLWV`
Epitope name RV9
Immunogen
Species (MHC) human (B*1302)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*1302 epitope.

HXB2 Location Nef (106–114)
Author Location Nef (106–114)
Epitope `RQDILDLWI`
Epitope name RI9
Immunogen HIV-1 infection
Species (MHC) human (B13)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, variant cross-recognition or cross-neutralization, optimal epitope
References Harrer *et al.* 2005

- An HLA-B13-restricted optimal epitope was defined in Nef, RI9. The frequency of CTLs specific for this epitope in B13-positive patients exceeded the number of CTLs against other epitopes, indicating that this is a dominant epitope in B13-positive subjects. Three B13-positive patients who had an immunodominant response to this epitope were good controllers of their infection, with low viral loads over long periods.
- In B13-positive patients with a previous diagnosis of AIDS, an RrDILDLWI escape variant was found.
- This is a well conserved epitope but natural variants were tested. Peptide titation experiments indicate a V9I RQDILDLWv variant and RQDILDLWI are equally well recognized. Other natural substitutions are less well recognized: RkDILDLWI, RQeILDLWI, aQDILDLWI, RQaILDLWI, RrDILDLWv.

HXB2 Location Nef (106–114)
Author Location Nef (106–114)
Epitope `RQDILDLWI`
Immunogen
Species (MHC) human (B13)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B13 epitope. Variant RQDILDLWv also noted.

HXB2 Location Nef (106–114)
Author Location Nef (106–114 SF2, HXBc2/Bal R5)
Epitope `RQDILDLWI`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A24, A25, B18, B7, Cw12, Cw7
Country United States
Assay type Cytokine production, Flow cytometric T-cell cytokine assay, Degranulation, CD107a and b cell surface mobilization
Keywords supervised treatment interruptions (STI), immunodominance, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells, drug resistance
References Daucher *et al.* 2008

- A detailed analysis of 6 chronically infected patients' CTL responses to autologous virus was performed after ART and SIT (structured interruption of therapy). Qualitative responses including degranulation and production of IFN-gamma, MIP-1beta, TNF-alpha, IL-2, but not memory CD27, CD45RO and CD57 T cells correlated with extended low plasma viremia. Frequency and breadth of CTL response as well as immune escape did not influence virological outcome.
- One patient exhibited drug resistance mutations K170R (to NNRTI efavirenz) and D76N, K70R (to NRTIs).
- Autologous epitopes were preferentially recognized over optimal, consensus sequences.
- Patients with favorable virological outcomes demonstrated CTL recognition within multiple, conserved regions of Gag and Nef.
- Patients with poor virological outcomes recognized optimal epitopes with much lower frequencies, though this was not significant.
- HLA-B7-restricted epitope, RQDILDLWI, elicited a response in 1 patient and is found in Nef immunodominant region IHSQRRQDILDLWIYGTQG. Patient autologous sequence was RQDILDLWv.

HXB2 Location Nef (106–114)
Author Location Nef (106–114)
Epitope `RQDILDLWI`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope RQDILDLWI showed some conservation to subtype B. Its HLA-restriction was predicted to be to HLA-A*24, -B*37, or -Cw*0602.

HXB2 Location Nef (106–114)
Author Location Nef
Epitope `RQDILDLWV`
Epitope name RV9(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope RQDILDLWV elicited an immune response in Chinese HIV-1 positive subjects as part of peptide QKRQDILDLWVYHTQGYF. This epitope differs from the previously described HLA-B13-restricted epitope RQDILDLWi at 1 residue, RQDILDLWv.
- 3 of the 29 HLA-B13 carriers responded to RQDILDLWv-containing peptide with average magnitude of CTL response of 50 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Nef (106–115)
Author Location Nef
Epitope `RQDILDLWIY`
Epitope name B7-RY10(Nef)
Immunogen HIV-1 infection
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (106–115)
Author Location
Epitope `RQDILDLWVY`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B7, Cw7)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- RQDILDLWVY is a known HLA-Cw7 and -B7-restricted epitope that is part of peptide RPMTYKAAFDLSFFLKEKG which elicited responses in 9/25 patients, and which belongs to peptide pool 3 that accounted for over 70% of Nef responses.

HXB2 Location Nef (106–115)
Author Location Nef
Epitope `RQDILDLWVY`
Epitope name RY10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw7)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 9, RQDILDLWiY, was found in the most polymorphic residue in the epitope.

HXB2 Location Nef (106–115)
Author Location Nef
Epitope `RQDILDLWVY`

CTL CD8+

Epitope name RY10(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope RQDILDLWVY elicited an immune response in Chinese HIV-1 positive subjects as part of peptide QKRQDILDLWVYHTQGYF. This epitope differs from the previously described HLA-B7-restricted epitope RQDILDLWIY, at 1 residue, RQDILDLWvY.
- 2 of the 9 HLA-B7 carriers responded to a RQDILDLWvY-containing peptide with average magnitude of CTL response of 45 SFC/million PBMC.

HXB2 Location Nef (106–120)
Author Location Nef (106–120)
Epitope `RQEILDLWVYHTQGY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw07)
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This epitope, RQeILDLWVYHTQGY, varies at position 3 from the consensus peptide KRQDILDLWVYHTQG.

HXB2 Location Nef (107–115)
Author Location (C consensus)
Epitope `QDILDLWIY`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*18)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the D2 residue of QDILDLWIY are associated with the presence of the HLA presenting molecule in the host.
- QDILDLWIY not optimized.

HXB2 Location Nef (107–115)
Author Location Nef (107–115 SF2, HXBc2/Bal R5)
Epitope `QDILDLWIY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B18)
Donor MHC A24, A25, B18, B7, Cw12, Cw7
Country United States
Assay type Cytokine production, Flow cytometric T-cell cytokine assay, Degranulation, CD107a and b cell surface mobilization
Keywords supervised treatment interruptions (STI), immunodominance, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells, drug resistance
References Daucher *et al.* 2008

- A detailed analysis of 6 chronically infected patients' CTL responses to autologous virus was performed after ART and SIT (structured interruption of therapy). Qualitative responses including degranulation and production of IFN-gamma, MIP-1beta, TNF-alpha, IL-2, but not memory CD27, CD45RO and CD57 T cells correlated with extended low plasma viremia. Frequency and breadth of CTL response as well as immune escape did not influence virological outcome.
- One patient exhibited drug resistance mutations K170R (to NNRTI efavirenz) and D76N, K70R (to NRTIs).
- Data confirmed that autologous epitopes were preferentially recognized over optimal, consensus sequences.
- Patients with favorable virological outcomes demonstrated CTL recognition within multiple, conserved regions of Gag and Nef.
- Patients with poor virological outcomes recognized optimal epitopes with much lower frequencies, though this was not significant.
- HLA-B18-restricted epitope, QDILDLWIY, elicited a response in 1 patient and is found in Nef immunodominant region IHSQRRQDILDLWIYGTQG. Patient autologous sequence was QDILDLWvY.

HXB2 Location Nef (107–115)
Author Location Nef (107–115)
Epitope `QDILDLWIY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ

Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope QDILDLWIY showed some conservation to subtype B. It is predicted to be restricted by HLA-B*37 or -Cw*0602.

HXB2 Location Nef (107–115)
Author Location Nef
Epitope QEILDLWVY
Subtype B, C, A1
Immunogen HIV-1 infection
Species (MHC) human
Country Sweden
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, HLA associated polymorphism
References Pérez *et al.* 2008

- Bioinformatic prediction using NetCTL 1.0, Episelect and NetMHCpan generated 184 CTL epitopes from Gag, Pol, Nef, Env and Tat in HIV subtypes A, B, C, D and CRF01_AE, restricted by MHC A1, A2, A3, A24, B7, B44 and B58. 45 of the 114 epitopes recognized experimentally in subjects were novel, and an elite subgroup comprising 21 epitopes were recognized by at least 13% of patients tested.
- Response magnitude was high—Gag and Nef, Env, Tat in descending order). While Gag, Pol, Env and Nef were highly immunocgenic, only 38% Tat epitopes elicited a response.
- 4 patterns of cross-subtype recognition found were (a) conserved epitopes recognized by patients infected with several HIV subtypes (b) infrequently found reference epitopes recognized by patients infected with several HIV subtypes (c) epitopes more prevalent in certain subtypes recognized by patients infected with several subtypes (d) rarely, subtype-specific epitopes unable to elicit cross-clade recognition
- Epitope QEILDLWVY is predicted to be restricted by HLA supertype B44. It was recognized by at least 4 patients with restricting HLA supertype who were infected with several different HIV subtypes.

HXB2 Location Nef (108–115)
Author Location
Epitope DILDLWIY
Epitope name Nef-DY8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (Cw*0701)
Donor MHC A*2601, A*3303, B*5801, B*8201, Cw*0302, Cw*0701
Keywords HAART, ART
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described; 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Subject 03RCH40 was African American, had a viral load of 2500, CD4 count of 372, was not on HAART, and also recognized the epitope ETKLGKAGY, RT(449-457), A*2601.
- Among HIV+ individuals who carried HLA Cw07, 2/18 (11%) recognized this epitope.

HXB2 Location Nef (108–115)
Author Location Nef (108–115)
Epitope DILDLWIY
Immunogen HIV-1 infection
Species (MHC) human (Cw7)
Donor MHC A1A1, B14, B8, Cw7, Cw8
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

HXB2 Location Nef (108–115)
Author Location Nef (108–115 SF2, HXBc2/Bal R5)
Epitope DILDLWIY
Subtype B
Immunogen HIV-1 infection

CTL CD8+

Species (MHC) human (Cw7)
Donor MHC A24, A25, B18, B7, Cw12, Cw7
Country United States
Assay type Cytokine production, Flow cytometric T-cell cytokine assay, Degranulation, CD107a and b cell surface mobilization
Keywords supervised treatment interruptions (STI), variant cross-recognition or cross-neutralization, characterizing CD8+ T cells, drug resistance
References Daucher *et al.* 2008

- A detailed analysis of 6 chronically infected patients' CTL responses to autologous virus was performed after ART and SIT (structured interruption of therapy). Qualitative responses including degranulation and production of IFN-gamma, MIP-1beta, TNF-alpha, IL-2, but not memory CD27, CD45RO and CD57 T cells correlated with extended low plasma viremia. Frequency and breadth of CTL response as well as immune escape did not influence virological outcome.
- One patient exhibited drug resistance mutations K170R (to NNRTI efavirenz) and D76N, K70R (to NRTIs).
- Autologous epitopes were preferentially recognized over optimal, consensus sequences.
- Patients with favorable virological outcomes demonstrated CTL recognition within multiple, conserved regions of Gag and Nef.
- Patients with poor virological outcomes recognized optimal epitopes with much lower frequencies, though this was not significant.
- HLA-Cw7-restricted epitope, DILDLWIY, elicited a response in 1 patient and is found in Nef immunodominant region IHSQRRQDILDLWIYGTQG. Patient autologous sequence was DILDLWvY.

HXB2 Location Nef (108–115)
Author Location Nef (108–115)
Epitope `DILDLWVH`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords rate of progression, immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-Cw7-restricted epitope DILDLWVH failed to generate CTL response. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location Nef (109–117)
Author Location
Epitope `ILDLWVYHT`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- ILDLWVYHT is a known HLA-A2-restricted epitope that is part of peptide RPMTYKAAFDLSFFLKEKG which elicited responses in 9/25 patients, and which belongs to peptide pool 3 that accounted for over 70% of Nef responses.

HXB2 Location Nef (109–117)
Author Location Nef (109–117)
Epitope `ILDLWIYHT`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope ILDLWIYHT showed some conservation to subtype B and was predicted to be HLA-A*03-restricted.

HXB2 Location Nef (112–126)
Author Location Nef (112–126)
Epitope `LWVYHTQGYFPDWQN`
Subtype C

Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location Nef (112–127)
Author Location Nef
Epitope `LWVYHTQGYFPDWQNY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, LWVYHTQGYFPDWQNY, had an overall frequency of recognition of 30% - 25.4% AA, 38.5% C, 31.8% H, 28.6% WI. This peptide is included in a 54 aa Nef highly reactive region to be used for vaccine design. It is also part of 'Region II', QKRQDILDLWVYHTQGYFPDWQNYTPGPGIRYPLTFGWCFKLVPVEPEKVEEAN, a 54 aa region recognized by >90% of subjects across ethnic groups.

HXB2 Location Nef (112–133)
Author Location Nef (111–132)
Epitope `LWIYHTQGYFPDWQNYTPGPGV`
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

HXB2 Location Nef (112–133)
Author Location Nef (111–132 SF2)
Epitope `LWIYHTQGYFPDWQNYTPGPGV`
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- Four of these 11 had CTL response to this peptide.
- The responding subjects were HLA-A2, B21; HLA-A1, A3, B7, B15; HLA-A2, A26, B7, B38.

HXB2 Location Nef (112–133)
Author Location Nef (111–132 SF2)
Epitope `LWIYHTQGYFPDWQNYTPGPGV`
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

HXB2 Location Nef (113–121)
Author Location Nef (111–119)
Epitope `WIYHTQGYF`
Immunogen HIV-1 infection
Species (MHC) human (A1)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 3/13 patients recognized this epitope.

HXB2 Location Nef (113–121)
Author Location Nef (113–121)
Epitope `WIYHTQGYF`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance

CTL CD8+

References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope WIYHTQGYF from the central region of Nef showed a 20-30% conservation with subtype B. Its HLA specificities are predicted to be with HLA-B*35 in one subject, and with HLA-Cw*0401 or -Cw*0602 in another subject.

HXB2 Location Nef (113–125)
Author Location Nef (113–125 BRU)
Epitope `WIYHTQGYFPDWQ`
Immunogen HIV-1 infection
Species (MHC) human (B17)
References Culmann *et al.* 1989

- Nef CTL clones from HIV+ donors.

HXB2 Location Nef (113–127)
Author Location Nef (128–142)
Epitope `WIYHTQGYFDPWQNY`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Guimaráes *et al.* 2002

- Nef sequences were obtained from Brazilians to study epitope diversity in this geographic region – WIYHTQGYFDPWQNY displayed an (H) to (N) substitution in Brazilian Nef-gene subtype C samples, and this substitution is often found in other subtypes tested.

HXB2 Location Nef (113–128)
Author Location Nef (113–128 BRU)
Epitope `WIYHTQGYFPDWQNYT`
Immunogen HIV-1 infection
Species (MHC) human (A1)
References Hadida *et al.* 1992

- HIV-1 specific CTLs detected in lymphoid organs of HIV-1 infected patients.

HXB2 Location Nef (113–128)
Author Location Nef (113–128 LAI)
Epitope `WIYHTQGYFPDWQNYT`
Epitope name N2
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A1)
Keywords HAART, ART
References Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNgamma production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

HXB2 Location Nef (113–128)
Author Location Nef (113–128)
Epitope `WVHHTQGYFPDWQNYT`
Epitope name VT15
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords rate of progression, immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-A1-restricted epitope WVHHTQGYFPDWQNYT was able to elicit CTL response only by the last time point. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location Nef (114–127)
Author Location Nef
Epitope `VYHTQGYFPDWQNY`
Immunogen HIV-1 infection
Species (MHC) human
References Jubier-Maurin *et al.* 1999

HXB2 Location Nef (115–124)

Author Location
Epitope YHTQGYFPDW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B17)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- YHTQGYFPDW is a known HLA-B17-restricted epitope that is part of peptide WVYHTQGYFPDWQNYTPGP which elicited responses in 3/25 patients, and which belongs to peptide pool 3 that accounted for over 70% of Nef responses.

HXB2 Location Nef (115–125)
Author Location Nef (115–125 BRU)
Epitope YHTQGYFPDWQ
Immunogen HIV-1 infection
Species (MHC) human (B17)
References Culmann *et al.* 1991

- Nef CTL clones from HIV+ donors.

HXB2 Location Nef (115–129)
Author Location Nef (115–129 HXB2)
Epitope YHTQGYFPDWQNYTP
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 22% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location Nef (116–124)
Author Location Nef (116–124)
Epitope HTQGYFPDW
Immunogen
Species (MHC) human (B*57)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Nef (116–124)
Author Location Nef (116–124)
Epitope HTQGYFPDW
Epitope name HW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country Australia, Canada, Germany, United States
Keywords escape, viral fitness and reversion, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- Escape (and reversion) rates for B*57-restricted epitopes were highest for Gag-TW10 (TSTLQEQIGW) > RT-IW9 (IVLPEKDSW) > Nef-YY9 (YTPGPGIRY) > Nef-HW9 (HTQGYFPDW) > Gag-IW9 (ISPRTLNAW) > Gag-KF11 (KAFSPEVIPMF) .
- HLA-B*57-associated substitution within optimally defined epitope HTQGYFPDW is at position H1, hTQGYFPDW. HW9 has a recognition frequency of ∼40% and its escapes appear at around months 3 and 12 post-infection.

HXB2 Location Nef (116–124)
Author Location Nef (116–124)
Epitope HTQGYFPDW
Epitope name HW9
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Navis *et al.* 2008

- HLA-B57/5801 progressing and long term non-progressing HIV-1-infected individuals were compared to observe the reason for the difference in their clinical outcomes. LTNP non-progression to AIDS was associated with protective HLA-alleles B57/5801 and preserved CTL IFN-gamma response against the WT Nef epitope HW9. Progressing HIV-1 positive subjects expressed the inhibitory receptor PD-1 which reflects an exhausted CTL phenotype.

- Epitope HTQGYFPDW had 1 variation in progressors - nTQGYFPDW.
- Epitope HTQGYFPDW variant in LTNPs was - nTQGYFPDW.
- Nef HW9 is previously known to be restricted by HLA-B57/5801.

HXB2 Location Nef (116–124)
Author Location
Epitope HTQGYFPDW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- HTQGYFPDW is a known, optimal HLA-B57 and -B5801-restricted epitope that is part of peptide WVYHTQGYFPDWQNYTPGP which elicited responses in 3/25 patients, and which belongs to peptide pool 3 that accounted for over 70% of Nef responses.

HXB2 Location Nef (116–124)
Author Location Nef (116–124)
Epitope HTQGYFPDW
Immunogen
Species (MHC) human (B57)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Nef (116–124)
Author Location
Epitope HTQGYFPDW
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, epitope processing
References Draenert *et al.* 2004a

- 96% of optimally defined epitopes have one of only nine amino acids serving as the C-terminal anchor position. Seven amino acids are never found in this position and four are only present in 4% of cases. CD8 T-cell response to an epitope is shown to be best detected when the epitope is situated at the C-terminal end of a longer peptide, and authors suggest that Elispot reagents would be better designed if peptides ended on known C-terminal anchors.
- HTQGYFPDW is suggested to be the optimal epitope instead of HTQGYFPDWQ since Gln is not described as a C-terminal anchor residue in any of the other optimally defined epitopes. HTQGYFPDW was also found to be recognized at two times lower peptide concentrations than HTQGYFPDWQ.

HXB2 Location Nef (116–124)
Author Location Nef (116–124)
Epitope HTQGYFPDW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A*3001, A*66, B*4201, B*5802, Cw*0602, Cw*1701; A*66, A*68, B*57, B*5802, Cw*0602, Cw*0701
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, acute/early infection
References Pillay *et al.* 2005

- HIV-specific CTLs in infants were shown to be able to select for viral escape variants early in life, despite a lack of escape with the same CTL specificity in the mother. Infant CTL responses may be compromised by transmission of escape variants that arose in the mother and also those that arose in the father, if the father was the source of the mother's infection.
- HTQGYFPDW is the C consensus form of the epitope; the autologous form in the mother was HTQGfFPDW, and this was transmitted to her infant. By 33 weeks a new dominant form of the epitope had emerged in the infant: nTQGfFPDW.

HXB2 Location Nef (116–124)
Author Location Nef
Epitope HTQGYFPDW
Epitope name B57-HW9(Nef)
Immunogen HIV-1 infection
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (116–124)
Author Location Nef
Epitope HTQGYFPDW

Epitope name HW9
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords responses in children, mother-to-infant transmission, escape, characterizing CD8+ T cells
References Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.
- While 2 mothers carried the form HTQGYFPDW, their children carried the escape H1N variant nTQGYFPDW.

HXB2 Location Nef (116–124)
Author Location Nef (116–124 BRU)
Epitope `HTQGYFPDW`
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (B57, B58)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 0/9 CRF02_AG-infected Ivorians, and 1/9 B-infected French subject
- HTQGYFPDW was invariant in 5 B clade infected individuals, including the one that recognized the epitope. It varied in 4/8 CRF02 Ivorian infections.

HXB2 Location Nef (116–125)
Author Location
Epitope `HTQGYFPDWQ`
Epitope name HQ10
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B*57-restricted optimal epitope HTQGYFPDWQ was tested for immune response.

HXB2 Location Nef (116–125)
Author Location Nef (116–125)
Epitope `HTQGYFPDWQ`
Epitope name HQ10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country Switzerland
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, HLA associated polymorphism
References Frater *et al.* 2007

- To study whether CTL responses restricted by "good" HLA I molecules exert stronger immune selection than other HLA I molecules, 54 and 70 optimal epitopes within HIV-1 Gag, Pol and Nef genes for Caucasian and African cohorts were tested in patients over a mean of 14 months. "Good", advantageous HLA allele-restricted epitopes were much more polymorphic than epitopes restricted by other, non-advantageous HLA in patients, suggesting that benefits associated with HLA Class I alleles of elite controllers of disease progression are epitope-specific. Such "driver" epitopes with high polymorphism had high frequency of immune response, allowing them to be ranked for recognition and polymorphism.
- Patients with higher proportions of mutated epitopes also had lower plasma viral loads, and mean epitope variability correlated negatively with relative hazard of disease progression.
- Variant nTQGYFPDWQ at position 1 was found in 100% of HLA-matched patients and in 28.8% of HLA-unmatched patients.

HXB2 Location Nef (116–125)
Author Location Nef (116–125)
Epitope `HTQGYFPDWQ`
Epitope name HQ10
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CTL suppression of replication
Keywords class I down-regulation by Nef
References Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Early protein Nef epitope HTQGYFPDWQ-recognizing CTLs were less affected by Nef.

HXB2 Location Nef (116–125)
Author Location Nef (116–125)
Epitope `HTQGYFPDWQ`
Epitope name nefHQ10
Immunogen HIV-1 infection
Species (MHC) human (B*57)

CTL CD8+

Country United Kingdom, Kenya
Assay type CD8 T-cell Elispot - IFNγ
Keywords TCR usage, structure, characterizing CD8+ T cells
References Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B*57-peptide complexes were studied.
- In addition, immunodominancy of the previously mapped B*57 epitopes during chronic infection was assessed. KGFNPEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

HXB2 Location Nef (116–125)
Author Location Nef (116–125 BRU)
Epitope HTQGYFPDWQ
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords subtype comparisons, optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*5701 epitope.
- Subtype of B57 not determined.

HXB2 Location Nef (116–125)
Author Location Nef (116–125)
Epitope HTQGYFPDWQ
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- One of the A2+ individuals was HLA A*0201, A1, B57 and responded to four B57 epitopes and two others.

HXB2 Location Nef (116–125)
Author Location Nef (116–125 BRU)
Epitope HTQGYFPDWQ
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Culmann *et al.* 1991

- Nef CTL clones from HIV+ donors, optimal peptide mapped.

HXB2 Location Nef (116–125)
Author Location Nef (116–125)
Epitope HTQGYFPDWQ
Epitope name HTQ
Immunogen HIV-1 infection
Species (MHC) human (B57)
Keywords HAART, ART, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- None of the 8 study subjects recognized this epitope but none were HLA B57+

HXB2 Location Nef (116–125)
Author Location
Epitope HTQGYFPDWQ
Epitope name Nef-HQ10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B57, 0/5 (0%) recognized this epitope.

HXB2 Location Nef (116–125)
Author Location Nef (114–123)
Epitope HTQGYFPDWQ
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 7 patients recognized this epitope.

HXB2 Location Nef (116–125)
Author Location Nef
Epitope HTQGYFPDWQ
Epitope name HQ10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 1, nTQGYFPDWQ, was found in the most polymorphic residue in the epitope.

HXB2 Location Nef (116–125)
Author Location
Epitope HTQGYFPDWQ

Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location Nef (116–125)
Author Location Nef
Epitope `HTQGYFPDWQ`
Epitope name HQ10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- HQ10, HTQGYFPDWQ, is a known HLA-B57-restricted epitope used as a positive control for eliciting CTL IFN-gamma response.

HXB2 Location Nef (116–125)
Author Location Nef
Epitope `HTQGYFPDWQ`
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B57, B63)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, cross-presentation by different HLA, optimal epitope
References Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This epitope was recognized by 30% of B63-positive subjects and 35% of B57/58-positive subjects.

HXB2 Location Nef (117–127)
Author Location Nef (117–127 LAI)
Epitope `TQGYFPDWQNY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1501)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*1501 epitope.

HXB2 Location Nef (117–127)
Author Location Nef (117–127 NL-43)
Epitope `TQGYFPDWQNY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1501)
Keywords class I down-regulation by Nef, escape
References Ali *et al.* 2003

- NL43 was passaged in the presence of Nef KEKGGLEGL-specific CTL clones STD11 and KM3, giving rise to rapid selection of escape mutations, including E93G, E93K, K94N+G99R, G95R+G99R, E98K, E98D, G99R, G99E, L100P, and L100I; insertions, deletions, frameshifts and an early stop codon. 34/36 (94%) of sequences carried mutations in the epitope by seven days, 36/36 (100%) by 14 days.
- NL43 was also passaged in the presence of a Nef TQGYFPDWQNY-specific CTL clone. 7/15 clones had a frameshifting or stop codon introduced by one week; F121T was also observed. The most common escape mutation for both Nef epitopes was an early stop codon at position 91.
- Several mutations selected by KEKGGLEGL-specific CTL were shown to impair the down regulation of class I MHC by Nef, in particular E93G, E93K, and a truncation mutation at position 51.
- Nef deletion mutants increased 100-fold NL-43 susceptibility to inhibition by CTL specific for epitopes in other proteins, the A2 epitopes ILKEPVHGV in RT and SLYNTVATL in p17 Gag.

HXB2 Location Nef (117–127)
Author Location Nef
Epitope `TQGYFPDWQNY`
Epitope name B15-TY11(Nef)
Immunogen HIV-1 infection
Species (MHC) human (B15)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins

CTL CD8+

References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (117–127)
Author Location Nef
Epitope TQGYFPDWQNY
Epitope name TY11(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B15)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-B15-restricted epitope TQGYFPDWQNY elicited an immune response in Chinese HIV-1 positive subjects as part of peptide LWVYHTQGYFPDWQNY.
- 9 of the 21 HLA-B15 carriers responded to TQGYFPDWQNY-containing peptide with average magnitude of CTL response of 327 SFC/million PBMC.

HXB2 Location Nef (117–127)
Author Location
Epitope TQGYFPDWQNY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B15)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- TQGYFPDWQNY is a known HLA-B15-restricted epitope that is part of peptide WVYHTQGYFPDWQNYTPGP which elicited responses in 3/25 patients, and which belongs to peptide pool 3 that accounted for over 70% of Nef responses.

HXB2 Location Nef (117–127)
Author Location Nef (117–127 LAI)
Epitope TQGYFPDWQNY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B62)
References Culmann 1998

- Optimal peptide defined by titration.

HXB2 Location Nef (117–127)
Author Location Nef (117–127)
Epitope TQGYFPDWQNY
Immunogen HIV-1 infection
Species (MHC) human (B62)
Keywords immunodominance
References Day *et al.* 2001

- No immunodominant responses were detected to four B62-restricted epitopes tested.

HXB2 Location Nef (117–127)
Author Location Nef (117–127)
Epitope TQGYFPDWQNY
Immunogen HIV-1 infection
Species (MHC) human
Keywords immunodominance
References Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the A2+ individuals was HLA A*0205/A*0208, A30, B27, B44 but responded to HLA Bw62 epitope TQGYFPDWQNY, and one of the other individuals that was A2+, but otherwise of unknown HLA type, reacted with seven epitopes including this one.

HXB2 Location Nef (117–128)
Author Location Nef (117–128 BRU)
Epitope TQGYFPDWQNYT
Immunogen HIV-1 infection
Species (MHC) human (B17, B37)
References Culmann *et al.* 1991

- Nef CTL clones from HIV+ donors.

HXB2 Location Nef (117–131)
Author Location Nef (117–131)
Epitope TQGYFPDWQNYTPGP
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression

References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the ES.

HXB2 Location Nef (117–147)
Author Location Nef (117–147 LAI)
Epitope `TQGYFPDWQNYTPGPGVRYPLTFGWCYKLVP`
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide
Species (MHC) human
References Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long amino acid peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 1/10 reacted to this Nef peptide.
- 9/12 tested mounted a CTL response to at least one of the six peptides; each of the six peptides elicited a CTL response in at least one individual.
- 10/12 tested had an IgG response to this peptide.

HXB2 Location Nef (118–127)
Author Location Nef (118–127 LAI)
Epitope `QGYFPDWQNY`
Subtype B
Immunogen
Species (MHC) human (B62)
Keywords review
References McMichael & Walker 1994

- Review of HIV CTL epitopes.

HXB2 Location Nef (118–135)
Author Location Nef
Epitope `QGYFPDWQNYTPGPGRF`
Epitope name NEF-17
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, QGYFPDWQNYTPGPgRf differs from the consensus C sequence QGYFPDWQNYTPGPvRy at 2 amino acid positions, i.e. by 11.1%.

HXB2 Location Nef (118–135)
Author Location Nef
Epitope `QGYFPDWQNYTPGPGIRY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.

- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, QGYFPDWQNYTPGPGIRY, had an overall frequency of recognition of 30.7% - 23.7% AA, 38.5% C, 40.9% H, 19% WI. This peptide is included in a 54 aa Nef highly reactive region to be used for vaccine design. It is also part of 'Region II', QKRQDILDLWVYHTQGYFPDWQNYTPGPGIRYPLTFGWCFKLVPVEPEKVEEAN, a 54 aa region recognized by >90% of subjects across ethnic groups.

HXB2 Location Nef (119–127)
Author Location Nef (119–127)
Epitope `GYFPDWQNY`
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (A24)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 0/9 CRF02_AG-infected Ivorians, and 1/9 B-infected French subjects. It was invariant among 5 French subjects,including the one that reacted with the epitope, and had single amino acid substitutions in 4/8 Ivorians.

HXB2 Location Nef (119–127)
Author Location
Epitope `GYFPDWQNY`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A24)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression, optimal epitope
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- GYFPDWQNY is a known HLA-A24-restricted epitope that is part of peptide WVYHTQGYFPDWQNYTPGP which elicited responses in 3/25 patients, and which belongs to peptide pool 3 that accounted for over 70% of Nef responses.

HXB2 Location Nef (120–127)
Author Location (C consensus)
Epitope `YFPDWQNY`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*29)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- YFPDWQNY is an optimal epitope.

HXB2 Location Nef (120–127)
Author Location (C consensus)
Epitope `YFPDWQNY`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*29, A*3002)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords cross-presentation by different HLA, characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location Nef (120–127)
Author Location
Epitope `YFPDWQNY`
Immunogen HIV-1 infection
Species (MHC) human (A29)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, epitope processing
References Draenert *et al.* 2004a

- 96% of optimally defined epitopes have one of only nine amino acids serving as the C-terminal anchor position. Seven amino acids are never found in this position and four are only present in 4% of cases. CD8 T-cell response to an epitope is shown to be best detected when the epitope is situated at the C-terminal end of a longer peptide, and authors suggest that Elispot reagents would be better designed if peptides ended on known C-terminal anchors.
- Instead of YFPDWQNYT, YFPDWQNY was found to be the optimal epitope in one patient.

HXB2 Location Nef (120–127)

Author Location
Epitope YFPDWQNY
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A29, B*5801, B57)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- YFPDWQNY is a known HLA-A29, -B57 and -B5801-restricted epitope that is part of peptide WVYHTQGYF-PDWQNYTPGP which elicited responses in 3/25 patients, and which belongs to peptide pool 3 that accounted for over 70% of Nef responses.

HXB2 Location Nef (120–127)
Author Location
Epitope YFPDWQNY
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords responses in children, mother-to-infant transmission, escape
References Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.
- YFPDWQNY responses were somewhat more frequent in adults.

HXB2 Location Nef (120–128)
Author Location Nef
Epitope YFPDWQNYT
Epitope name YT9(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*29)
Country China
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords optimal epitope
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- HLA-A*29-restricted epitope YFPDWQNYT elicited an immune response in Chinese HIV-1 positive subjects as part of peptide QGYFPDWQNYTPGPGRF.
- >10% of the 4 HLA-A*29 carriers responded to YFPDWQNYT-containing peptide with average magnitude of CTL response of ∼100 SFC/million PBMC.

HXB2 Location Nef (120–128)
Author Location
Epitope YFPDWQNYT
Immunogen HIV-1 infection
Species (MHC) human (A01)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope YFPDWQNYT elicited a magnitude of response of 685 SFC with a functional avidity of 5nM.

HXB2 Location Nef (120–128)
Author Location Nef (120–128)
Epitope YFPDWQNYT
Immunogen HIV-1 infection
Species (MHC) human (A01, B*3701, B*5701)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.

- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope YFPDWQNYT was predicted to be restricted by A1, B*3701 and B*5701.

HXB2 Location Nef (120–128)
Author Location Nef (118–126 SF2)
Epitope YFPDWQNYT
Immunogen HIV-1 infection
Species (MHC) human (A1)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A1+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 0/2 group 2, and 1/2 group 3.

HXB2 Location Nef (120–128)
Author Location Nef
Epitope YFPDWQNYT
Epitope name A1-YT9(Nef)
Immunogen HIV-1 infection
Species (MHC) human (A1)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (120–128)
Author Location Nef
Epitope YFPDWQNYT
Epitope name YT9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A1)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords superinfection
References Streeck *et al.* 2008b

- Loss of viral replication control by an elite controller after superinfection was found to coincide with rapid recombination events in 2, ∼50 residue regions of Gag and Env that include immunodominant epitopes KK10 (KRWIILGLNK) and CL9 (CAPAGFAIL). Viral escape was seen at both epitopes and consequent CTL responses against the epitope-variants.
- CTL responses to previously described, HLA-A1-restricted YFPDWQNYT were seen post-superinfection and -recombination.

HXB2 Location Nef (120–128)
Author Location Nef
Epitope YFPDWQNYT
Epitope name YT9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A1)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- A variant of YFPDWQNYT, fFPDWQNYT was found in a different untreated patient whose epitope also did not vary with time.
- 215 days after first testing, this epitope, YFPDWQNYT, went from 3-4 functional to monofunctional in the response it was able to elicit, with no variation in an untreated patient. Previously published HLA-restriction for YT9 is HLA-A1.

HXB2 Location Nef (120–128)
Author Location
Epitope YFPDWQNYT
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A1)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay

Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- YFPDWQNYT is a known HLA-A1-restricted epitope that is part of peptide WVYHTQGYFPDWQNYTPGP which elicited responses in 3/25 patients, and which belongs to peptide pool 3 that accounted for over 70% of Nef responses.

HXB2 Location Nef (120–128)
Author Location Nef
Epitope `YFPDWQNYT`
Epitope name YT9(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A1, A29)
Country China
Assay type CD8 T-cell Elispot - IFNγ
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Previously described HLA-A29-restricted eiptope YFPDWQNYT elicited an immune response in Chinese HIV-1 positive subjects as part of peptide QGYFPDWQNYTGPGRF.
- Although the tested peptide sequence, QGYFPDWQNYTGPGRF, contains the exact sequence of a previously described HLA-A1 optimal epitope, YFPDWQNYT, none of the 4 HLA-A1 carriers responded to it. 1 of the 8 HLA-A29 carriers responded to YFPDWQNYT-containing peptide with a magnitude of CTL response of 90 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Nef (120–128)
Author Location Nef (120–128)
Epitope `YFPDWQNYT`
Immunogen HIV-1 infection
Species (MHC) human (A29)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Nef (120–128)
Author Location Nef (120–128)
Epitope `YFPDWQNYT`
Epitope name YT9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*37)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*37-associated substitution within optimally defined epitope YFPDWQNYT is at position Q6, YFPDWqNYT.

HXB2 Location Nef (120–128)
Author Location Nef (120–128 LAI)
Epitope `YFPDWQNYT`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*3701)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*3701 and B*5701 epitope.

HXB2 Location Nef (120–128)
Author Location
Epitope `YFPDWQNYT`
Epitope name YT9
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B*57-restricted optimal epitope YFPDWQNYT was tested for immune response.

HXB2 Location Nef (120–128)
Author Location Nef (120–128)
Epitope `YFPDWQNYT`
Epitope name YT9
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CTL suppression of replication
Keywords class I down-regulation by Nef
References Adnan *et al.* 2006

CTL CD8+

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Early protein Nef epitope YFPDWQNYT-recognizing CTLs were less affected by Nef.

HXB2 Location Nef (120–128)
Author Location Nef (120–128)
Epitope YFPDWQNYT
Epitope name nefYT9
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country United Kingdom, Kenya
Assay type CD8 T-cell Elispot - IFNγ
Keywords TCR usage, structure, characterizing CD8+ T cells
References Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B*57-peptide complexes were studied.
- In addition, immunodominancy of the previously mapped B*57 epitopes during chronic infection was assessed. KGFNPEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

HXB2 Location Nef (120–128)
Author Location Nef (120–128 LAI)
Epitope YFPDWQNYT
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5701)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*5701 epitope.
- Subtype of B57 not determined.

HXB2 Location Nef (120–128)
Author Location Nef (120–128)
Epitope YFPDWQNYT
Epitope name YT9
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Navis *et al.* 2008

- HLA-B57/5801 progressing and long term non-progressing HIV-1-infected individuals were compared to observe the reason for the difference in their clinical outcomes. LTNP non-progression to AIDS was associated with protective HLA-alleles B57/5801 and preserved CTL IFN-gamma response against the WT Nef epitope HW9. Progressing HIV-1 positive subjects expressed the inhibitory receptor PD-1 which reflects an exhausted CTL phenotype.
- Epitope YFPDWQNYT had one variation in LTNPs - YFPDWhNYT.
- Nef YT9 is previously known to be restricted by HLA-B57/5801.

HXB2 Location Nef (120–128)
Author Location Nef (120–128 IIIB)
Epitope FFPDWKNYT
Immunogen HIV-1 infection
Species (MHC) human (B15)
Keywords responses in children, mother-to-infant transmission, escape
References Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- LFPDWKNYT is an escape mutant.

HXB2 Location Nef (120–128)
Author Location Nef (120–128 LAI)
Epitope YFPDWQNYT
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B37, B57)
References Culmann 1998

- Nef CTL clones from HIV+ donors – optimum peptide mapped by titration.

HXB2 Location Nef (120–128)
Author Location
Epitope YFPDWQNYT
Immunogen HIV-1 infection
Species (MHC) human (B37, B57)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- Based on a prediction of the minimum number of HLA alleles needed to cover the HLA representation in all responders to this epitope, a minimum set of 6 alleles was found: 2 alleles previously known to be associated (B37, B57) and 5 additional alleles (A01, A02, A23, Cw02, Cw06).

HXB2 Location Nef (120–128)
Author Location Nef (120–128)
Epitope FFPDWKNYT
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8

Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 5 epitopes from this individual that varied over time where the internal mutations became fixed; a dramatic decrease in CTL activity against the wild type epitope was observed as the mutation arose. YfpdwQnyt and YfpdwHnyt variants found at 2 months postseroconversion (psc); YfpdwHnyt, YfpdwQSyt, YLpdwQSyt and YfpdwDnyt variants found 20 months psc; YfpdwDnyt and YfpdwQSyt variants found 47 months psc.

HXB2 Location Nef (120–128)
Author Location
Epitope `YFPDWQNYT`
Epitope name Nef-YT9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B57, 1/5 (20%) recognized this epitope.

HXB2 Location Nef (120–128)
Author Location Nef
Epitope `YFPDWQDYT`
Epitope name YT9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 7, YFPDWQnYT, was found not to correspond to the most polymorphic residue in the epitope.

HXB2 Location Nef (120–128)
Author Location
Epitope `YFPDWQNYT`
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (B57)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location Nef (120–128)
Author Location Nef
Epitope `YFPDWQNYT`
Epitope name YT9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- YT9, YFPDWQNYT, is a known HLA-B57-restricted epitope used as a positive control for eliciting CTL IFN-gamma response.

HXB2 Location Nef (120–128)
Author Location Nef
Epitope `YFPDWQNYT`
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B57, B63)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, cross-presentation by different HLA, optimal epitope
References Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment.

CTL CD8+

Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This epitope was recognized by 40% of B63-positive subjects and 27% of B57/58-positive subjects.

HXB2 Location Nef (120–128)
Author Location
Epitope YFPDWQNYT
Immunogen
Species (MHC) human (Cw6)
Keywords optimal epitope
References Llano *et al.* 2009
- C. Brander notes that this is an Cw6 epitope.

HXB2 Location Nef (120–128)
Author Location Nef (120–128)
Epitope YFPDWQNYT
Immunogen HIV-1 infection
Species (MHC) human
Keywords immunodominance
References Betts *et al.* 2000
- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INFγ responses to other epitopes.
- 1/11 of the A2+ individuals was HLA A*0205/A*0208, A30, B27, B44 but responded to HLA B37 epitope IYKRWIILGL, and one of the other individuals that was A2+, but otherwise of unknown HLA type, reacted with seven epitopes including this one.

HXB2 Location Nef (120–128)
Author Location Nef (120–128)
Epitope YFPDWQDYT
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A3, A32, B15, B51
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006
- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, YFPDWQDYT, was found to be 0.002/day (optimistic escape rate = 0.012), with SE of 0.001.
- In the subject studied, the fluctuating outgrowth of a Q125D mutation in Nef was observed over a period of 1,361 days.

HXB2 Location Nef (120–144)
Author Location Nef (120–144 SF2)
Epitope YFPDWQNYTPGPGIRYPLTFGWCYK
Immunogen HIV-1 infection
Species (MHC) human (A24)
References Jassoy *et al.* 1992
- Epitope recognized by CTL clone derived from CSF.

HXB2 Location Nef (121–128)
Author Location Nef (121–128)
Epitope FPDWQNYT
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (A1)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003
- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of 31 that the vaccinated volunteers responded to.

HXB2 Location Nef (121–128)
Author Location Nef (121–128 HXB2)
Epitope FPDWQNYT
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A1)
Country Viet Nam
Assay type HLA binding
Keywords subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization, vaccine antigen design
References Lazaro *et al.* 2005
- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.

- CRF01_AE has 2 forms, FPDWQNYT, like the HXB2 form, and FPDWhNYT. Both are predicted to bind to A1.

HXB2 Location Nef (121–129)
Author Location Nef (125–133)
Epitope FPDWQNYTP
Epitope name FP9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5401)
Country Japan
Assay type Intracellular cytokine staining, Chromium-release assay
Keywords optimal epitope
References Kitano *et al.* 2008

- Asian-expressed HLA-B*5401-restricted epitopes were identified using overlapping-peptide methods and characterized. 5 epitopes from Pol and Nef induced CTL responses that killed target cells in more than 25% of B*5401-carrying tested patients.
- 7 peptides from Pol and Nef are listed in Fig. 2 as candidates for B*5401 restriction. No Gag-specific epitopes were identified in this study from the patient whose lymphocytes were screened.
- FPDWQNYTP was defined as an optimal epitope for HLA-B*5401 restriction, using truncated peptides.

HXB2 Location Nef (121–135)
Author Location Nef (121–135)
Epitope FPDWQNYTPGPGIRY
Epitope name NY10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A24)
Donor MHC A24, A3, B7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide has identity with the consensus peptide FPDWQNYTPGPGIRY.

HXB2 Location Nef (122–136)
Author Location Nef (122–136)
Epitope PDWQNYTPGPGVRYP
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 8 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location Nef (122–141)
Author Location Nef
Epitope PDWQNYTPGPGVRYPLTFGW
Epitope name Nef13 (containing epitope TL10)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords rate of progression, acute/early infection, memory cells
References Sabbaj *et al.* 2007

- CD127 hi memory CTLs were correlated with different patient groups - subjects with chronic HIV-1 infection or controllers or those treated early with ART. For patients with chronic infection, CD127 hi CTL levels decrease greatly. Early ART treatment alone maintained these long-lived memory T cells.
- In response to peptide Nef13, containing epitope TL10, TPGPGVRYPL, a patient with oscillating ART had IFN-gamma secretion by CD127 lo cells during viremia and CD127hi cell-IFN-gamma production during viremic control. Shortly after ART cessation, CD127 mixed cells secreted IFN-gamma. TL10 HLA-restriction is to -B*35.

HXB2 Location Nef (122–141)
Author Location Nef (121–140 SF2)
Epitope PDWQNYTPGPGVRYPLTFGW
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- Three of these 11 had CTL response to this peptide.
- The responding subjects were HLA-A2, B21; HLA-A3, A24, B7, B38.

HXB2 Location Nef (123–137)
Author Location Nef (123–137 IIIB)
Epitope QWQNYTPGPGVRYPL
Immunogen HIV-1 infection
Species (MHC) human
Keywords responses in children, mother-to-infant transmission, escape
References Wilson *et al.* 1996

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.

CTL CD8+

- FFPDYTPGPGTRFPL and FFPDYKPGPGTRFPL, naturally occurring variants, were found in mother and are not recognized.
- LFPDYKPGPGTRFPL and FFPDYKPGPGTRFPL, naturally occurring variants, were found in infant and are not recognized.

HXB2 Location Nef (125–143)
Author Location Nef
Epitope QNYTPGPGRFPLTFGWCF
Epitope name NEF-18
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, immunodominance
References Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher interclade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, QNYTPGPgRfPLTFGWCF differs from the consensus C sequence QNYTPGPvRyPLTFGWCF at 2 amino acid positions, i.e. by 10.5%.

HXB2 Location Nef (126–135)
Author Location Nef (126–135 BRU)
Epitope NYTPGPGVRY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A24)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- NYTPGPGVRY was recognized in 3/10 (30%) of individuals with HLA A24. It was a moderate affinity HLA-A24 binder.

HXB2 Location Nef (126–138)
Author Location Nef (126–138 BRU)
Epitope NYTPGPGVRYPLT
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Culmann *et al.* 1991

- Nef CTL clones from HIV+ donors.

HXB2 Location Nef (126–140)
Author Location Nef (126–140)
Epitope NYTPGPGTRYPLTFG
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A24)
Donor MHC A24, A3, B7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, NYTPGPGtRYPLTFG, varies at position 8 (threonine) from the consensus peptide QNYTPGPGIRYPLTF.

HXB2 Location Nef (126–140)
Author Location Nef (126–140)
Epitope NYTPGPGTRYPLTFG
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing

Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This epitope, NYTPGPGtRYPLTFG, varies from the consensus peptide at position 8.

HXB2 Location Nef (126–140)
Author Location Nef (126–140)
Epitope `NYTPGPGTRYPLTFG`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A23, B62
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b
- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- NYTPGPGtRYPLTFG is a previoulsy unpublished epitope, varying from the consensus at position 8 (threonine).

HXB2 Location Nef (126–143)
Author Location Nef
Epitope `NYTPGPGIRYPLTFGWCF`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004
- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, NYTPGPGIRYPLTFGWCF, had an overall frequency of recognition of 37.3% - 42.4% AA, 38.5% C, 31.8% H, 33.3% WI. This peptide is included in a 54 aa Nef highly reactive region to be used for vaccine design. It is also part of 'Region II', QKRQDILDLWVYHTQGYFPDWQNYTPGPGIRYPLTFGWCFKLVPVEPEKVEEAN, a 54 aa region recognized by >90% of subjects across ethnic groups.

HXB2 Location Nef (127–135)
Author Location Nef (127–135)
Epitope `YTPGPGIRY`
Epitope name YY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Country Australia, Canada, Germany, United States
Keywords escape, viral fitness and reversion, HLA associated polymorphism
References Brumme *et al.* 2008a
- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- Escape (and reversion) rates for B*57-restricted epitopes were highest for Gag-TW10 (TSTLQEQIGW) > RT-IW9 (IVLPEKDSW) > Nef-YY9 (YTPGPGIRY) > Nef-HW9 (HTQGYFPDW) > Gag-IW9 (ISPRTLNAW) > Gag-KF11 (KAFSPEVIPMF) .
- HLA-B*57-associated substitution within optimally defined epitope YTPGPGIRY is at position I7, YTPGPGiRY. YY9 has a recognition frequency above 20% and its escapes appear by 3 months post-infection.

HXB2 Location Nef (127–135)
Author Location
Epitope `YTPGPGIRY`
Immunogen

Species (MHC) human (B57)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B57 epitope.

HXB2 Location Nef (127–135)
Author Location Nef
Epitope YTPGPGIRY
Epitope name YY9
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B57, B58)
Donor MHC A02, A33, B35, B57, Cw04, Cw07
Assay type CD8 T-cell Elispot - IFNγ
Keywords cross-presentation by different HLA, optimal epitope
References Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This is a putative HLA-B63/57/58 epitope containing the B58 supertype binding motif. The optimal epitope was defined in a person carrying B57, and reactivity to the peptide was enriched in those with B57/B58, just a trend for B63.

HXB2 Location Nef (127–135)
Author Location
Epitope YTPGPGIRY
Immunogen
Species (MHC) human (B63)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B63 epitope.

HXB2 Location Nef (127–141)
Author Location Nef (127–141)
Epitope YTPGPGVRYPLTFGW
Epitope name RW8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A24)
Donor MHC A24, A3, B7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, YTPGPGvRYPLTFGW, varies at position 7 (valine) from the consensus peptide PGPGIRYPLTFGWCF.

HXB2 Location Nef (127–141)
Author Location Nef (127–141)
Epitope YTPGPGVRYPLTFGW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 8 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

HXB2 Location Nef (128–135)
Author Location Nef (128–135 LAI)
Epitope TPGPGVRY
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (B*0702)
Keywords epitope processing
References Lucchiari-Hartz *et al.* 2000

- Five naturally processed MHC class I ligands were identified in Nef in the conserved immunogenic region Nef between 123-152.
- All five could be transported by TAP, and 4/5 had N-termini that were major cleavage points for the proteasome, only one had extended precursor fragments.
- Both TPGPGVRYPL and TPGPGVRY are naturally processed ligands that can be eluted from HLA-B7 molecules, both are recognized by the same CTL, and both peptides seem to be the direct product of a proteasomal digest.
- The peptide TPGPGVRY is present in a high copy number, TPGPGVRYPL at a more moderate level, possibly due to a major cleavage site between the Y and P.

HXB2 Location Nef (128–135)
Author Location Nef (128–135)
Epitope TPGPGVRY
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (B7 supertype)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

CTL CD8+

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

HXB2 Location Nef (128–136)
Author Location Nef (128–136)
Epitope TPGPGVRYP
Epitope name TP9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*07)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords rate of progression, acute/early infection, memory cells
References Sabbaj *et al.* 2007

- CD127 hi memory CTLs were correlated with different patient groups - subjects with chronic HIV-1 infection or controllers or those treated early with ART. For patients with chronic infection, CD127 hi CTL levels decrease greatly. Early ART treatment alone maintained these long-lived memory T cells.
- In response to epitope TP9, TPGPGVRYP, IFN-gamma was produced by CD127 mix cells in patients with chronic infection and viremia. Chronically infected patients with low VL did not secrete IFN-gamma. HLA-restriction was to -B*07.

HXB2 Location Nef (128–136)
Author Location
Epitope TPGPGVRYP
Epitope name Nef-TP9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B07, 4/9 (44%) recognized this epitope.

HXB2 Location Nef (128–137)
Author Location Nef (128–137)
Epitope TPGPGVRYPL
Epitope name TL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*07, B*42)
Country Australia, Canada, Germany, United States
Keywords escape, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*07 and B*42-associated substitution within optimally defined epitope TPGPGVRYPL is at position V6, TPGPGvRYPL. TL10 has a 20% frequency of recognition, and escapes emerged at several time points post-infection.

HXB2 Location Nef (128–137)
Author Location Nef (128–137 LAI)
Epitope TPGPGVRYPL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*0702 epitope.

HXB2 Location Nef (128–137)
Author Location Nef (128–137 LAI)
Epitope TPGPGVRYPL
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (B*0702)
Keywords epitope processing
References Lucchiari-Hartz *et al.* 2000

- Five naturally processed MHC class I ligands were identified in Nef in the conserved immunogenic region Nef between 123-152.
- All five could be transported by TAP, and 4/5 had N-termini that were major cleavage points for the proteasome, only one had extended precursor fragments.
- Both TPGPGVRYPL and TPGPGVRY are naturally processed ligands that can be eluted from HLA-B7 molecules, both are recognized by the same CTL, and both peptides seem to be the direct product of a proteasomal digest.
- The peptide TPGPGVRY is present in a high copy number, TPGPGVRYPL at a more moderate level, possibly due to a major cleavage site between the Y and P.

HXB2 Location Nef (128–137)
Author Location (C consensus)
Epitope TPGPGVRYPL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0702)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- TPGPGVRYPL is an optimal epitope for B*4201 and B*0702.

CTL CD8+

HXB2 Location Nef (128–137)
Author Location
Epitope TPGPGVRYPL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0702, B7)
Donor MHC A*3204, A*7412, B*0702, B*4403, Cw*0210, Cw*0702
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression, immunodominance
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- TPGPGVRYPL is a known HLA-B7/-B*0702-restricted epitope that is part of peptide PGPGVRYPLTFGWCFKLVP which elicited the most dominant response in 8/10 patients. Response to a peptide containing this epitope was detected in 1 rapid progressor 12 weeks post-infection.

HXB2 Location Nef (128–137)
Author Location Nef (127–136)
Epitope TPGPGVRYPL
Epitope name TL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*3501)
Donor MHC A*0201, A*0301, B*3501, B*51, Cw*04, Cw*06
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords escape, acute/early infection
References Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- Point mutation at position 2 (P to S, TsGPGVRYPL) was detected at a chronic infection time point, month 33. This escape variant had lower avidity.
- The response to the peptide that carried this epitope was initially strong and diminished over time.

HXB2 Location Nef (128–137)
Author Location Nef (128–137 LAI)
Epitope TPGPGVRYPL
Subtype B
Immunogen
Species (MHC) human (B*4201)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is a B*4201 epitope.

HXB2 Location Nef (128–137)
Author Location Nef (128–137)
Epitope TPGPGVRYPL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Donor MHC A*30, A*3001, B*1503, B*4201, Cw*0202, Cw*1701; A*0301, A*3001, B*4201, B*5802, Cw*0602, Cw*1701
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, acute/early infection
References Pillay *et al.* 2005

- HIV-specific CTLs in infants were shown to be able to select for viral escape variants early in life, despite a lack of escape with the same CTL specificity in the mother. Infant CTL responses may be compromised by transmission of escape variants that arose in the mother and also those that arose in the father, if the father was the source of the mother's infection.
- Escape variants tSgpgvrypl and tQgpgvrypl were rapidly selected in an infant, by 26 weeks, but were not found in the infant's mother. These forms were demonstrated to be escape mutations by Elispot, and also had reduced binding to B*4201 in a competitive inhibition assay.

HXB2 Location Nef (128–137)
Author Location (C consensus)
Epitope TPGPGVRYPL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- TPGPGVRYPL is an optimal epitope for B*4201 and B*0702.

HXB2 Location Nef (128–137)
Author Location
Epitope TPGPGVRYPL
Epitope name TL10
Immunogen HIV-1 infection
Species (MHC) human (B*4201)
Country South Africa
Assay type proliferation, Tetramer binding, Intracellular cytokine staining
References Day *et al.* 2006

CTL CD8+

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

HXB2 Location Nef (128–137)
Author Location (C consensus)
Epitope TPGPGVRYPL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*0702, B*4201)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords cross-presentation by different HLA, characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location Nef (128–137)
Author Location
Epitope TPGPGVRYPL
Immunogen HIV-1 infection
Species (MHC) human (B07)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope TPGPGVRYPL elicited a magnitude of response of 210 SFC with a functional avidity of 0.5nM and binding affinity of 5.1nM.

HXB2 Location Nef (128–137)
Author Location Nef (128–137 BRU)
Epitope TPGPGVRYPL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- TPGPGVRYPL was recognized in 8/16 (50%) of individuals with HLA B7, and 1/9 (11%) of individuals with HLA B35. It was a high affinity HLA binder.

HXB2 Location Nef (128–137)
Author Location Nef (128–137)
Epitope TPGPGTRYPL
Epitope name TL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, acute/early infection, immune evasion
References Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- 2 PTE-B peptide sequences were identified, NYTPGPGtRYPLTFG and YTPGPGvRYPLTFGW, containing variants of this consensus epitope sequence TL10, viz. TPGPGtRYPL and TPGPGvRYPL, both of which elicited a IFN-gamma immune response.
- HLA-B35 restriction for TL10 was presumed based on the subject having the HLA allele and publication in the Los Alamos database.

HXB2 Location Nef (128–137)
Author Location
Epitope TPGPGVRYPL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords acute/early infection
References Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.

CTL CD8+

- All three patients were B*2705, with HLA alleles: A1, A30/31, B*2705, B35; A1, A*0301, B7, B*2705; and A*0201, A*0301, B*2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B*2705 epitope KRWIILGGLNK.
- The subject with A*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A*301-RLRPGGKKK, A*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A*0301, B7, B*2705.
- No acute response was detected to the following epitopes: A*201-ILKEPVHGV, A*301-KIRLRPGGK, A*301-AIFQSSMTK, A*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

HXB2 Location Nef (128–137)
Author Location Nef (128–137 LAI)
Epitope TPGPGVRYPL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Haas *et al.* 1996; Haas *et al.* 1997

- There was a high degree of variation in three CTL epitopes in Nef in four slow and non-progressors, and variant specific CTLs arose over time to eliminate variants, indicating immune selection.
- The epitope position was taken from Haas *et al.* [1997]

HXB2 Location Nef (128–137)
Author Location Nef
Epitope TPGPGVRYPL
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B7)
Keywords subtype comparisons, HIV exposed persistently seronegative (HEPS)
References Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The D subtype consensus is identical to the B clade epitope.
- The A subtype consensus is TPGPGIRYPL.

HXB2 Location Nef (128–137)
Author Location Nef (subtype B)
Epitope TPGPGVRYPL
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B7)
Keywords subtype comparisons
References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among B and D clade viruses.
- The Clade A version of the epitope: TPGPGIRYPL.

HXB2 Location Nef (128–137)
Author Location Nef (128–137)
Epitope TPGPGVRYPL
Immunogen in vitro stimulation or selection
Species (MHC) human (B7)
Keywords immunodominance, dendritic cells, Th1
References Wilson *et al.* 1999b

- Dendritic cells are the most potent for priming T cell responses – DCs can stimulate autologous CTL responses from T cells cultured from HIV negative donors.
- Th1-biasing cytokines IL-12 or IFN alpha enhance CTL responses *in vitro* whether the epitope is delivered by pulsing from peptide, or expressed from within.
- CTL from a B7 donor displayed no reactivity to this epitope, although it had been immunodominant in another study Haas *et al.* [1996]

HXB2 Location Nef (128–137)
Author Location Nef (128–137 SF2)
Epitope TPGPGVRYPL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 0/4 group 1, 0/3 group 2, and 1/1 group 3.

HXB2 Location Nef (128–137)
Author Location Nef (128–137)
Epitope TPGPGVRYPL
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B7)
Keywords HIV exposed persistently seronegative (HEPS), immunodominance
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B7 women, 4/5 HEPS and 5/6 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in 3 of the 4/5 HEPS cases and in 2 of the 5/6 HIV-1 infected women.
- Subject ML 1203 started with CTL responses to A*6802 DTVLEDINL and to B7 FPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A*6802 ETAYFILKL which became dominant, B7 TPGPG(V/I)RYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV.

HXB2 Location Nef (128–137)
Author Location Nef (128–137)
Epitope TPGPGVRYPL
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Appay *et al.* 2000

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN-γ and MIP-1β with a distinct subset that failed to produce TNF-α

HXB2 Location Nef (128–137)
Author Location Nef (128–137)
Epitope TPGPGVRYPL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes.
- An acute seroconvertor homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconvertor failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

HXB2 Location Nef (128–137)
Author Location Nef (128–137 BRU)
Epitope TPGPGVRYPL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- TPGPGVRYPL was recognized in 8/16 (50%) of individuals with HLA B7, and 1/9 (11%) of individuals with HLA B35. It was a high affinity HLA binder.

HXB2 Location Nef (128–137)
Author Location Nef
Epitope TPGPGVRYPL
Epitope name B7-TL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A3, B7, Cw7
Keywords dynamics, supervised treatment interruptions (STI), acute/early infection
References Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 2/4 individuals had detectable responses to this epitope after STI.

HXB2 Location Nef (128–137)
Author Location Nef
Epitope TPGPGVRYPL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A2, A3, B7, Bw6
Keywords HAART, ART
References Appay *et al.* 2002

CTL CD8+

- Four HIV patients with prolonged clinically successful antiviral therapy but with ongoing evidence of replication and Nef mRNA transcription, showed specific T-cell responses by Elispot and Tetramer staining, maintained for 2-4 years after initiation of HAART.
- Nef epitope recognition was detected in all 4 subjects, gp120, Pol and Gag-specific in 1 or 2 subjects.
- The HIV-specific CD8+ T-cells had an intermediate maturation phenotype characterized by low levels of perforin and high levels of CD27 expression.

HXB2 Location Nef (128–137)
Author Location Nef
Epitope TPGPGVRYPL
Subtype B, C
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human, macaque (B7)
Keywords subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location Nef (128–137)
Author Location Nef
Epitope TPGPGVRYPL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords HIV exposed persistently seronegative (HEPS)
References Koning *et al.* 2004

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A*11, A*31 and Cw*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
- No one, 0/9 HLA B7+ infection-resistant men, and 0/4 pre-seroconversion men who went on to become infected, reacted to this epitope.

HXB2 Location Nef (128–137)
Author Location Nef (126–135)
Epitope TPGPGVRYPL
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 6/7 patients recognized this epitope, it was the most commonly recognized of 11 B*07 epitopes.

HXB2 Location Nef (128–137)
Author Location (B consensus)
Epitope TPGPGVRYPL
Epitope name TL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A31, A68, B07, B70, Cw1, Cw7
Country United States
Assay type Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords assay standardization/improvement, memory cells, characterizing CD8+ T cells
References Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

HXB2 Location Nef (128–137)
Author Location Nef
Epitope TPGPGVRYPL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country United Kingdom
Assay type Tetramer binding, T-cell Elispot, Intracellular cytokine staining

Keywords rate of progression, acute/early infection, characterizing CD8+ T cells, immune dysfunction
References Papagno *et al.* 2004

- Acute HIV-1 infection induces massive activation of HIV-specific and non-HIV-specific CD8+ T-cells resulting in differentiation of these cells. High differentiation of CD8+ T-cells is correlated with disease progression. Differentiation is a natural process but it can be driven by elevated immune activation, such as in HIV infection.

HXB2 Location Nef (128–137)
Author Location Nef
Epitope TPGPGVRYPL
Epitope name TL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords superinfection
References Streeck *et al.* 2008b

- Loss of viral replication control by an elite controller after superinfection was found to coincide with rapid recombination events in 2, ∼50 residue regions of Gag and Env that include immunodominant epitopes KK10 (KRWIILGLNK) and CL9 (CAPAGFAIL). Viral escape was seen at both epitopes and consequent CTL responses against the epitope-variants.
- CTL responses to previously described, HLA-B7-restricted TPGPGVRYPL were seen post-superinfection and -recombination.

HXB2 Location Nef (128–137)
Author Location Nef
Epitope TPGPGIRYPL
Epitope name Nef1133
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Previously published epitope TPGPGIRYPL elicits IFN-gamma ELISpot responses in 5/7 subjects; and bound HLA-B7 with high affinities in soluble and cell-based assays.

HXB2 Location Nef (128–137)
Author Location Nef (128–137)
Epitope TPGPGVRYPL
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (B7 supertype)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

HXB2 Location Nef (128–137)
Author Location Nef (128–137 subtype B)
Epitope TPGPGVRYPL
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B*8101, B7)
References Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T cell epitopes: DTVLEDINL (3 individuals), SLYNTVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

HXB2 Location Nef (128–137)
Author Location Nef (subtype B)
Epitope TPGPGVRYPL
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B*8101, B7)
Keywords subtype comparisons
References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- Clade A version of the epitope: TPGPGIRYPL, clade D version: TPGPGIRYPL.

HXB2 Location Nef (128–137)
Author Location Nef
Epitope TPGPGIRYPL
Immunogen HIV-1 infection
Species (MHC) human

CTL CD8+

Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized by 1/22 HEPS control sex workers, ML851.

HXB2 Location Nef (128–137)
Author Location Nef (128–137)
Epitope TPGPGVRYPL
Epitope name TL10
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Other
Keywords supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism
References Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alelles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope restriction
- Statistically significant associations between numbers of HLA-0702 and -B4201 expressing subjects and epitope TPGPGVRYPL were found.
- Only B*0702 was found to be associated with polymorphism in TL10.

HXB2 Location Nef (128–137)
Author Location Nef
Epitope TPGPGRFPL
Epitope name TL10(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope TPGPGRFPL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide QNYTPGPGRFPLTFGWCF. This epitope differs from the previously described HLA-B7 epitope TPGPGVRYPL, at 1 residue, TPGPGrf-PL.
- 1 of the 9 HLA-B7 carriers responded to TPGPGrf-PL-containing peptide with average magnitude of CTL response of 120 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Nef (129–143)
Author Location Nef (129–143)
Epitope PGPGTRFPLTFGWCF
Epitope name RW8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A23)
Donor MHC A23, B62
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, PGPGtRfPLTFGWCF, varies at positions 5 and 7 from the consensus peptide PGPGIRYPLTFGWCF.

HXB2 Location Nef (129–143)
Author Location Nef (129–143)
Epitope PGPGTRFPLTFGWCF
Subtype B
Immunogen computer prediction, HIV-1 and GBV-C co-infection
Species (MHC) human (A24)
Donor MHC A24, A3, B7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, PGPGtRfPLTFGWCF, varies at positions 5 (threonine) and 7 (phenylalanine) from the consensus PCPCIRYPLTFGWCF.

HXB2 Location Nef (129–143)
Author Location Nef (129–143)
Epitope `PGPGTRFPLTFGWCF`
Epitope name YF9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- The peptide PGPGtRfPLTFGWCF varies at positions 5 and 7 from the consensus peptide PGPGIRYPLTFGWCF.

HXB2 Location Nef (129–143)
Author Location Nef (129–143)
Epitope `PGPGIRYPLCFGWCF`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- The peptide PGPGIRYPLcFGWCF varies at position 10 from the consensus peptide IRYPLTFGWCFKLVP.

HXB2 Location Nef (129–143)
Author Location Nef
Epitope `PGPGIRYPLTFGWCF`
Epitope name nef-5171
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A1, A19, B*3501, B44, Cw16, Cw7; A*0201, A19, B14, B44, Cw16, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
References Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than interperson sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, PGPGIRYPLTFGWCF was mutated in the daughter D2 isolate to PGPGtRfPLTFGWCF.

HXB2 Location Nef (130–139)
Author Location Nef (130–139 BRU)
Epitope `GPGVRYPLTF`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.

CTL CD8+

- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- GPGVRYPLTF was recognized in 0/10 (0%) of individuals with HLA B7, and 1/11 (9%) of individuals with HLA B35, although it was a high affinity HLA binder.

HXB2 Location Nef (130–139)
Author Location
Epitope GPGVRYPLTF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B35)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression, immunodominance
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- GPGVRYPLTF is a known HLA-B35-restricted epitope that is part of peptide PGPGVRYPLTFGWCFKLVP which elicited the most dominant response in 8/10 patients.

HXB2 Location Nef (130–139)
Author Location Nef
Epitope GPGTRFPLTR
Epitope name Nef1139
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Previously published epitope GPGTRFPLTR elicits IFN-gamma ELISpot responses in 5/7 subjects; and bound HLA-B7 with low and high affinities in soluble and cell-based assays respectively.

HXB2 Location Nef (130–143)
Author Location Nef (130–143 LAI)
Epitope GPGVRYPLTFGWCY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*57)
References Goulder *et al.* 1996b

- CTL response to this epitope observed in 4 long-term survivors.
- Peptide defined on the basis of B*5801 binding motif, yet not cross-restricted except at high concentrations.

HXB2 Location Nef (130–143)
Author Location
Epitope GPGIRYPLTFGWCF
Epitope name GF14
Immunogen HIV-1 infection
Species (MHC) human (B*57)
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite supressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B*57-restricted peptide GPGIRYPLTFGWCF was tested for immune response.

HXB2 Location Nef (130–143)
Author Location Nef (130–143)
Epitope GPGIRYPLTFGWCF
Epitope name GF14
Immunogen HIV-1 infection
Species (MHC) human (B*5801, B57)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape
References Navis *et al.* 2008

- HLA-B57/5801 progressing and long term non-progressing HIV-1-infected individuals were compared to observe the reason for the difference in their clinical outcomes. LTNP non-progression to AIDS was associated with protective HLA-alleles B57/5801 and preserved CTL IFN-gamma response against the WT Nef epitope HW9. Progressing HIV-1 positive subjects expressed the inhibitory receptor PD-1 which reflects an exhausted CTL phenotype.
- Epitope GPGIRYPLTFGWCF had various variants in progressors - GPGvRYPLTFGWCF, GPGIRYPLcFGWCF, GPGvRfPLTFGWCF and GPGtRfPLTFGWCF.
- Epitope GPGIRYPLTFGWCF variants in LTNPs were - GPGvRhPLcFGWCF, GPGvRYPLcFGWCF, GPGvRYPLTFGWCF, GPGIRYPvTFGWCF and GPGvRYPLTFGWCy.
- Nef GF14 is previously known to be restricted by HLA-B57/5801.

HXB2 Location Nef (130–143)
Author Location Nef (121–141)
Epitope GPGVRYPLTFGWCY
Immunogen HIV-1 infection
Species (MHC) human (B57)
References Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

CTL CD8+

HXB2 Location Nef (130–143)
Author Location Nef (128–141)
Epitope GPGVRYPLTFGWCY
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 7/7 patients recognized this epitope.

HXB2 Location Nef (130–144)
Author Location Nef (130–144 HXB2)
Epitope GPGVRYPLTFGWCYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords supervised treatment interruptions (STI), immunodominance, early treatment
References Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 24% of the study subjects, and it was one of the 25 most frequently recognized peptides.

HXB2 Location Nef (131–145)
Author Location Nef (131–145)
Epitope PGIRYPLTFGWCFKL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A23)
Donor MHC A23, B62
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, PGIRYPLTFGWCFKL, has identity with the consensus peptide IRYPLTFGWCFKLVP from positions 133-145.

HXB2 Location Nef (131–145)
Author Location Nef (131–145)
Epitope PGIRYPLTFGWCFKL
Subtype B
Immunogen computer prediction, HIV-1 and GBV-C co-infection
Species (MHC) human (A24)
Donor MHC A24, A3, B7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, PGIRYPLTFGWCFKL, is a variant of the consensus peptide IRYPLTFGWCFKLVP.

HXB2 Location Nef (131–145)
Author Location Nef (131–145)
Epitope PGIRYPLTFGWCFKL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This epitope, PGIRYPLTFGWCFKL, has identity with the consensus peptide IRYPLTFGWCFKLVP from positions 133-145.

HXB2 Location Nef (132–144)
Author Location Nef
Epitope GIRYPLTFGWCFK
Immunogen
Species (MHC) human
Keywords subtype comparisons
References Jubier-Maurin *et al.* 1999

- 41 new HIV-1 strains describing envelope subtypes of HIV-1 A-H were genetically characterized in the nef region – 34 subtypes were classified in the same subtype in nef and env and 7 of the 41 strains were recombinants.
- This region was defined as a CTL epitope region that is conserved among HIV-1 M group subtypes.

HXB2 Location Nef (132–146)
Author Location Nef (132–146)
Epitope GVRYPLTLGWCFKLV
Subtype B
Immunogen computer prediction, HIV-1 and GBV-C co-infection
Species (MHC) human (A24)
Donor MHC A24, A3, B7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, GvRYPLTlGWCFKLV, varies at positions 2 (valine) and 8 (leucine) from the consensus peptide IRYPLTFGWCFKLVP .

HXB2 Location Nef (132–147)
Author Location Nef (132–147 BRU)
Epitope GVRYPLTFGWCYKLVP
Immunogen HIV-1 infection
Species (MHC) human (A1, B8)
References Hadida *et al.* 1992

- HIV-1 specific CTLs detected in lymphoid organs.

HXB2 Location Nef (132–147)
Author Location Nef (132–147 BRU)
Epitope GVRYPLTFGWCYKLVP
Immunogen HIV-1 infection
Species (MHC) human (B18)
References Culmann *et al.* 1991

- Nef CTL clones from HIV+ donors.

HXB2 Location Nef (132–147)
Author Location Nef (132–147)
Epitope GVRYPLTFGWCYKLVP
Immunogen vaccine
Vector/Type: DNA, DNA with protein boost *Strain:* B clade LAI *HIV component:* Gag, Nef, Tat *Adjuvant:* IL-18
Species (MHC) mouse (H-2^d)
Keywords Th1
References Billaut-Mulot *et al.* 2001

- DNA vaccinated BALB/c mice primed and boosted with the multiepitopic vaccine with IL18 showed lymphoproliferative responses 7 weeks post immunization.
- Strong but non-lasting HIV-specific CTL responses were detected by a Cr-release assay and DNA prime/DNA boost was more effective than DNA prime protein boost.
- Immunization with either the multiepitopic DNA or with the mixed DNA vaccine induced HIV-1 specific Th1 cytokines (IL-2 and IFN-gamma)
- Co-administration of IL18 increased T-cell responses but decreased anti-HIV antibody levels.

HXB2 Location Nef (132–147)
Author Location Nef (132–147)
Epitope GIRYPLTFGWCFKLVP
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords rate of progression, immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL,

AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-A1 and B8-restricted epitope GIRYPLTFGWCFKLVP failed to generate CTL response. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location Nef (133–141)
Author Location Nef (133–141)
Epitope TRYPLTFGW
Epitope name TW9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*33)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a
- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-A*33-associated substitution within optimally defined epitope TRYPLTFGW is at position Y3, TRyPLTFGW.

HXB2 Location Nef (133–141)
Author Location Nef (133–141)
Epitope TRYPLTFGW
Immunogen HIV-1 infection
Species (MHC) human (A33)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Nef (133–141)
Author Location
Epitope VRYPLTFGW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression, immunodominance
References Gray *et al.* 2009
- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- VRYPLTFGW is a known HLA-B27-restricted epitope that is part of peptide PGPGVRYPLTFGWCFKLVP which elicited the most dominant response in 8/10 patients.

HXB2 Location Nef (133–141)
Author Location Nef
Epitope GRFPLTFGW
Epitope name TW9(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008
- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope GRFPLTFGW elicited an immune response in Chinese HIV-1 positive subjects as part of peptide QNYTPGPGRFPLTFGWCF. This epitope differs from the previously described HLA-A33-restricted epitope, TRYPLTFGW, at 2 residues, gRfPLTFGW.
- 5 of the 20 HLA-A33 carriers responded to gRfPLTFGW-containing peptide with average magnitude of CTL response of 343 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Nef (133–147)
Author Location Nef (133–147)
Epitope TRYPLTFGWCYKLVP
Subtype B
Immunogen computer prediction, HIV-1 and GBV-C co-infection
Species (MHC) human (A24)
Donor MHC A24, A3, B7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b
- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.

- The peptide TRYPLTFGWCyKLVP is a variant of the consensus peptide IRYPLTFGWCFKLVP and it varies at the 11th position.

HXB2 Location Nef (133–147)
Author Location Nef (133–147)
Epitope `TRYPLTFGWCYKLVP`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- The peptide, TRYPLTFGWCyKLVP, varies at position 11 from the consensus peptide IRYPLTFGWCFKLVP.

HXB2 Location Nef (133–148)
Author Location Nef (133–148 LAI)
Epitope `VRYPLTFGWCYKLVPV`
Subtype B
Immunogen
Species (MHC) human (B57)
References Brander & Walker 1996

- P. Goulder, pers. comm.

HXB2 Location Nef (134–141)
Author Location (C consensus)
Epitope `RYPLTFGW`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location Nef (134–141)
Author Location (C consensus)
Epitope `RYPLTFGW`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords epitope processing, rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in a residue outside of the optimized epitope of RYPLTFGW are associated with the presence of the HLA presenting molecule in the host.

HXB2 Location Nef (134–141)
Author Location
Epitope `RYPLTFGW`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2301, A24)
Donor MHC A*2301, A*2902, B*1510, B*4501, Cw*0602, Cw*1601; A*2301, A*2902, B*4101, B*4201, Cw*1701
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression, immunodominance
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- RYPLTFGW is a known HLA-A*2301 and -A24-restricted epitope that is part of peptide PGPGVRYPLTFGWCFKLVP which elicited the most dominant response in 8/10 patients. Response to a peptide containing this epitope was detected in both an early controller and 2 rapid progressors 12 weeks post-infection.

HXB2 Location Nef (134–141)
Author Location Nef (134–141)
Epitope `RYPLTFGW`
Epitope name RW8
Subtype B
Immunogen HIV-1 infection

Species (MHC) human (A*24)
Country Australia, Canada, Germany, United States
Keywords viral fitness and reversion, HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-A*24-associated substitutions within optimally defined epitope RYPLTFGW are at positions Y2 and F6, RyPLTfGW. Codon 135, i.e. RW8 position Y2 was the most rapidly reverting Nef epitope-associated mutation.

HXB2 Location Nef (134–141)
Author Location Nef (138–147 LAI)
Epitope RYPLTFGW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*2402 epitope.

HXB2 Location Nef (134–141)
Author Location Nef (169–176)
Epitope RYPLTFGW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Assay type Other
Keywords HLA associated polymorphism
References Boutwell & Essex 2007

- Publicly available HIV-1 subtype C sequences from South Africa and Botswana were analyzed, and 94 HLA-associated amino acid polymorphisms were found. Many polymorphisms were associated with multiple HLA allele classes. 12% associations were negative: association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles accounted for 50% of associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes.
- RYPLTFGW was a previously defined A*2402 presented epitope that encompassed an A*24 associated polymorphism, RyPLTFGW,in the second position.

HXB2 Location Nef (134–141)
Author Location Nef
Epitope RYPLTFGW
Immunogen peptide-HLA interaction
Species (MHC) human (A*2402)
Assay type Tetramer binding
Keywords binding affinity
References Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, RYPLTFGW (MHC Class I restriction, serotype Bw4) complexed with MHC A*2402 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C. However, the A*2402-KYKLKHIVW complex does bind inhibitory KIR3DL1 subtype KIR3DL1*005.

HXB2 Location Nef (134–141)
Author Location Nef (138–147 SF2)
Epitope RYPLTFGW
Immunogen HIV-1 infection
Species (MHC) human (A24)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with preseroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A24+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 2/3 group 2, and 0/0 group 3.

HXB2 Location Nef (134–141)
Author Location Nef
Epitope RYPLTFGW
Epitope name A24-RW8(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A24)
Donor MHC A24, B27, B7
Keywords HAART, ART, supervised treatment interruptions (STI)
References Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (`http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html`) for each person's class I HLA alleles.

CTL CD8+

- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient C displayed the greatest response to B27-KK10(p24), and in decreasing order also responded to A24-RW8(Nef), B7-IL9(gp41), A24-RL9(gp41), A24-YL8(gp41), and B7-TM9(Nef).

HXB2 Location Nef (134–141)
Author Location Nef
Epitope RYPLTFGW
Epitope name A24-WR8(Nef)
Immunogen HIV-1 infection
Species (MHC) human (A24)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (134–141)
Author Location
Epitope RYPLTFGW
Immunogen HIV-1 infection
Species (MHC) human (A24)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope KTKPPLPSVKK elicited a magnitude of response of 252 SFC with a functional avidity of 0.001nM.

HXB2 Location Nef (134–141)
Author Location
Epitope RYPLTFGW
Immunogen HIV-1 infection
Species (MHC) human (A24)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- Based on a prediction of the minimum number of HLA alleles needed to cover the HLA representation in all responders to this epitope, a minimum set of 6 alleles was found: 1 allele previously known to be associated (A24) and 5 additional alleles (A01, A02, A23, Cw04, Cw07).

HXB2 Location Nef (134–141)
Author Location Nef (134–141)
Epitope RYPLTFGW
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A33)
Donor MHC A3, A33, B14, B35, Cw*0401, Cw*0802
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.

- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

HXB2 Location Nef (134–141)
Author Location Nef (134–141 LAI)
Epitope RYPLTFGW
Subtype B
Immunogen
Species (MHC) human (B27)
References Culmann 1998

- Optimal peptide defined by titration.

HXB2 Location Nef (134–141)
Author Location Nef
Epitope RYPLTFGW
Epitope name RW8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- RW8, RYPLTFGW, is a known HLA-B27-restricted epitope used as a positive control for eliciting CTL IFN-gamma response.

HXB2 Location Nef (134–141)
Author Location Nef
Epitope RFPLTFGW
Epitope name RW8(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope RFPLTFGW elicited an immune response in Chinese HIV-1 positive subjects as part of peptide QNYTPGPGRFPLTFGWCF. This epitope differs from the previously described HLA-A24 epitope, RYPLTFGW, at 1 residue, RfPLTFGW.
- 16 of the 30 HLA-A24 carriers responded to RfPLTFGW-containing peptide with average magnitude of CTL response of 558 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Nef (134–143)
Author Location Nef (134–143)
Epitope RYPLTFGWCF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*24)
Donor MHC A*03, A*24, B*35, B*40
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, variant cross-recognition or cross-neutralization, superinfection, characterizing CD8+ T cells
References Yang *et al.* 2005b

- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
- The response to the peptide that carried this epitope, RYPLTFGWCF, was present before superinfection but waned afterward. The epitope from the second strain had a mutation, ryplCfgwcf. A second overlapping epitope in the reactive peptide might be involved, the B*35 epitope YPLTFGWCF.

HXB2 Location Nef (134–143)
Author Location Nef (138–147 SF2)
Epitope RYPLTFGWCF
Epitope name Nef138-10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Country Japan
References Ikeda-Moore *et al.* 1997

- Defined using reverse immunogenetics – 59 HLA-A*2402 binding peptides were predicted by searching for A*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A*2402.

CTL CD8+

- This peptide induced CTL in 3/4 HIV-1 + people tested.
- RYPLTFGWCF bound to A*2402 strongly, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

HXB2 Location Nef (134–143)
Author Location Nef (138–147)
Epitope RYPLTFGWCF
Epitope name Nef138-10
Subtype B
Immunogen vaccine
Vector/Type: Sendai virus vector system (SeV)
Species (MHC) human (A*2402)
References Kawana-Tachikawa *et al.* 2002

- A Sendai virus vector system (SeV) was developed that expressed HLA-A*2402-restricted class I/peptide complexes; this system could be used to detect responses and has the potential to elicit immune responses.
- MHC class I/peptide tetramers could be made using this system that bound to epitope-specific CTLs in PBMCs.
- Cells transfection with SeV modified to express A*2402-HIV epitope complexes induced CTL mediated specific cell lysis.

HXB2 Location Nef (134–143)
Author Location Nef
Epitope RYPLTFGWCF
Epitope name Nef138-10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Donor MHC A*2402
Country Japan
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords binding affinity, epitope processing, immunodominance, escape
References Furutsuki *et al.* 2004

- 70% of Japanese people carry HLA A*2402, and the rFpltfgwcf (2F) escape variant of this A*2402 epitope was found to be positively selected in Japan; reversion to wild-type in HLA-A24 negative individuals occurred very slowly over years. The 2F escape variant appears to be common in Japan due to escape and then transmission of this form in the population. The mechanism of escape appeared to be in processing of Nef and antigen presentation rather than HLA binding since both wild-type and 2F variant bound to HLA-A*2402 with almost same efficiency; the authors suggest the epitope may be cleaved at position 5 with a higher frequency when the 2F mutation is present.

HXB2 Location Nef (134–143)
Author Location Nef
Epitope RYPLTFGWCF
Epitope name Nef138-10
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Country Japan
Assay type Tetramer binding
Keywords supervised treatment interruptions (STI), immunodominance, escape, immune evasion
References Tanuma *et al.* 2008

- A longitudinal study of 3 immunodominant epitopes in early-ART patients given 5 STI series was undertaken to determine escape mechanisms during STI. Since all 12 patients' Nef138-10, RYPLTFGWCF, escaped to its Y2F variant RfPLTFGWCF, it is suggested that mutations in the immunodominant CTL epitope may be one mechanism of escape, limiting immune control.
- Frequency of epitope Nef138-10 did not correlate with plasma viral load. Nef138-2F (RfPLTFGWCF) and Nef138-5C (RYPLcFGWCF) however, are escape mutations whose recognizing-CTLs are not competent to control viral load.
- Epitope RYPLTFGWCF variants are RfPLTFGWCF, RYPiTFGWCF, RfPiTFGWCF, RfPLcFGWCF and RYPLcFGWCF (Nef138-5C).

HXB2 Location Nef (134–143)
Author Location Nef (138–147 SF2)
Epitope RYPLTFGWCF
Epitope name Nef138-10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Donor MHC A*2402
Country Japan
Assay type Tetramer binding, Chromium-release assay, CTL suppression of replication, HLA binding
Keywords escape
References Fujiwara *et al.* 2008

- To clarify mechanisms of escape mutation accumulation in the population, the Japanese Nef138-10 (RYPLTFGWCF) epitope was studied amongst hemophiliacs and others, to determine replication suppression abilities of both the wild type and 2F (RfPLTFGWCF) mutant virus. This mutant is conserved due to reduced CTL suppression of viral replication, also preventing viral reversion to WT upon transfer to a new host.
- 2F mutant for strain SF-2, RfPLTFGWCF, is associated with HLA-A*2402, but has also accumulated in the HLA-A*2402- population. It was shown to be an escape mutation due to the inability of Nef138-10 clones to lyse or suppress replication of 2F10F mutant-infected cells.
- CTL clones specific for the 2F mutant are elicited when the 2F virus infects a new host. Such clones are able to recognize and suppress replication of NL-432-2F10F-infected cells. 2F epitope presentation however, was weaker than that of the WT epitope in one patient harboring both viruses.
- RYPLTFGWCF epitope mutations found were RfPLTFGWCF (25/41), RYPLTFGWCy (8/41), RYPLcFGWCF (3/41), RfPLcFGWCF (1/41), RfPLlFGWCF (1/41), RfPiTFGWCF (1/41), RYPLTFGWpF (1/41) and RlPLTFGWCF (1/41) in 41 HLA-A*2402+ Japanese patients. In 22 HLA-A*2402- Japanese patients, mutations found were RfPLTFGWCF (3/22), RYPLTFGWCy (2/22), RYPLcFGWCF (2/22) and RfPLTFGWsF (1/22).

HXB2 Location Nef (134–143)
Author Location Nef (138–147 NL-432 or NL-M20A)

Epitope RYPLTFGWCY
Epitope name Nef138-10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Donor MHC A*2402
Country Japan
Assay type Tetramer binding, Chromium-release assay, CTL suppression of replication, Other, HLA binding
Keywords escape
References Fujiwara *et al.* 2008

- To clarify mechanisms of escape mutation accumulation in the population, the Japanese Nef138-10 (RYPLTFGWCF) epitope was studied amongst hemophiliacs and others, to determine replication suppression abilities of both the wild type and 2F (RfPLTFGWCF) mutant virus. This mutant is conserved due to reduced CTL suppression of viral replication, also preventing viral reversion to WT upon transfer to a new host.
- Strain NL-432 or NL-M20A epitope, RYPLTFGWCY, was used to confirm that A*2402-restricted Nef138-10 specific-CTLs have cytolytic activity and suppress viral replication within CD4+ infected cells. These CTLs also recognized the corresponding SF2-strain epitope RYPLTFGWCF.
- CTL clones recognizing 2F mutant, RfPLTFGWCY, for strains NL-432 and NL-M20A suppressed viral replication completely.

HXB2 Location Nef (134–143)
Author Location Nef (138–147)
Epitope RYPLTFGWCF
Immunogen HIV-1 infection
Species (MHC) human (A*2402)
Country Japan
Assay type Cytokine production, Tetramer binding, CTL suppression of replication, Other, HLA binding
Keywords escape
References Ueno *et al.* 2008

- The balance between Nef selective pressures to modulate HLA I or its escape mutations reducing Nef HLA I down-regulating activity is studied.
- Nef mutations had the effect of decreasing cytolytic activity of CTL clones with other specificities like HLA-A*2402-restricted CTLs specific for Nef-RYPLTFGWCF against double mutant (TF) infected cells.

HXB2 Location Nef (134–143)
Author Location Nef (134–143 BRU)
Epitope RYPLTFGWCY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A24)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- RYPLTFGWCY was recognized in 5/12 (42%) of individuals with HLA A24. It was a moderate affinity HLA-A24 binder.

HXB2 Location Nef (134–143)
Author Location Nef (134–143)
Epitope RYPLTFGWCY
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (A24)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

HXB2 Location Nef (134–143)
Author Location Nef (134–143 HXB2)
Epitope RYPLTFGWCY
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A24)
Country Viet Nam
Assay type HLA binding
Keywords subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization, vaccine antigen design
References Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- CRF01_AE variant ryplCfgwcy had same HLA-binding score as the HXB2 epitope.

HXB2 Location Nef (134–143)
Author Location Nef
Epitope RYPLTFGWCF
Immunogen HIV-1 infection
Species (MHC) human (A24)

Donor MHC A*24, A*32, B*07, B*18, Cw*07
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, characterizing CD8+ T cells, viral fitness and reversion
References Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- Variant rFpltfgwcf was detected in increasing frequencies in clones from an A24+ infant, but was absent in all sequences from the A24- mother at delivery, revealing selective pressure as early as 3 months of age.

HXB2 Location Nef (134–143)
Author Location Nef (134–143)
Epitope RYPLTFGWCY
Immunogen HIV-1 infection
Species (MHC) human (A24)
Donor MHC A2, A26, B51, B62; A2, B39, B60
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords HAART, ART, escape, viral fitness and reversion
References Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimates of reversion rates for this epitope, RYPLTFGWCY/F, in 2 subjects were found to be -0.014 and 0.005/day with SEs of 0.
- A Y135F substitution was shown to confer escape from an A24-restricted response by prevention of epitope processing. In an HLA A24- individual, the mutation rapidly reverted to wild type. Reversion of the Y135F escape mutant was observed in a second A24- individual. The model fitted the data well, giving a rate of 0.005/day. In this subject, the 135F-138C variant was out-competed by a 135Y-138C variant rather than by the wild type (135Y-138T). The rate of reversion with respect to the wild type is zero.

HXB2 Location Nef (134–143)
Author Location Nef (134–143 BRU)
Epitope RYPLTFGWCY
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (A24, B35)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 3/9 CRF02_AG-infected Ivorians, and 1/9 B-infected French subjects.
- A C-term F was most common in both the CRF02 and B clade infected subjects, and subjects that carried the F, RYPLTFGWCf, reacted with the peptide. One Ivorian that recognized the peptide carried the form RfPLTFGWCf.

HXB2 Location Nef (134–144)
Author Location Nef (134–144 LAI)
Epitope RYPLTFGWCYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B18)
Keywords review, escape
References Couillin *et al.* 1994; Goulder *et al.* 1997a

- Mutational variation in HIV epitopes in individuals with appropriate HLA types can result in evasion of CTL response.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

HXB2 Location Nef (134–144)
Author Location Nef (134–144)
Epitope RYPLTFGWCYK
Epitope name RYP
Immunogen HIV-1 infection
Species (MHC) human (B18)
Keywords HAART, ART, acute/early infection
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- None of the 8 study subjects recognized this epitope but none were HLA B18+

HXB2 Location Nef (134–148)
Author Location Nef
Epitope RYPLTFGWCFKLVPV

Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, RYPLTFGWCFKLVPV, had an overall frequency of recognition of 32% - 35.6% AA, 26.9% C, 31.8% H, 33.3% WI. This peptide is included in a 54 aa Nef highly reactive region to be used for vaccine design. It is also part of 'Region II', QKRQDILDLWVYHTQGYFPDWQNYTPGPGIRYPLTFGWCFKLVPVEPEKVEEAN, a 54 aa region recognized by >90% of subjects across ethnic groups.

HXB2 Location Nef (135–143)
Author Location p17
Epitope `YPLTFGWCF`
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type Intracellular cytokine staining
Keywords immunodominance, genital and mucosal immunity
References Kaul *et al.* 2003

- Predefined immunodominant peptide responses were used to compare CD8+ T cells responses in the blood and cervix of 16 HIV+ Kenyan sex workers. Cervical responses were detected in 8/10 women from whom adequate samples could be obtained. The frequency of the CD8+ T cell response in the genital tract was comparable to the blood, with a trend toward being slightly higher.
- The immunodominant response was to this epitope in the PBMC of 1/16 patients (Kaul *et al.* 2001, AIDS, 107:1303).

HXB2 Location Nef (135–143)
Author Location Nef (135–143 LAI)
Epitope `YPLTFGWCY`
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (B*0702)
Keywords epitope processing
References Lucchiari-Hartz *et al.* 2000

- Five naturally processed MHC class I ligands were identified in Nef in the conserved immunogenic region Nef between 123-152.
- All five could be transported by TAP, and 4/5 had N-termini that were major cleavage points for the proteasome, only one had extended precursor fragments.
- YPLTFGWCY is the naturally processed ligand for B7, and this epitope is the only one of the five that may require trimming at the N-termini.
- YPLTFGWCY is present in low copy number in the cell, possibly due to a predominant proteasomal cleavage site between Y and P.

HXB2 Location Nef (135–143)
Author Location (C consensus)
Epitope `YPLTFGWCF`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*18)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- YPLTFGWCF is an optimal epitope for B*5301, B*18, and B*35.

HXB2 Location Nef (135–143)
Author Location Nef
Epitope `YPLTFGWCF`
Epitope name YF9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*18)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords immunodominance
References Cao *et al.* 2008

- For the first time, viral immune evasion is reported via an insertion mutation, in an ART-naive patient. A 3 aa repeat, SPT inserted within p6<sup>Pol<sup> epitope NL8 is reported. This insertion is associated often with ART drug resistance to NRTI drugs. Thus immune pressure and drug resistance may cause HIV-1 to select the same variation.

- A concomitant insertion mutation APP, is seen in p6<sup>Gag<sup>, permitting viral budding.
- Epitope YPLTFGWCF elicited an early, dominant response in subject PIC1362.

HXB2 Location Nef (135–143)
Author Location Nef (135–143 LAI)
Epitope `YPLTFGWCY`
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B*1801)
Keywords optimal epitope
References Llano *et al.* 2009
- C. Brander notes this is a B*1801 epitope.

HXB2 Location Nef (135–143)
Author Location Nef (135–143 HXB2)
Epitope `YPLTFGWCF`
Epitope name YF9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1801)
Donor MHC A*0201, A*2501, B*1801, B*5101, Cw*0102, Cw*1203
Assay type CD8 T-cell Elispot - IFNγ
Keywords escape, immune evasion, optimal epitope
References Liu *et al.* 2006b
- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.

HXB2 Location Nef (135–143)
Author Location Nef (135–143)
Epitope `YPLTFGWCF`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Donor MHC A*03, A*24, B*35, B*40
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords acute/early infection, variant cross-recognition or cross-neutralization, superinfection
References Yang *et al.* 2005b
- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
- The response to the peptide that carried this epitope, YPLTFGWCF, was present before superinfection but waned afterward. The epitope from the second strain had a mutation, yplCfgwcf. A second overlapping epitope in the reactive peptide might be involved, the A*24 epitope RYPLTFGWCF.

HXB2 Location Nef (135–143)
Author Location (C consensus)
Epitope `YPLTFGWCF`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- YPLTFGWCF is an optimal epitope for B*5301, B*18, and B*35.

HXB2 Location Nef (135–143)
Author Location Nef
Epitope `YPLTFGWCF`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*3501, B*5301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords viral fitness and reversion, HLA associated polymorphism
References Matthews *et al.* 2008
- HLA-associated polymorphisms were studied in a cohort of 710 chronic subtype C patients from South Africa. 84 HLA Class I-associated polymorphisms were identified, 73% of them with HLA-B. The viral set points associated with HLA allele correlated with the number of reversions associated with that allele, (HLA-B in Gag, HLA-C in Pol).
- YPLTFGWCF is a previously described HLA-B*3501 and -B*5301-restricted epitope (part of Nef reacting peptide DWQNYTPGPGvRYPLTFGWCF) that contains a B*3501 and B*5301-associated reversion at residue V upstream of the epitope.

HXB2 Location Nef (135–143)
Author Location Nef (135–143)
Epitope `YPLTFGWCF`
Epitope name YF9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*53)
Country Australia, Canada, Germany, United States
Keywords HLA associated polymorphism
References Brumme *et al.* 2008a

- 98 newly infected patients were studied to track early host HLA and Gag/Pol/Nef epitope immune responses' association with viral evolution. Response hierarchies were the same as those for later infection, and 50% of the most rapidly substituting epitopes were restricted by protective HLA, e.g. Gag B*57-associated mutations which were the most rapidly reverting upon transmission to a non-B*57-host. While there are great differences in mutation rates and reversions across the HIV proteome, most early viral change is driven by immune pressure.
- HLA-driven epitope evolution was seen in 80% of published CTL epitopes.
- HLA-B*53-associated substitution within optimally defined epitope YPLTFGWCF is at position F9, YPLTFGWCf.

HXB2 Location Nef (135–143)
Author Location Nef (135–143)
Epitope `YPLTFGWCY`
Immunogen
Species (MHC) human (B*5301)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Nef (135–143)
Author Location (C consensus)
Epitope `YPLTFGWCF`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5301)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, optimal epitope
References Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- YPLTFGWCF is an optimal epitope for B*5301, B*18, and B*35.

HXB2 Location Nef (135–143)
Author Location Nef
Epitope `YPLTFGWCY`
Immunogen HIV-1 infection
Species (MHC) human (B*5301)
Country Kenya
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons, cross-presentation by different HLA, variant cross-recognition or cross-neutralization
References Currier *et al.* 2006

- The pattern of immunodominance and epitope clustering within Gag and Nef proteins in subtype A infected individuals was similar to that seen in subtype B and C infections. An immunodominant HLA-C restricted epitope, YVDRFFKTL (YL9 from Gag protein) was observed and restricted to Cw0304.
- The sequence girYPLTFGWCfklv is associated with HLA-B*5301 and contains the epitope YPLTFGWCY.

HXB2 Location Nef (135–143)
Author Location
Epitope `YPLTFGWCF`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5301, B18, B35)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression, immunodominance
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- YPLTFGWCF is a known HLA-B18, -B35 and -B5301-restricted epitope that is part of peptide PGPGVRYPLTFGWCFKLVP which elicited the most dominant response in 8/10 patients. A peptide containing this epitope elicited a response in a rapid progressor 12 weeks post-infection.

HXB2 Location Nef (135–143)
Author Location
Epitope `YPLTFGWCY`
Epitope name Nef-YY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5301, B35)
Donor MHC A*3002, A*3201, B*4501, B*5301, Cw*0401, Cw*1202
Keywords HAART, ART
References Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Subject 00RCH33 was on HAART had a viral load of 2900 and CD4 count of 727 and also recognized the epitopes HIGPGRAFY, gp160(310-318), HLA A*3002; AETFYVDGA, RT(437-445), HLA B*4501; and RSLYNTVATLY, p17(76-86), HLA A*3002.
- Among HIV+ individuals who carried HLA B53, 8/15 (53%) recognized this epitope – one subject also carried B7, previously shown to restrict this epitope.
- Among HIV+ individuals who carried HLA B35, 13/19 (68%) recognized this epitope.

HXB2 Location Nef (135–143)
Author Location Nef (subtype D)
Epitope `YPLTFGWCF`

Subtype D
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B18)
References Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T cell epitopes: DTVLEDINL (3 individuals), SLYNTVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

HXB2 Location Nef (135–143)
Author Location Nef (135–143 LAI)
Epitope YPLTFGWCY
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B18)
References Culmann *et al.* 1991; Culmann-Penciolelli *et al.* 1994

- Nef CTL clones from HIV+ donors.

HXB2 Location Nef (135–143)
Author Location Nef (135–143 SF2)
Epitope YPLTFGWCY
Immunogen HIV-1 infection
Species (MHC) human (B18)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B18+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 1/2 group 2, and 0/0 group 3.

HXB2 Location Nef (135–143)
Author Location Nef
Epitope YPLTFGWCF
Immunogen HIV-1 infection
Species (MHC) human (B18)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2002

- Neisseria gonorrhea cervititis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
- Ghonorrhea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

HXB2 Location Nef (135–143)
Author Location Nef
Epitope YPLTFGWCY
Epitope name B18-YY9(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B18)
Donor MHC A30, A32, B18, B27
Keywords HAART, ART, supervised treatment interruptions (STI)
References Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (`http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html`) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient D displayed the greatest response to B27-KK10 (p24), and also responded to A30-RY11(p17), A32-PW10(RT), A30-KY11(RT), A32-RW10(gp120), and B18-YY9(Nef).

HXB2 Location Nef (135–143)
Author Location Nef (135–143)
Epitope YPLTFGWCY
Epitope name YY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B18)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States

Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords optimal epitope
References Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- This epitope did not vary.

HXB2 Location Nef (135–143)
Author Location Nef (135–143)
Epitope YPLTFGWCY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B18)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location Nef (135–143)
Author Location
Epitope YPLTFGWCY
Immunogen HIV-1 infection
Species (MHC) human (B18)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- Based on a prediction of the minimum number of HLA alleles needed to cover the HLA representation in all responders to this epitope, a minimum set of 6 alleles was found: 1 allele previously known to be associated (B18) and 5 additional alleles (A02, A11, A23, A24, Cw04).

HXB2 Location Nef (135–143)
Author Location
Epitope YPLTFGWCY
Immunogen HIV-1 infection
Species (MHC) human (B18)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords supertype, cross-presentation by different HLA
References Frahm *et al.* 2007b

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B18), 2 additional HLAs (B35, B53) were statistically predicted to be associated with this epitope.

HXB2 Location Nef (135–143)
Author Location (C consensus)
Epitope YPLTFGWCF
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (B*5301, B18)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords cross-presentation by different HLA, characterizing CD8+ T cells
References Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

HXB2 Location Nef (135–143)
Author Location Nef (135–143)
Epitope YPLTFGWCF
Epitope name YF9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B18, B35)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, acute/early infection, immune evasion
References Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON

CTL CD8+

peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.

- 5 additional variants of this epitope, YPLTFGWCF, were found using the PTE-B set - fPLTFGWCF, YPLcFGWCF, fPLcFGWCF, YPLTFGWCy and YPLTlGWCF. Only the last variant, YPLTlGWCF, was not recognized when restricted by HLA-B35. The first variant alone, fPLTFGWCF, was present as a patient autologous sequence. While no epitope variants were seen in the T-cell HLA-B18 restricted response, these T cells did react with 3 out of 6 possible epitopic variants viz. YPLTFGWCF, fPLTFGWCF and YPLTFGWCy. Each of the 6 possible variants was associated predominantly with certain HIV-1 clades: YPLTFGWCF with clades B, C, A; fPLTFGWCF with clades A, B, C; YPLTFGWCy with clades A, C; YPLTlGWCF with clade F; fPLcFGWCF with circulating recombinant forms and YPLcFGWCF with clade B.
- HLA-B18 restriction was previously fine-mapped to YF9; HLA-B35 restriction was presumed based on the subject carrying the allele and publication in the Los Alamos database.

HXB2 Location Nef (135–143)
Author Location Nef (135–143)
Epitope YPLTFGWCY
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (B18, B49)
Keywords HIV exposed persistently seronegative (HEPS), immunodominance
References Kaul *et al.* 2001a

- Variants YPLTFGWC(Y/F) are specific for the B/D clades.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B18 women, 1/4 HEPS and 8/9 HIV-1 infected women recognized this epitope, likelihood ratio 5.3, p value 0.04, and HEPS women tended to respond to FRDYVDRF(Y/F)K, while infected women tended to respond to YPLTFGWC(Y/F)
- The dominant response to this HLA allele was to this epitope for the one reactive HEPS case and in all 8/9 HIV-1 infected women.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.

HXB2 Location Nef (135–143)
Author Location Nef (139–147 SF2)
Epitope YPLTFGWCF
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Shiga *et al.* 1996

- Binds HLA-B*3501.

HXB2 Location Nef (135–143)
Author Location Nef (135–143 BRU)
Epitope YPLTFGWCY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- YPLTFGWCY was recognized in 2/13 (15%) of individuals with HLA B7, and 11/14 (79%) of individuals with HLA B35, and it was a moderate affinity HLA binder.

HXB2 Location Nef (135–143)
Author Location Nef
Epitope YPLTFGWCY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC A11, A3, B35, B51
Keywords mother-to-infant transmission
References Sabbaj *et al.* 2002

- IFNgamma T-cell responses in breast milk of 5 HIV-1 infected women from the US and 6 from Zambia were tested with using Elispot. 11/11 women responded to Gag, 8/11 responded to Pol, 7/11 women to Nef, and 2/5 women to Env peptide pools. These responses were shown to be primarily due to CD8+ T-cells in one woman, and another woman had cytolytic responses measured by Cr-release.
- T-cells in breast milk from a volunteer who was HLA A3, A11, B35, B51 induced IFNgamma after stimulation with a peptide that carries known B35 epitope YPLTFGWCY.
- The frequencies of responses in the two compartments differed, and 2/4 women that responded to epitopes in Nef 101-205 and Pol 601-710 showed responses in breast milk but no detectable responses in peripheral blood cells.

HXB2 Location Nef (135–143)
Author Location Nef (135–143)
Epitope YPLTFGWCY
Epitope name YY9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
Donor MHC A*0201, A*0301, B*3501, B*51, Cw*04, Cw*06
Country United States

Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords escape, acute/early infection
References Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- The response to this peptide was initially low, but increased over time.

HXB2 Location Nef (135–143)
Author Location
Epitope YPLTFGWCY
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease
Species (MHC) human (B35)
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, characterizing CD8+ T cells
References Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

HXB2 Location Nef (135–143)
Author Location Nef
Epitope YPLTFGWCY
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B49)
Keywords subtype comparisons, HIV exposed persistently seronegative (HEPS)
References Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A subtype consensus is identical to the B clade epitope.
- The D subtype consensus is ypltfgwcF.

HXB2 Location Nef (135–143)
Author Location Nef (subtype B)
Epitope YLPTFGWCY
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (B49)
Keywords subtype comparisons
References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among A and B clade viruses.
- The Clade D version of the epitope, YPLTFGWCF, was preferentially recognized by CTL.

HXB2 Location Nef (135–143)
Author Location
Epitope YPLTFGWCY
Immunogen HIV-1 infection
Species (MHC) human (B49)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope, YPLTFGWC(Y/F), was recognized in 1/22 HEPS sex worker controls (ML1668)

HXB2 Location Nef (135–143)
Author Location Nef (135–143)
Epitope YPLTFGWCF
Immunogen
Species (MHC) human (B53)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Nef (135–143)
Author Location Nef
Epitope YPLTFGWCY
Epitope name B53-YY9(Nef)
Immunogen HIV-1 infection
Species (MHC) human (B53)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.

- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (135–143)
Author Location Nef (135–143 BRU)
Epitope YPLTFGWCY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- YPLTFGWCY was recognized in 2/13 (15%) of individuals with HLA B7, and 11/14 (79%) of individuals with HLA B35, and it was a moderate affinity HLA binder.

HXB2 Location Nef (135–143)
Author Location Nef
Epitope YPLTFGWCF
Epitope name Nef1127
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (B7)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, HLA associated polymorphism
References De Groot *et al.* 2008

- 45 highly conserved, putative HLA-B7-restricted epitopes were identified with EpiMatrix and evaluated for HLA binding and ELISpot assays. 40 epitopes were functional and 18 of them are novel, 7 were not previously described as HLA-B7-restricted.
- Epitope YPLTFGWCF elicits IFN-gamma ELISpot responses in 1/7 subjects; and bound HLA-B7 with low and high affinities in soluble and cell-based assays respectively. The authors claim previously published HLA restrictions of this epitope include B57 (LANL database), A*2402 (Immune Epitope Database).

HXB2 Location Nef (135–143)
Author Location Nef (135–143)
Epitope YPLTFGWCY
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (B7 supertype)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the most frequently recognized of the 31 epitopes that the vaccinated volunteers responded to.

HXB2 Location Nef (135–143)
Author Location Nef (135–143)
Epitope YPLTFGWCY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B18, B35, B49, B53, B7)
Donor MHC A3, A31, B18, B39; A1, A3, B35, B8
Country United States
Assay type Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, escape, variant cross-recognition or cross-neutralization
References Casazza *et al.* 2005

- Evidence of continued viral evolution during HAART therapy despite low viral load was found in 1/5 patients studied.
- A predominant sequence of ypltfgwcF was found in 2 patients (in 11/11 and 15/15 sequences) that cross-recognized the peptide used for screening, YPLTFGWCY. In patient B, CD8 T-cell response of 0.95% was found for the dominant variant, while the response for the screening epitope ypltfgwcy was 0.58%. In patient F, the frequency of response did not differ significantly between the 2 variants. Assays for both patients were done immediately prior to the initiation of therapy.

HXB2 Location Nef (135–143)
Author Location Nef (135–143 BRU)
Epitope YPLTFGWCY
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (B18, B53, B7)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 3/9 CRF02_AG-infected Ivorians, and 0/9 B-infected French subjects.

- The three Ivorians that recognized this peptide carried three different variants of the epitope: identical to LAI: YPLTFGWCY, YPLTFGWCf, and fPLTFGWCf. 6/8 Ivorians carried a variant, 5/5 B clade infections were not identical.

HXB2 Location Nef (136–144)
Author Location Nef (136–144 BRU)
Epitope PLTFGWCYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- PLTFGWCYK was recognized in 3/12 (25%) of individuals with HLA A3. It was a low affinity HLA-A3 binder.

HXB2 Location Nef (136–145)
Author Location Nef (136–145)
Epitope PLTFGWCYKL
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Keywords binding affinity, dendritic cells, Th1
References Wilson *et al.* 1999b

- Dendritic cells are the most potent for priming T cell responses – DCs can stimulate autologous CTL responses from T cells cultured from HIV negative donors.
- Th1-biasing cytokines IL-12 or IFN alpha enhance CTL responses *in vitro* whether the epitope is delivered by pulsing from peptide, or expressed from within.
- B7 and A2 Nef epitopes were studied and the relative binding affinity of A2 epitopes for A2 was: PLTFGWCYKL greater than VLEWRFDSRL which was much greater than AFHHVAREL.
- Noted in Brander *et al.*, 1999 this database, to be A*0201.

HXB2 Location Nef (136–145)
Author Location Nef (136–145 LAI)
Epitope PLTFGWCYKL
Subtype B
Immunogen
Species (MHC) human (A*0201)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*0201 epitope.

HXB2 Location Nef (136–145)
Author Location Nef (136–145 LAI)
Epitope PLTFGWCYKL
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Keywords epitope processing
References Lucchiari-Hartz *et al.* 2000

- Five naturally processed MHC class I ligands were identified in Nef in the conserved immunogenic region Nef between 123-152.
- All five could be transported by TAP, and 4/5 had N-termini that were major cleavage points for the proteasome, only one had extended precursor fragments.
- The CTL that recognized PLTFGWCYKL also recognized PLTFGWCYKLV, and both forms of the epitope are naturally processed and both seem to be the direct product of a proteasomal digest, although in low copy number.

HXB2 Location Nef (136–145)
Author Location Nef (136–145)
Epitope PLTFGWCYKL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords Th1, characterizing CD8+ T cells
References Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- Three of seven patients responded to this peptide with GzB producing cells and three of the patients responded with IFN-gamma producing cells. Only one patient had both a GzB and IFN-gamma response.

HXB2 Location Nef (136–145)
Author Location Nef
Epitope PLTFGWCFKL
Epitope name P10L
Immunogen vaccine
Vector/Type: measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140ΔV3
Species (MHC) transgenic mouse (A*0201)
Assay type Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells
References Lorin *et al.* 2005a

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

HXB2 Location Nef (136–145)
Author Location Nef (136–145)
Epitope PLTFGWCFKL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords subtype comparisons
References Durali *et al.* 1998

- Cross-clade CTL response was studied by determining the CTL activity in seven patients from Bangui, (6 A subtype, and 1 AG recombinant infections) and one A subtype infection from a person living in France originally from Togo, to different antigens expressed in vaccinia.
- Pol reactivity: 8/8 had CTL to A subtype, and 7/8 to B subtype, and HIV-2 Pol was not tested.
- Gag reactivity: 7/8 reacted with A or B subtype gag, 3/8 with HIV-2 Gag.
- Nef reactivity: 7/8 reacted with A subtype, and 5/8 with B subtype, none with HIV-2 Nef.
- Env reactivity: 3/8 reacted with A subtype, 1/8 with B subtype, none with HIV-2 Env.
- Patient B18 had the greatest breadth and diversity of response, and recognized Gag SLYNTVATL and Nef PLTFGWCFKL.

HXB2 Location Nef (136–145)
Author Location Nef (157–166)
Epitope PLTFGWCFKL
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost
Species (MHC) human (A2)
References Woodberry *et al.* 1999

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2.
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D^d – this transgene is the only MHC molecule expressed in the mice.
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost.
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFDSRL)
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested.
- PLTFGWCFKL was recognized by 1 of the HLA-A2 patients.

HXB2 Location Nef (136–145)
Author Location Nef (135–144 93TH253 subtype CRF01)
Epitope PLTFGWCYKL
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords subtype comparisons
References Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- 0/4 tested FSWs recognized the E clade version of this epitope PLCFGWCFKL, which differs from the previously defined B clade version by two amino acids, PLTFGWCYKL.
- This epitope was only conserved in CRF01 (subtype E) and subtype B.

HXB2 Location Nef (136–145)
Author Location Nef (136–145)
Epitope PLTFGWCYKL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.

HXB2 Location Nef (136–145)
Author Location
Epitope PLTFGWCYKL
Epitope name Nef-PL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
References Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A02, 3/29 (10%) recognized this epitope.

HXB2 Location Nef (136–145)
Author Location Nef (136–145 BRU)
Epitope PLTFGWCYKL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords binding affinity, epitope processing
References Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.

- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- PLTFGWCYKL was recognized in 9/28 (32%) of individuals with HLA A2. It was a low affinity HLA-A2 binder.

HXB2 Location Nef (136–145)
Author Location Nef (136–145)
Epitope PLTFGWCYKL
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (A2)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This was one of the most highly recognized of the 31 peptides that were shown to elicit a response.

HXB2 Location Nef (136–145)
Author Location Nef (136–145)
Epitope PLTFGWCYKL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords acute/early infection, optimal epitope
References Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized in chronic infection.

HXB2 Location Nef (136–145)
Author Location Nef (136–145 HXB2)
Epitope PLTFGWCYKL
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Viet Nam
Assay type HLA binding
Keywords subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization, vaccine antigen design
References Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- CRF01_AE variant plCfgwcFkl had a higher HLA-binding score than the HXB2 epitope.

HXB2 Location Nef (136–145)
Author Location Nef
Epitope PLTFGWCYKL
Epitope name A2-PL11(Nef)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (136–145)
Author Location Nef
Epitope PLTFGWCFKL
Epitope name PL11(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.

- Author defined epitope PLTFGWCFKL elicited an immune response in Chinese HIV-1 positive subjects as part of peptides QNYTPGPGRFPLTFGWCF and RFPLTFGWCFK-LVPV. This epitope differs from the previously published HLA-A2-restricted epitope PLTFGWCYKL, at 1 residue, PLTFGWCfKL.
- 10 of the 55 HLA-A2 carriers responded to PLTFGWCfKL-containing peptide with average magnitude of CTL response of 192 SFC/million PBMC.

HXB2 Location Nef (136–146)
Author Location Nef (136–146 LAI)
Epitope PLTFGWCYKLV
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (A*0201)
Keywords epitope processing
References Lucchiari-Hartz *et al.* 2000

- Five naturally processed MHC class I ligands were identified in Nef in the conserved immunogenic region Nef between 123-152.
- All five could be transported by TAP, and 4/5 had N-termini that were major cleavage points for the proteasome, only one had extended precursor fragments.
- The CTL that recognized PLTFGWCYKL also recognized PLTFGWCYKLV, and both forms of the epitope are naturally processed and both seem to be the direct product of a proteasomal digest, although in low copy number.

HXB2 Location Nef (137–145)
Author Location Nef (137–145)
Epitope LTFGWCFKL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

HXB2 Location Nef (137–145)
Author Location Nef (139–147 HXB3)
Epitope LTFGWCFKL
Immunogen vaccine
Vector/Type: DNA, peptide *Strain:* B clade HXB3 *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (A*0201)
Keywords binding affinity, computational epitope prediction
References Sandberg *et al.* 2000

- Ten Nef 9-mer peptides were predicted to have a strong binding affinity with HLA-A*0201 – of these, four did bind strongly by a T2 class I stabilization assay, several others bound weakly.
- A CTL immune response to only 3/10 peptides was detected by a 51Cr-release assay after immunization of HLA-A201 transgenic mice with either nef DNA under the control of a CMV promotor, coated on gold particles delivered to abdominal skin by gene gun – LTFGWCFKL did not elicit a CTL response.
- LTFGWCFKL was also tested by subcutaneous injection of Nef peptides in Freund's adjuvant, because it bound strongly to HLA-A*0201, and the peptide vaccination did elicit a response.
- The lack of response to the nef DNA vaccine and the response to the peptide suggests LTFGWCFKL may not be processed.

HXB2 Location Nef (137–145)
Author Location Nef (137–145)
Epitope LTFGWCFKL
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Chromium-release assay, Other, HLA binding
Keywords vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism
References Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- In addition to the published restriction above, epitope LTFG-WCFKL was predicted to be restricted by HLA A*0201.

HXB2 Location Nef (137–145)
Author Location Nef (221–)
Epitope LTFGWCFKL
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* multiple epitope immunogen
Species (MHC) human (A*0201)

Country Botswana, United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine antigen design
References Gorse *et al.* 2008

- This is a trial of a multi-epitope DNA vaccine that included 21 CTL epitopes, which are conserved among clades A,B,C,D and CRFs and are supertype binding peptides of A1, A3 and B7 supertypes. Participants were from US and Botswana.
- The vaccine was safe and well-tolerated, but the rate of CTL induction was low. CD8+ responses (and no CD4+ responses) were detected in 3/26 subjects using chromium release assay and in 2/42 subjects using IFN-γ ELISPOT assay.
- This epitope was included in the vaccine.

HXB2 Location Nef (137–145)
Author Location Nef (137–)
Epitope `LTFGWCFKL`
Epitope name Nef137
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This epitope was one of the previously identified HLA-A2 epitopes studied.
- 3/17 HIV-infected HLA-A2+ people recognized this epitope.

HXB2 Location Nef (137–145)
Author Location Nef (137–145)
Epitope `LTFGWCYKL`
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (A2)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This was one of the most highly recognized of the 31 peptides that were shown to elicit a response.

HXB2 Location Nef (137–145)
Author Location Nef (137–145)
Epitope `LTFGWCFKL`
Epitope name Nef137-145
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, immunodominance, characterizing CD8+ T cells
References Chandwani *et al.* 2004

- Responses to five HLA-A2 presented epitopes in Nef were characterized in a population of 19 HIV infected adults and 21 children. The CD8 T-cell response to Nef was stronger and broader in adults than children, averaging 652 and 87 SFCs/10^6 PBMC, and 2.6 and 0.9 recognized epitopes per person, respectively.
- This epitope was second in an immunodominance hierarchy of the five A02 Nef epitopes studied.

HXB2 Location Nef (137–145)
Author Location
Epitope `LTFGWCFKL`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression, immunodominance
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- LTFGWCFKL is a known HLA-A2-restricted epitope that is part of peptide PGPGVRYPLTFGWCFKLVP which elicited the most dominant response in 8/10 patients.

HXB2 Location Nef (137–145)
Author Location Nef
Epitope `LTFGWCFKL`
Epitope name Nef221
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* Other
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords vaccine antigen design
References Wilson *et al.* 2008

- DNA vaccine EP HIV-1090 evaluation in patients receiving ART was done. This vaccine is composed of multiple CTL epitopes, all associated with certain HLA supertypes. Differences of CTL response rate in vaccine and placebo recipients however, was not significant.

CTL CD8+

- LTFGWCFKL is a Nef epitope encoded in the EP HIV-1090 polyepitope vaccine.

HXB2 Location Nef (137–145)
Author Location Nef (158–166)
Epitope LTFGWCFKL
Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind all five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802)

HXB2 Location Nef (137–145)
Author Location Nef
Epitope LTFGWCFKL
Epitope name Nef221
Subtype A, B, C
Immunogen HIV-1 infection
Species (MHC) human, mouse (A2 supertype)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords binding affinity, supertype, vaccine-specific epitope characteristics, cross-presentation by different HLA
References Wilson *et al.* 2003

- 21 supertype-A2, -A3 and -B7-restricted epitopes predicted to be immunogenic by HLA-peptide binding motifs and phenotypic frequency in individuals were recognized by HIV-1 + subjects in ELISpot assays and shown to bind with high affinity to minimum 3 HLA-alleles of the restricting supertype. These epitopes were included in DNA vaccine EP HIV-1090 that avoided immunodominant responses and did not restrict subject immunity to predicted HLA-type when tested in mice. Transgenic mice mounted a vaccine-response similar to that induced by ELISpot assay in humans.
- Epitope LTFGWCFKL of the HLA-A2 supertype bound most strongly to HLA-A*6802, -A*0202, -A*0201 and -A*0206, but also to -A*0203. It was conserved 75% in subtype A, 74% in B, 100% in C and 0% in subtype D. 5/22 HLA-A2 supertype expressing HIV-1 + subjects mounted a positive ELISpot response to Nef221.

HXB2 Location Nef (137–145)
Author Location Nef
Epitope LTFGWCFKL
Epitope name LL9
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*1517, B57)
Donor MHC A*36, A*66, B*1517, B*53, Cw*04, Cw*06; A*02, A*23, B*35, B*57, Cw*04, Cw*07
Assay type CD8 T-cell Elispot - IFNγ
Keywords cross-presentation by different HLA, optimal epitope
References Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- Optimal epitope was defined in 2 people, 1 carrying HLA-B*1517(B63), the other carrying B57.

HXB2 Location Nef (137–145)
Author Location
Epitope LTFGWCFKL
Immunogen
Species (MHC) human (B57)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B57 epitope.

HXB2 Location Nef (137–145)
Author Location
Epitope LTFGWCFKL
Immunogen
Species (MHC) human (B63)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes that this is an B63 epitope.

HXB2 Location Nef (137–146)
Author Location Nef
Epitope LTFGWCFKLV
Immunogen HIV-1 infection
Species (MHC) human (A02)
Assay type CD8 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, immunodominance, optimal epitope
References Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope LTFGWCFKLV elicited a magnitude of response of 60 SFC with a functional avidity of 0.05nM.

HXB2 Location Nef (137–146)
Author Location Nef (221A)
Epitope LTFGWCFKLV
Epitope name Nef-221a
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords binding affinity, subtype comparisons, supertype, computational epitope prediction
References Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- 1/22 individuals with chronic HIV-1 infection recognized this epitope in ELISPOT.
- 2/12 acutely infected individuals recognized this epitope.
- LTFGWCFKLV binds to five HLA-A2 supertype alleles:A*0203, A*0201 (highest affinity), A*0206, A*6802 and A*0202.

HXB2 Location Nef (137–146)
Author Location Nef (137–146)
Epitope LTFGWCFKLV
Epitope name LV10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords optimal epitope
References Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- This epitope did not vary.

HXB2 Location Nef (137–146)
Author Location Nef (137–146)
Epitope LTFGWCFKLV
Epitope name LV10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
Keywords escape, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells
References Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- This epitope did not vary over time.

HXB2 Location Nef (137–146)
Author Location Nef (137–146)
Epitope LTFGWCFKLV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Donor MHC A11, A2, B18, B44, Cw12, Cw5
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location Nef (137–146)
Author Location Nef (135–146)
Epitope LTFGWCFKLV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords acute/early infection, optimal epitope
References Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized during chronic infection.

HXB2 Location Nef (137–146)
Author Location Nef (158–167)
Epitope LTFGWCFKLV
Immunogen HIV-1 infection
Species (MHC) human (A2 supertype)
Keywords supertype, rate of progression
References Propato *et al.* 2001

CTL CD8+

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind all five HLA-A2 supertypes alleles (A*0201, A*0202, A*0203, A*0206 and A*6802)
- Tetramer staining with A2, beta2microglobulin, and either SLYNTVATL, KLVGKLNWA, or LTFGWCFKL revealed that tetramers detected more HIV-specific sells in LTNP than in progressors, activated effector cells were the minority population, and ELISPOT correlated better with the effector cell subpopulation than the total tetramer stained population.

HXB2 Location Nef (137–146)
Author Location Nef (137–146)
Epitope `LTFGWCYKLV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope LTFGWCYKLV showed some conservation to subtypes A and non-Indian C. It is predicted to be restricted by HLA-A*6901.

HXB2 Location Nef (141–148)
Author Location Nef (141–)
Epitope `WCFKLVPV`
Epitope name Nef141
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* Nef
Adjuvant: Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was an intermediate A2 binder, and induced a CD8+ T-cell IFN gamma response in 1/6 mice. Responses were detected in 2/17 HIV+ HLA-A2 subjects.

HXB2 Location Nef (141–148)
Author Location
Epitope `WCFKLVPV`
Epitope name Nef 141
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay
References Thorn *et al.* 2007

- 11 HLA-A2+ (A*0201, A*0220, A*0234 or A*0236), patients' HIV were sequenced. Of 28 epitopes studied, most were conserved and elicited a subdominant CTL response. 9 epitopes in 7 proteins showed T-cell cross reaction. These epitopes were optimized to induce more immunogenic but cross-reacting responses.
- Epitopes in Gag, Pol, Env, Nef were more conserved than epitopes in shorter proteins Vpu, Vif, Vpr and Rev. Most natural epitopes were untargeted or targeted by 1 or 2 patients.
- Nef 141 WCFKLVPV epitope, the only one studied in Nef, was found in 9 patients but only 2 had a CTL immune responses to it.

HXB2 Location Nef (141–148)
Author Location Nef
Epitope `WCFKLVPV`
Epitope name Nef141
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Denmark
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression, acute/early infection
References Fomsgaard *et al.* 2008

- Comparative genetic and immunological study was conducted of two subjects - patient DK1 with no viremia for >10 years after transient ART and despite continued sexual contact with patient UG1 (his wife) who was an HIV-1-positive non-controller.

- DK1 and UG1 shared most crossover points of recombination but while DK1 had subtype A1 Env, UG1's Env was subtype D. In the shared subtype A1/D regions, homology between the patients' sequences was 98%.
- Out of 23 conserved HLA-A02 epitopes, HLA-A2+ DK1 produced CTL response and IFN-gamma response only to epitope ILKEPVHGV.
- DK1 produced neutralizing antibody only to homologous isolates. It is suggested that early, transient ART may have resulted in full control of viremia and disease via the very narrow specific CTL response and neutralizing antibody.
- Despite carrying HLA-A2, DK1 did not respond to HLA-A2 Vpr epitope WCFKLVPV, though it did elicit response in a cohort of 11 other HIV-1 + HLA-A2+ patients.

HXB2 Location Nef (146–156)
Author Location Nef (150–160)
Epitope VPVEPEKVEEA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*5401)
Country Japan
Assay type Intracellular cytokine staining, Chromium-release assay
Keywords optimal epitope
References Kitano *et al.* 2008

- Asian-expressed HLA-B*5401-restricted epitopes were identified using overlapping-peptide methods and characterized. 5 epitopes from Pol and Nef induced CTL responses that killed target cells in more than 25% of B*5401-carrying tested patients.
- 7 peptides from Pol and Nef are listed in Fig. 2 as candidates for B*5401 restriction. No Gag-specific epitopes were identified in this study from the patient whose lymphocytes were screened.
- VPVEPEKVEEA was defined as optimal epitope for HLA-B*5401 restriction, using truncated peptides.

HXB2 Location Nef (160–174)
Author Location Nef (160–174)
Epitope ENNSLLHPMSLHGMD
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A23, B62
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- ENNSLLHPMSLHGMD is a previoulsy unpublished epitope.

HXB2 Location Nef (161–179)
Author Location
Epitope NNCLLHPMSQHGMEDADRE
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Gray *et al.* 2009

- 47 HIV-1 subtype C infected patients were followed longitudinally to determine whether there was a relation between magnitude and breadth of CTL responses in primary, acute infection (measured by IFN-gamma ELISpot) and disease progression (measured as viral load at 12 months). CTL responses to Nef were dominant (targeting 6 epitopic regions), followed by responses to Gag, Pol, Rev, Vpr, Env, Vpu, Vif and finally Tat.
- This reactive peptide (1 responder), NNCLLHPMSQHGMEDADRE, is towards the N-terminal of Nef and has no previously described epitope.

HXB2 Location Nef (162–181)
Author Location Nef (161–180)
Epitope TSLLHPVSLHGMDDPEREVL
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

HXB2 Location Nef (162–181)
Author Location Nef (161–180 SF2)
Epitope TSLLHPVSLHGMDDPEREVL
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- One of these 11 had CTL response to this peptide.

HXB2 Location Nef (162–181)
Author Location Nef (101–120 SF2)
Epitope TSLLHPVSLHGMDDPEREVL
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

HXB2 Location Nef (162–181)
Author Location Nef (161–180 SF2)
Epitope TSLLHPVSLHGMDDPEREVL
Immunogen HIV-1 infection

Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- One of these 11 had CTL response to this peptide.

HXB2 Location Nef (166–177)
Author Location Nef (160–179 SF2)
Epitope HPVSLHGMDDPE
Immunogen HIV-1 infection
Species (MHC) human (B35)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 1/2 group 1, 0/2 group 2, and 0/1 group 3.

HXB2 Location Nef (172–191)
Author Location Nef (171–190 SF2)
Epitope GMDDPEREVLEWRFDSRLAF
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-A2, B21.

HXB2 Location Nef (175–184)
Author Location Nef (175–184)
Epitope DPEKEVLQWK
Immunogen HIV-1 infection
Species (MHC) human (B7)
References Jin *et al.* 2000b

- This a B7 epitope, a subdominant CTL response, was defined by an un-conventional approach used to predict epitopes in an HLA B7+ long-term non-progressor.
- Three additional sub-dominant HLA B7 epitopes were defined using EpiMatrix, a non-anchor based strategy for defining potential epitopes, which highlighted 2078 possible epitopes in the autologous HIV-1 derived from the study subject, followed by B7 anchor residue prediction which narrowed the set to 55 peptides, three of which could serve as functional CTL epitopes.

HXB2 Location Nef (175–184)
Author Location Nef
Epitope DPEKEVLQWK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B7)
Donor MHC A*0301, A*2301, B*0702, B*1503
Country United States
Keywords escape, acute/early infection
References Bernardin *et al.* 2005

- Full HIV genomes from nine individuals were analyzed for mutations prior to seroconversion and 7 to 28 days later. It was found that the influence of the host's HLA type was reflected within weeks of infection; a statistically significant number of early nonsynonymous mutations were observed within previously reported CTL epitopes.
- K to E mutation was observed in position 10.

HXB2 Location Nef (175–189)
Author Location Nef (175–189)
Epitope DPEREVLEWRFDSRL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- DPEREVLEWrFDSRL is a previously unpublished epitope that varies from the consensus at position 10 (arginine).

HXB2 Location Nef (176–193)
Author Location Nef
Epitope PEKEVLVWKFDSRLAFHH
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Haiti, United States
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords binding affinity, immunodominance
References Frahm *et al.* 2004

CTL CD8+

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors infuencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly. The virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, PEKEVLVWKFDSRLAFHH, had an overall frequency of recognition of 15.3% - 22% AA, 11.5% C, 18.2% H, 9.5% WI.

HXB2 Location Nef (177–185)
Author Location Nef
Epitope `EREVLVWKF`
Epitope name EF9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B27)
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction
References Schellens *et al.* 2008

- Peptide prediction programs based on MHC binding, proteasomal cleavage and TAP transport were applied to select novel epitopes absent from the Los Alamos HIV database. 22 novel epitopes were tested by IFN-gamma ELISpot and 19 (11 HLA-B27 restricted, 8 HLA-B57 restricted) induced strong positive responses.
- Magnitude of response generated was similar to that of previously identified epitopes, but the number of individuals responding was lower. This could be explained by less stringent HLA-typing of subjects and perhaps high sequence variability within these novel epitopes.
- EF9, EREVLVWKF, is a novel HLA-B27-restricted epitope that elicits a CTL IFN-gamma response significantly lower than Los Alamos database peptides.

HXB2 Location Nef (179–193)
Author Location Nef (175–189)
Epitope `EVLQWKFDSRLALRH`
Epitope name WF9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- The peptide EVLqWKFDSRLAlrH is a variant at positions 4, 13 and 14 from the consensus peptide EREVLEWKFDSRLAF.

HXB2 Location Nef (180–189)
Author Location Nef (180–189)
Epitope `VLEWRFDSRL`
Epitope name VL10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- This epitope, VLEWRFDSRL, was primarily recognized as wild type. Other variants seen were VLEWRFDSsL, VLEWRFgSRL and the 184K emerging variant VLEWkFDSRL. Position 184 fell under 2 overlapping CTL responses restricted by HLAs A2 and B15.

CTL CD8+

- In Table 2, epitope VLvWRFDSRL is printed as the epitope studied. We chose to record the epitope as VLEWRFDSRL seen twice elsewhere in this paper, as it is more commonly annotated as such in the literature.

HXB2 Location Nef (180–189)
Author Location Nef
Epitope VLEWRFDSRL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Donor MHC A1, A2, B49, B8, Cw7
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords immune evasion
References Maurer *et al.* 2008

- The Nef HLA-B8-restricted dominant epitope FL8, FLKEKGGL, was studied both longitudinally over time as well as horizontally in a 56 subject cohort of HIV-1 infected patients to chart FL8 variants. FL8 mutants were associated with higher pVL and lower CD4 cell counts.
- Patient 01 who was studied over time accumulated mutations in VLEWRFDSRL to VLkWRFDSRL and VLEWkFDSRL, concomitant with a strong viremic increase but did not react to this epitope.
- HLA restrictions in this study are previously published and correlate with the subject's HLA.

HXB2 Location Nef (180–189)
Author Location Nef (180–189 LAI)
Epitope VLEWRFDSRL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
References Haas *et al.* 1996; Haas *et al.* 1997

- There was a high degree of variation in three CTL epitopes in Nef in four slow and non-progressors, and variant specific CTLs arose over time to eliminate variants, indicating immune selection.
- Noted in Brander *et al.*, 1999 this database, to be A*0201.

HXB2 Location Nef (180–189)
Author Location Nef (180–189 LAI)
Epitope VLEWRFDSRL
Subtype B
Immunogen
Species (MHC) human (A*0201)
Keywords optimal epitope
References Llano *et al.* 2009

- C. Brander notes this is an A*0201 epitope.

HXB2 Location Nef (180–189)
Author Location Nef (180–189 LAI)
Epitope VLMWQFDSRL
Subtype B
Immunogen vaccine
Vector/Type: peptide *Strain:* natural variants *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) transgenic mouse (A*0201)
Keywords binding affinity, vaccine-specific epitope characteristics
References Boissonnas *et al.* 2002

- Ten naturally occurring variants of this epitope were tested for their affinity to HLA-A*0201 and for their ability to induce gamma-IFN and cytotoxic functions through vaccination of HLA-A*0201 transgenic mice.
- Only two variants could induce vaccine responses: VLMWQFDSRL, a high affinity binder, and VLQWRFDSRL a medium affinity binder to A*0201.
- In vivo priming with Nef peptide VLMWQFDSRL induced cross-reactive CTL to 6/7 peptides tested (AlmwKfdsKl, vlmwKfdsrl, vlmwKfdsKl, vlQwRfdsKl, vlVwrfdTrl, and vlAwKLdsrl but not the LAI peptide vlEwrfdsrl)
- In vivo priming with Nef peptide VLQWRFDTRL induced cross-reactive CTL to 3/6 variant Nef peptides (vlMwQfdsrl, vlqwrfdSrl and vlEwrfdsrl).

HXB2 Location Nef (180–189)
Author Location Nef (190–198)
Epitope VLEWRFDSRL
Immunogen vaccine
Vector/Type: DNA *HIV component:* HIV-1
Species (MHC) mouse (A*0201)
Keywords epitope processing, vaccine-specific epitope characteristics, immunodominance
References Singh *et al.* 2002; Sykes & Johnston 1999

- C3H (H-2k) transgenic mice carrying a fused HLA-A*0201 alpha1 and alpha2 and H-2Dk alpha3 hybrid class I molecule were immunized using an epidermal gene gun with an ubiquitin expression library of 32 plasmids that spanned the HIV-1 genome. Ubiquitin targets the expressed HIV-1 peptides to the proteasome.
- A single immunization with the UB-HIV-1 library vaccine induced potent, stable and multivalent CTL responses against all library members.
- Immunodominant epitopes SLYNTVATL (Gag), ILKEPVHGV (Pol), RIQRGPGRAFVTIGK (Env) and AFHHVAREK (Nef) elicited strong CD8+/IFN- responses and stimulated CTL that were functional in a Cr-release assay and against wild type antigen.
- The presence of multiple plasmids HLA-A*0201-restricted CTL epitopes did not decrease CTL immunogenicity, and CTL responses to single peptide immunizations were comparable to responses based on mixtures of either 16 or 32 peptides.

HXB2 Location Nef (180–189)
Author Location Nef (180–189)
Epitope VLEWRFDSRL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords Th1, characterizing CD8+ T cells
References Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- Three of seven patients responded to this peptide with GzB producing cells, while one of the three patients responded with IFN-gamma producing cells.

HXB2 Location Nef (180–189)
Author Location Nef (180–189)
Epitope VLEWRFDSRL
Immunogen in vitro stimulation or selection
Species (MHC) human (A2)
Keywords binding affinity, dendritic cells, Th1
References Wilson *et al.* 1999b

- Dendritic cells are the most potent for priming T cell responses – DCs can stimulate autologous CTL responses from T cells cultured from HIV negative donors.
- Th1-biasing cytokines IL-12 or IFN alpha enhance CTL responses *in vitro* whether the epitope is delivered by pulsing from peptide, or expressed from within.
- B7 and A2 Nef epitopes were studied and the relative binding affinity of A2 epitopes for A2 was: PLTFGWCYKL greater than VLEWRFDSRL which was much greater than AFHHVAREL.

HXB2 Location Nef (180–189)
Author Location Nef (180–189)
Epitope VLEWRFDSRL
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost
Species (MHC) human (A2)
References Woodberry *et al.* 1999

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2.
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D^{d} – this transgene is the only MHC molecule expressed in the mice.
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost.
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFDSRL)
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested.
- VLEWRFDSRL was recognized by 2 of the HLA-A2 patients.

HXB2 Location Nef (180–189)
Author Location Nef (180–189 LAI)
Epitope VLEWRFDSRL
Epitope name N3
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HAART, ART
References Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNgamma production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

HXB2 Location Nef (180–189)
Author Location Nef (179–188 93TH253 subtype CRF01)
Epitope VLEWRFDSRL
Subtype CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords subtype comparisons
References Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- 0/4 tested FSWs recognized the E clade version of this epitope VLIWKFDSAL, which differs from the previously defined B clade version by three amino acids, VLEWRFDSRL.

HXB2 Location Nef (180–189)
Author Location Nef (180–189)
Epitope VLEWRFDSRL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords rate of progression, acute/early infection
References Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.

HXB2 Location Nef (180–189)
Author Location Nef (178–187)
Epitope VLEWRFDSRL

CTL CD8+

Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 5/19 patients recognized this epitope.

HXB2 Location Nef (180–189)
Author Location Nef (180–189)
Epitope VLEWRFDSRL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, HLA binding
Keywords acute/early infection, optimal epitope
References Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized in chronic infection, and even then was recognized infrequently.

HXB2 Location Nef (180–189)
Author Location Nef (180–189 HXB2)
Epitope VLEWRFDSRL
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country Viet Nam
Assay type HLA binding
Keywords subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization, vaccine antigen design
References Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- CRF01_AE variant lMwKfdsAl had a higher HLA-binding score than the HXB2 epitope, which isn't predicted to bind to A2.

HXB2 Location Nef (180–189)
Author Location Nef
Epitope VLEWRFDSRL
Epitope name A2-VL10(Nef)
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (180–189)
Author Location Nef
Epitope VLMWKFDSRL
Epitope name VL10(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope VLMWKFDSRL elicited an immune response in Chinese HIV-1 positive subjects as part of peptide PEKEVLMWKFDSRLAFHH. This epitope differs from the previously described HLA-A2-restricted epitope VLEWRFDSRL, at 2 residues, VLmWkFDSRL.
- 5 of the 55 HLA-A2 carriers responded to a VLmWkFDSRL-containing peptide with average magnitude of CTL response of 400 SFC/million PBMC.

HXB2 Location Nef (180–194)
Author Location Nef (180–194)
Epitope VLVWKFDSRLAFRHM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Donor MHC B*1503, B35, B7 supertype, Cw7

Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- The peptide VLvWKFDSRLAFrHM is a variant at positions 3 and 13, of consensus peptide LEWKFDSRLAFHHMA.

HXB2 Location Nef (180–194)
Author Location Nef (180–194)
Epitope VLMWKFDSRLAFHHI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
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- This epitope, VLmWKFDSRLAFHHI, varies at position 3 (methionine) from the consensus peptide LEWKFDSRLAFHHMA.

HXB2 Location Nef (181–189)
Author Location Nef (181–189)
Epitope LEWRFDSRL
Epitope name Nef181-189
Immunogen HIV-1 infection
Species (MHC) human (A2)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, immunodominance, characterizing CD8+ T cells
References Chandwani *et al.* 2004

- Responses to five HLA-A2 presented epitopes in Nef were characterized in a population of 19 HIV infected adults and 21 children. The CD8 T-cell response to Nef was stronger and broader in adults than children, averaging 652 and 87 SFCs/10^6 PBMC, and 2.6 and 0.9 recognized epitopes per person, respectively.
- This was not the immunodominant response.

HXB2 Location Nef (181–195)
Author Location Nef (181–195)
Epitope LVWKFDSSLAFHHRA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

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- This peptide, LvWKFDSsLAFHHrA, varies at positions 2, 8 and 14 from the consensus peptide LEWKFDSRLAFHHMA.

HXB2 Location Nef (181–195)
Author Location Nef (181–195)
Epitope LVWKFDSHLAFHHMA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

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- This peptide, LvWKFDShLAFHHMA, varies at positions 2 and 8 from the consensus peptide LEWKFDSRLAFHHMA.

HXB2 Location Nef (181–195)
Author Location Nef (181–195)
Epitope LEWKFDSRLAFHHMA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Bailey *et al.* 2008

- This is the first documentation of transmission of HIV-1 from a patient who developed AIDS (Progressor) to an Elite Suppresssor (ES).
- Both patients are HLA-B*5703-positive. The ES also has B*27 allele. Escape mutations in HLA-B*57-restricted epitopes were present in both patients, suggesting that they by themselves cannot explain the difference in the outcomes.
- The study concluded that viral replication is controlled in ES by at least two mechanisms: (i) direct inhibition of viral replication by polyfunctional HIV-1 specific CD8+ T cells that proliferate in response to autologous viral peptides; (ii) selection for and maintenance of escape mutations that have a negative impact on viral fitness.
- This epitope elicited IFN-γ response in the Progressor. Both patients had E182V, K184R, M194V substitutions.

HXB2 Location Nef (182–189)
Author Location Nef (182–189)
Epitope EWRFDSRL
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (B8)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

HXB2 Location Nef (182–189)
Author Location Nef (182–189)
Epitope EWRFDSRL
Epitope name EL8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B8)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, acute/early infection, immune evasion
References Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- 2 PTE-B peptides, DPEREVLEWrFDSRL and VLvWKFDSRLAFrHM contained the epitope EWRFDSRL (EL8) and elicited IFN-gamma immune responses.
- HLA-B08 restriction for EL8 was presumed based on the subject's having the HLA allele and publication in the Los Alamos database.

HXB2 Location Nef (182–196)
Author Location Nef (182–196)
Epitope VWRFDSHLAFRHMAR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, VWrFDShLAFrHMAR, varies at positions 3, 7 and 11 from the consensus peptide LEWKFDSRLAFHHMA.

HXB2 Location Nef (182–198)
Author Location Nef (182–198 BRU)
Epitope EWRFDSRLAFHHVAREL
Immunogen HIV-1 infection
Species (MHC) human (A1, B8)
References Hadida *et al.* 1992

- HIV-1 specific CTLs detected in lymphoid organs of HIV-1 infected patients.

HXB2 Location Nef (182–198)
Author Location Nef (182–198 LAI)
Epitope EWRFDSRLAFHHVAREL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2, A25)
References Hadida *et al.* 1995

- The C-terminal region of Nef (182-205) contains multiple CTL epitopes with 5 distinct HLA restrictions.

HXB2 Location Nef (182–198)

CTL CD8+

Author Location Nef (182–198 BRU)
Epitope EWRFDSRLAFHHVAREL
Immunogen HIV-1 infection
Species (MHC) human (A25)
References Cheynier *et al.* 1992
- CTL isolated in children born to HIV-1 positive mothers.

HXB2 Location Nef (182–198)
Author Location Nef (182–198 LAI)
Epitope EWRFDSRLAFHHVAREL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Hadida *et al.* 1995
- The C-terminal region of Nef (182-205) contains multiple CTL epitopes with 5 distinct HLA restrictions.

HXB2 Location Nef (182–198)
Author Location Nef (182–198 LAI)
Epitope EWRFDSRLAFHHVAREL
Subtype B
Immunogen vaccine
Vector/Type: vaccinia, Mengo virus *Strain:* B clade LAI *HIV component:* Nef
Species (MHC) mouse (H-2^{d})
References Van der Ryst *et al.* 1998
- Macaca mulatta did not have a detectable response to Rec Mengo virus-HIV-1 Nef 65-206 vaccine.
- BALB/c mice had a weak response to this epitope in the Mengo virus construct – in contrast, HIV-1 Nef induces a strong CTL response in mice when presented in a vaccinia background.

HXB2 Location Nef (182–201)
Author Location Nef (191–205 SF2)
Epitope EWRFDSRLAFHHVARELHPE
Immunogen HIV-1 infection
Species (MHC) human
References Lieberman *et al.* 1997a
- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-A2, B21.

HXB2 Location Nef (182–205)
Author Location Nef (182–205 LAI)
Epitope EWRFDSRLAFHHVARELHPEYFKN
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide
Species (MHC) human
References Gahery-Segard *et al.* 2000
- Anti-HIV lipopeptide vaccine consisting of six long amino acid peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 4/10 reacted to this Nef peptide.
- 9/12 tested mounted a CTL response to at least one of the six peptides; each of the six peptides elicited a CTL response in at least one individual.
- None of the 12 tested had an IgG response to this peptide.

HXB2 Location Nef (183–191)
Author Location Nef (183–191)
Epitope WRFDSRLAF
Epitope name WF9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*15)
Country United States
Assay type Intracellular cytokine staining, Other
Keywords rate of progression, escape, immune evasion
References Karlsson *et al.* 2007
- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- No CTL responses were detected against the WF9 epitope, WRFDSRLAF. A 184K variant, WkFDSRLAF was found, that did elicit a potent HLA-B15 restricted immune response. Sporadic changes were seen in WF9 to WkFDSRLA (R185K).

HXB2 Location Nef (183–191)
Author Location
Epitope WRFDSRLAF
Epitope name Nef-WF9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Donor MHC A*2904, A*3002, B*1503, B*5802, Cw*0202, Cw*0602
Keywords HAART, ART
References Sabbaj *et al.* 2003
- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.

CTL CD8+

- This epitope was newly defined in this study.
- Subject 01RCH50 also recognized the epitope RMRGAHTNDV, RT(356-365), A*3002 – she was African American, was on HAART, had a viral load of 960 and CD4 count of 728.
- Among HIV+ individuals who carried HLA B15, 3/17 (18%) recognized this epitope.

HXB2 Location Nef (183–191)
Author Location Nef (183–191)
Epitope WRFDSRLAF
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Keywords optimal epitope
References Llano *et al.* 2009

HXB2 Location Nef (183–191)
Author Location Nef (183–191)
Epitope WRFDSRLAF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Donor MHC A*2301, B*1503, B*3501, Cw2, Cw7
Assay type CD8 T-cell Elispot - IFNγ
Keywords binding affinity, acute/early infection, early-expressed proteins
References Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

HXB2 Location Nef (183–191)
Author Location Nef
Epitope WRFDSRLAF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Donor MHC A*0301, A*2301, B*0702, B*1503
Country United States
Keywords escape, acute/early infection
References Bernardin *et al.* 2005

- Full HIV genomes from nine individuals were analyzed for mutations prior to seroconversion and 7 to 28 days later. It was found that the influence of the host's HLA type was reflected within weeks of infection; a statistically significant number of early nonsynonymous mutations were observed within previously reported CTL epitopes.
- K to E mutation was observed in position 2.

HXB2 Location Nef (183–191)
Author Location Nef (183–191)
Epitope WKFDSRLAF
Epitope name WF9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, acute/early infection, immune evasion
References Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- 5 additional variants of this epitope, WKFDSRLAF, were determined using PTE-B - WKFDSRLAl, WrFDShLAF, WrFDSRLAF, WKFDSsLAF and WKFDShLAF. The last 2 variants show reduced magnitude of response as compared to the consensus epitope while variant WKFaSRLAF was the only patient autologous epitope sequence detected.
- HLA-restriction for WF9 was performed and found to be to -B*1503.

HXB2 Location Nef (183–191)
Author Location Nef
Epitope WKFDSRLAF
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, rate of progression, immunodominance
References Frahm *et al.* 2006

- CTL responses restricted by HLA-B*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects inspite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominanat CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.
- WKFDSRLAF of clade B is a potential HLA-B*1503-restricted epitope, with epitope WKFDSqLAF found in clade C.

HXB2 Location Nef (183–191)

Author Location Nef
Epitope WRFDSRLAF
Epitope name B15-WF9(Nef)
Immunogen HIV-1 infection
Species (MHC) human (B15)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (183–191)
Author Location Nef
Epitope WKFDSRLAF
Epitope name WF9(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope WKFDSRLAF elicited an immune response in Chinese HIV-1 positive subjects as part of peptide PEKEVLMWKFDSRLAFHH. This epitope differs from teh previously described HLA-B15-restricted epitope, WRFDSRLAF, at 1 residue, WkFDSRLAF.
- 2 of the 21 HLA-B15 carriers responded to WkFDSRLAF-containing peptide with average magnitude of CTL response of 165 SFC/million PBMC (author communication and Fig.1).

HXB2 Location Nef (183–192)
Author Location Nef (183–192)
Epitope WRFDSRLAFH
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A1)
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

HXB2 Location Nef (183–192)
Author Location Nef
Epitope WRFDSRLAFH
Epitope name A1-WH10(Nef)
Immunogen HIV-1 infection
Species (MHC) human (A1)
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, early-expressed proteins
References Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

HXB2 Location Nef (183–192)
Author Location Nef
Epitope WRFDSRLAFH
Epitope name WH10(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A1)
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords non-susceptible form
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.

CTL CD8+

- The tested peptide sequence, PEKEVLMWRFDSRLAFHH, contains a variant, WkFDSRLAFH that differs by 1 substitution from the previously described HLA-A1-restricted epitope WRFDSRLAFH. None of the 4 HLA-A1 carriers responded to variant WkFDSRLAFH (author communication and Fig.1).

HXB2 Location Nef (183–193)
Author Location Nef
Epitope `WRFDSRLAHH`
Epitope name WH10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A1)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Streeck *et al.* 2008a

- T-cells were studied for exhaustion and dysfunction in chronic HIV infection. Polyfunctionality of CTL immune response to HIV-1 decreased with persistence of antigen presence over time in chronic infection. CTL exhaustion can thus be halted by reduction in viral antigen load - either by ART or through escape mutations.
- PD-1, marker for activation and apoptosis increases over time, but it decreases when epitope mutations develop. CD127 however, is not impacted by viral escape.
- 215 days after first testing, epitope WRFDSRLAHH varied to WkFDSlLAHH in an untreated patient. Previously published HLA-restriction for WH10 is HLA-A1.

HXB2 Location Nef (183–197)
Author Location Nef (183–197)
Epitope `WRFDSRLAFHHMARE`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*1503)
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, WrFDSRLAFHHMARE, varies at position 2 (arginine) from the consensus peptide LEWKFDSRLAFHHMA.

HXB2 Location Nef (183–202)
Author Location Nef
Epitope `WKFDSRLAFHHMARELHPEY`
Epitope name WY20
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A*6801, A01, B08, B51, Cw07, Cw15, DQ2, DQ3, DR3, DR4
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immune evasion
References Kemal *et al.* 2008

- An LTNP was followed longitudinally over 6 years and 3 sampling time points, until transition to disease. His HLA were heterozygous and not associated with nonprogressive infection, but 3 alleles were associated with poor clinical prognosis. No attenuating mutations in initial samplings, but an insertion in the V2 loop and continuing CCR5 coreceptor use were found.
- A decrease in IFN-gamma response was seen over time, suggesting CTL dysfunction. An increase in T-cell epitopes targeted (e.g. emergence of YL8, YLKDQQLL and WY20, WKFDSRLAFHHMARELHPEY variants and gain of response to EL9, EIKDTKEAL, NL10, NSNPDCKTIL, AK9, AIFQSSMTK, WM8, WSMVRERM, VT15, WVHHTQGYFPDWQNYT) was seen concomitant with disease progression, reflecting viral replication and/or variants.
- HLA-B51-restricted autolgous peptide epitope WKFDSRLAFHHMARELHPEY (WY20) was tested at the last time point only, eliciting immune responses to both it and an H10R variant, WKFDSRLAFrHMARELHPEY which elicited a decreased CTL response. HLA restriction was predicted in this study based on the patient's HLA alleles and previous publication.

HXB2 Location Nef (184–191)
Author Location Nef (184–191 HXB2)
Epitope `RFDSRLAF`
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A1)
Country Viet Nam
Assay type HLA binding
Keywords subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization, vaccine antigen design
References Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- CRF01_AE common variant KfdsAlaR had same HLA-binding score as the HXB2 epitope.

HXB2 Location Nef (186–193)
Author Location Nef (186–193 LAI)
Epitope `DSRLAFHH`

Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35)
References Hadida *et al.* 1995

- The C-terminal region of Nef (182-205) contains multiple CTL epitopes with 5 distinct HLA restrictions.

HXB2 Location Nef (186–194)
Author Location Nef (186–194)
Epitope DSRLAFHHM
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A24)
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location Nef (186–194)
Author Location Nef (186–194)
Epitope DSRLAFHHM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A24)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords Th1, characterizing CD8+ T cells
References Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- Two of seven patients responded to this peptide with GzB producing cells, while none of the patients responded with IFN-gamma producing cells.

HXB2 Location Nef (186–194)
Author Location Nef (186–194)
Epitope DSRLAFHHM
Epitope name DM9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A24)
Donor MHC A*24, A*31, B*15, B*47, Cw*04, Cw*07; A*24, A*30, B*39, B*47, Cw*12, Cw*17; A*23, A*24, B*07, B*39, Cw*12, Cw*17
Country United Kingdom
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, acute/early infection, viral fitness and reversion
References Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- DSRLAFHHM is a known A24 epitope. A known escape variant, DSRLAFqHM, was transmitted from an A24- mother to her A24+ infant, where it was gradually lost over time, present in 6/10 clones at 2 months, 7/10 at 4 months, and 0/10 at 15 months.
- Another escape variant was present in an A24+ mother, DStLAFqHk and this form was transmitted to her A24+ infant where it persisted in 30/30 sequences sampled over 12 months.
- DSRLAFHHM had higher responder cell frequencies in the A24+ mother than DStLAFqHk. Her A24+ infant did not recognize either form. The variant DSRLAFqHM also stimulated lower responder cell frequencies.

HXB2 Location Nef (186–194)
Author Location Nef (186–194 BRU)
Epitope DSRLAFHHV
Immunogen
Species (MHC) human (B51)
References Connan *et al.* 1994

- Resulted in the assembly of HLA-B51.

HXB2 Location Nef (186–194)
Author Location Nef (186–194)
Epitope DSRLAFHHV
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 7 epitopes from this individual that varied over time, although the internal mutations did not become fixed.The dsLlaLRhM variant residues arose at early time points, and the dsrlaVhhv variant residue arose at intermediate time points.

HXB2 Location Nef (186–194)
Author Location Nef
Epitope DSRLAFHHV
Epitope name DV9
Subtype B
Immunogen HIV-1 infection

CTL CD8+

Species (MHC) human
Donor MHC A28, A29, B14, B44, Cw8
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- An escape mutation at position 7, DSRLAFqHV, was found not to correspond to the most polymorphic residue in the epitope. This is a novel unmapped epitope.

HXB2 Location Nef (188–196)
Author Location Nef (192–200 SF2)
Epitope KLAFHHMAR
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (A*3303)
Assay type Chromium-release assay
Keywords binding affinity, computational epitope prediction
References Hossain *et al.* 2003

- HLA-A*3303 is a common HLA allele in east and southeast Asia. Pol, Gag and Nef SF2 proteins were scanned for potential A*3303 epitopes. 99 potential epitopes were synthesized, and 52/99 bound to A*3303. Six of these served as peptide-targets for lysis by PBMC from infected individuals, and clones derived from 4 of these 6 could lyse HIV-vaccinia infected target cells, indicating proper processing.
- This epitope is one of the 2/6 peptides that could induce CTL responses in the PBMC of infected individuals, but was not properly processed in a vaccinia-HIV infected target cell.

HXB2 Location Nef (188–196)
Author Location Nef (188–196)
Epitope RLAFHHVAR
Immunogen peptide-HLA interaction
Species (MHC) (A11, A3)
Assay type HLA binding
Keywords binding affinity, immunodominance
References Racape *et al.* 2006

- Interaction between purified HLA-A3 molecules and several dominant CD8 epitopes was characterized. Amplitude, stability, and kinetic parameters of the interaction between HLA-A3, peptides, and anti-HLA mAbs were tested.
- Epitopes tested bound strongly to HLA-A3 and formed very stable complexes.
- Gag epitope RLRPGGKKK and Nef epitope RLAFHHVAR complexes with HLA-A3 were not recognized by the A11.1 mAb specific to HLA-A3 alleles. The proposed explanation was that Arg at position P1 of the peptide may push the α2 helix residue and affect mAb recognition.

HXB2 Location Nef (188–196)
Author Location Nef (188–196 LAI)
Epitope RLAFHHVAR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B52)
References Hadida *et al.* 1995

- The C-terminal region of Nef (182-205) contains multiple CTL epitopes with 5 distinct HLA restrictions.

HXB2 Location Nef (188–196)
Author Location Nef
Epitope RLAFHHMAR
Epitope name RR9(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- Author defined epitope RLAFHHMAR elicited an immune response in Chinese HIV-1 positive subjects as part of peptide KFDSRLAFHHMAREKH. This epitope differs from the previously described HLA-B52-restricted epitope, RLAFHHVAR, at 1 residue, RLAFHHmAR.
- 1 of the 5 HLA-B52 carriers responded to RLAFHHmAR-containing peptide with average magnitude of CTL response of 40 SFC/million PBMC.

HXB2 Location Nef (188–201)
Author Location Nef (188–201 LAI)
Epitope RLAFHHVARELHPE
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B35, Cw4)
References Buseyne *et al.* 1993a

- Vertical transmission of HIV ranges from 13% to 39%
- Primary assays showed that cytotoxic activity against at least one HIV protein was detected in 70% of infected children.
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
- Patient EM13, who had a CTL response to three epitopes in Nef, was infected via blood transfusion after birth and went from CDC stage P2A to P2E during the study.

HXB2 Location Nef (188–202)
Author Location Nef (188–202)
Epitope SLAFHHRARELHPEY
Subtype B
Immunogen computer prediction, HIV-1 and GBV-C co-infection

CTL CD8+

Species (MHC) human
Donor MHC A24, A3, B7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- SLAFHHrARELHPEY is a previously unpublished epitope that varies from the consensus at position 7.

HXB2 Location Nef (188–202)
Author Location Nef (188–202)
Epitope SLAFHHRARELHPEY
Subtype B
Immunogen computer prediction, HIV-1 and GBV-C co-infection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- SLAFHHrARELHPEY is a previously unpublished epitope, that varies from the consensus at the seventh position, arginine.

HXB2 Location Nef (189–198)
Author Location Nef (189–198)
Epitope LAFHHVAREL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, immunodominance
References Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade B peptides) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef. 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope LAFHHVAREL is predicted to be restricted by HLA-A*6901. It shows some conservation of sequence to Indian subtype C.

HXB2 Location Nef (190–198)
Author Location Nef
Epitope AFHHVAREL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A*02)
Donor MHC A1, A2, B49, B8, Cw7
Country Germany
Assay type CD8 T-cell Elispot - IFNγ
Keywords immune evasion
References Maurer *et al.* 2008

- The Nef HLA-B8-restricted dominant epitope FL8, FLKEKGGL, was studied both longitudinally over time as well as horizontally in a 56 subject cohort of HIV-1 infected patients to chart FL8 variants. FL8 mutants were associated with higher pVL and lower CD4 cell counts.
- Patient 01 who was studied over time accumulated mutations in AFHHVAREL to AFrHVAREL that later reverted and to AFHHmAREL, concomitant with a strong viremic increase but did not react to this epitope.
- HLA restrictions in this study are previously published and correlate with the subject's HLA.

HXB2 Location Nef (190–198)
Author Location Nef
Epitope AFHHVAREL
Epitope name Nef AL9
Immunogen HIV-1 infection
Species (MHC) human (A*0201)
Keywords subtype comparisons, supertype, computational epitope prediction
References Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, including Nef AL9, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)

CTL CD8+

- RT VL9 was not recognized by any of the 22 HLA-A2 patients with chronic HIV-1 infection or the 13 HLA-A2 patients with acute HIV-1 infection included in this study.

HXB2 Location Nef (190–198)
Author Location Nef
Epitope ALKHRAYEL
Subtype A
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag
Species (MHC) human, macaque (A*0201)
Keywords subtype comparisons, epitope processing, immunodominance
References Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

HXB2 Location Nef (190–198)
Author Location Nef (190–198 LAI)
Epitope AFHHVAREL
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A2)
Keywords subtype comparisons, HIV exposed persistently seronegative (HEPS)
References Rowland-Jones *et al.* 1998a

- CTL recognition reported in the context of HLA-B52 and A2.1, A2.2 and A2.4.
- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A subtype consensus is ALKHRAYEL.
- The D subtype consensus is AfEHKAREm.
- Hunziker *et al.* [1998] suggests that HLA-A2 does not in fact present this epitope, and notes that it does not promote A2 assembly Connan *et al.* [1994] – also see Brander *et al.* [1998b]
- Hunziker *et al.* [1998] maintains that HLA-A2 does not present this epitope contrary to an earlier report Hadida *et al.* [1995], (also see Brander *et al.* [1998a])—despite the position of Hunziker *et al.*, Rowland-Jones and colleagues are confident that this epitope in its A clade form is presented by HLA-A*0201 and A*0202, and it is one of the most common responses seen in both seropositive and exposed-uninfected donors from Nairobi (Rupert Kaul, pers. comm.)

HXB2 Location Nef (190–198)
Author Location Nef (190–198)
Epitope AFHHVAREL
Immunogen in vitro stimulation or selection
Species (MHC) human (A2)
Keywords binding affinity, dendritic cells, Th1
References Wilson *et al.* 1999b

- Dendritic cells are the most potent for priming T cell responses – DCs can stimulate autologous CTL responses from T cells cultured from HIV negative donors.
- Th1-biasing cytokines IL-12 or IFN alpha enhance CTL responses *in vitro* whether the epitope is delivered by pulsing from peptide, or expressed from within.
- B7 and A2 Nef epitopes were studied and the relative binding affinity of A2 epitopes for A2 was: PLTFGWCYKL greater than VLEWRFDSRL which was much greater than AFHHVAREL.

HXB2 Location Nef (190–198)
Author Location Nef (190–198)
Epitope AFHHVAREL
Immunogen vaccine
Vector/Type: vaccinia
Species (MHC) human (A2)
References Woodberry *et al.* 1999

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2.
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D^d – this transgene is the only MHC molecule expressed in the mice.
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost.
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFDSRL)
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested.
- AFHHVAREL was recognized by 2 of the patients.

HXB2 Location Nef (190–198)

Author Location Nef (190–198 SF2)
Epitope AFHHVAREL
Immunogen HIV-1 infection
Species (MHC) human (A2)
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A2+ individuals that had a CTL response to this epitope broken down by group: 0/10 group 1, 1/6 group 2, and 0/4 group 3.

HXB2 Location Nef (190–198)
Author Location Nef (190–198)
Epitope ALKHRAYEL
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human (A2)
Keywords subtype comparisons, HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001a

- Variants ALKHRAYEL and AFHHVAREL are A/B clade specific.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

HXB2 Location Nef (190–198)
Author Location Nef (190–)
Epitope AFHHVAREL
Epitope name Nef190
Immunogen HIV-1 infection
Species (MHC) human (A2)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords binding affinity, subtype comparisons, computational epitope prediction
References Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A*0204, immunogenicity in HLA-A*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This epitope was one of the previously identified HLA-A2 epitopes studied.
- None of the 17 HIV-infected HLA-A2+ people in this study recognized this epitope.

HXB2 Location Nef (190–198)
Author Location Nef (190–198)
Epitope ALHHVAREL
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (A2)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of 31 that the vaccinated volunteers responded to.

HXB2 Location Nef (190–198)
Author Location Nef (subtype B)
Epitope AFHHVAREL
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human (A*0201, A*0202, A2)
Keywords subtype comparisons
References Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- Clade A version of the epitope: ALKHRAYEL, Clade D epitope: AFEHKAREM.
- This epitope was recognized by two different exposed and uninfected prostitutes.

HXB2 Location Nef (190–198)
Author Location Nef (190–198)
Epitope AFHHVAREL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A2, B52)
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell Elispot granzyme B
Keywords Th1, characterizing CD8+ T cells
References Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.

CTL CD8+

- Three of seven patients responded to this peptide with GzB producing cells, while one of three patients also responded with IFN-gamma producing cells.

HXB2 Location Nef (190–198)
Author Location Nef (190–198 HXB2)
Epitope AFHHVAREL
Subtype B, CRF01_AE
Immunogen HIV-1 infection
Species (MHC) human (A24)
Country Viet Nam
Assay type HLA binding
Keywords subtype comparisons, computational epitope prediction, escape, variant cross-recognition or cross-neutralization, vaccine antigen design
References Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- ArrHiAREL, ArtHiAREL, and ArkHiAREL variants are the three forms found in CRF01, and none are predicted to bind to A24.

HXB2 Location Nef (190–198)
Author Location Nef (190–198 LAI)
Epitope AFHHVAREK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A3)
References Hadida *et al.* 1995

- Naturally occurring L to K anchor substitution abrogates A2 binding, but permits HLA-A3 binding.

HXB2 Location Nef (190–198)
Author Location Nef (190–198)
Epitope AFHHVAREK
Immunogen HIV-1 infection
Species (MHC) human (A3)
Country Spain
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, supervised treatment interruptions (STI), immune dysfunction
References Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 14 patients recognized this epitope.

HXB2 Location Nef (190–198)
Author Location Nef (190–198)
Epitope AFHHVAREK
Epitope name AL9
Immunogen HIV-1 infection
Species (MHC) human (A3)
Donor MHC A*03, A*31, B*08, B*15, Cw*04, Cw*07
Country United Kingdom
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children, mother-to-infant transmission, escape, characterizing CD8+ T cells, viral fitness and reversion
References Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- AFHHVAREK is an A3 epitope, and a mixture of variants was present in the mother and in her A3- (A31+) infant at 2 months. One of the variants was AFqHmAREl, and this form was not found in 10 clones at the 15 month time point.

HXB2 Location Nef (190–198)
Author Location Nef (190–198)
Epitope AFHHVAREK
Immunogen HIV-1 infection
Species (MHC) human (B51)
Donor MHC A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8
Country Netherlands
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords rate of progression, escape
References Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occured sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 7 epitopes from this individual that varied over time, although the internal mutations did not become fixed. The aLRhMarek variant residues arose at early time points, the aVhhvarek variant residue arose at intermediate time points, and afhhvaXeI variant residues arose at late time points.

HXB2 Location Nef (190–198)
Author Location Nef
Epitope AFHHVAREL
Epitope name AL9(Nef)
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B52)
Country China
Assay type CD8 T-cell Elispot - IFNγ
Keywords non-susceptible form
References Zhai *et al.* 2008

- 49 ART-naive chronically HIV-1 infected Chinese subjects' CTLs were tested with 413 OLPs in IFN-gamma assays, determining optimal epitopes specific for Chinese Clade B HIV-1 sequences.
- An inverse correlation was found between CTL response and viral load.
- Targeted peptides have lower entropy than peptides that are not CTL targeted. This correlation is independent of HLA-restriction.
- The tested peptide sequence, AFHHmAREkHPEYYKDC, contains a variant, AFHHmAREk that differs by 2 substitutions from the previously described HLA-B52 epitope AFHHVAREL. None of the 4 HLA-B52 carriers responded to variant AFHHMAREK.

HXB2 Location Nef (190–198)
Author Location
Epitope ALKHRAYEL
Immunogen HIV-1 infection
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS)
References Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was in 1/22 HEPS controls, ML1749.

HXB2 Location Nef (190–198)
Author Location Nef (190–198)
Epitope AFHHVAREL
Epitope name AL9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords assay standardization/improvement, acute/early infection, immune evasion
References Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- 2 PTE-B peptides, KFDSRLAFHHVAREL and KFSRLAFHHiAREkH contained the epitope AFHHvAREL (AL9) and elicited IFN-gamma immune responses.

HXB2 Location Nef (190–204)
Author Location Nef (190–204)
Epitope AFRHVARELHPEYFK
Subtype B
Immunogen computer prediction, HIV-1 and GBV-C co-infection
Species (MHC) human (A3)
Donor MHC A24, A3, B7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This epitope,AFrHvARELHPEYfK, is a variant of the consensus peptide at positions 3, 5 and 14.

HXB2 Location Nef (190–204)
Author Location Nef (190–204)
Epitope AFHHMARELHPEYYK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- The unpublished epitope AFHHMARELHPEYYK is a variant of the consensus peptide LAFHHMARELHPEYY.

HXB2 Location Nef (190–204)
Author Location Nef (190–204)
Epitope AFRHVARELHPEYFK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC B*1503, B35, B7 supertype, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ

CTL CD8+

Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, AFrHvARELHPEYfK, varies at positions 3 and 5 from the consensus peptide HMARELHPEYYKDC.

HXB2 Location Nef (190–206)
Author Location Nef
Epitope AFRHMARELHPEYYKNC
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A1, A3, B57, B7, Cw6, Cw7
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
References Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host.The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Novel unmapped epitope.
- AFRHMARELHPEYYKNC acquired a substitution over time, AFRHMAREmHPEYYKNC.

HXB2 Location Nef (191–205)
Author Location Nef (191–205)
Epitope FHHKARELHPEYYKD
Subtype B
Immunogen computer prediction, HIV-1 and GBV-C co-infection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords computational epitope prediction, vaccine-induced epitopes
References Li *et al.* 2006b

- To assess the efficiency of vacine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide FHHkARELHPEYYKD, varies from the consensus at the fourth position, lysine.

HXB2 Location Nef (192–206)
Author Location Nef (192–206 BRU)
Epitope HHVARELHPEYFKNC
Immunogen HIV-1 infection
Species (MHC) human (A1)
References Hadida *et al.* 1992

- HIV-1 specific CTLs detected in lymphoid organs of HIV-1 infected patients.

HXB2 Location Nef (195–202)
Author Location Nef (195–202)
Epitope ARELHPEY
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21
Species (MHC) human (A1)
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization
References Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B-and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of 31 that were recognized in the vaccinees.

HXB2 Location Nef (195–202)
Author Location Nef (195–202 BRU)
Epitope ARELHPEY
Subtype B, CRF02_AG
Immunogen HIV-1 infection
Species (MHC) human (A1)
Country Cote D'Ivoire
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02_AG infected Ivorian subjects.
- This epitope was recognized by 0/9 CRF02_AG-infected patients, and by 1/9 B-infected patients. Sequence variants with two amino acid substitutions were found in 5/6 Ivorian subjects.
- An epitope variant was found in 1/4 French patients, and it happened to be the one patient that recognized the epitope: AREmHPEY.

HXB2 Location Nef (195–202)
Author Location Nef (195–202)
Epitope ARELHPEY
Epitope name AY8
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (A1)
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, acute/early infection, immune evasion
References Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- A PTE-B peptide, FHHkARELHPEYYKD contained the epitope ARELHPEY (AY8) and elicited a IFN-gamma immune response.
- HLA-A01 restriction for AY8 was presumed based on the subject's having the HLA allele and publication in the Los Alamos database.

HXB2 Location Nef
Author Location Nef
Epitope
Immunogen HIV-1 infection
Species (MHC) human (A*0201, Cw*08)
References Shacklett *et al.* 2000

- HIV-1 specific, MHC class I-restricted CTL killing was detected in duodenal and rectal gut associated lymphoid tissue (GALT) sites from three infected individuals – the distribution of class I restricted CTL was different in the peripheral blood samples and GALT samples.

HXB2 Location Nef
Author Location Nef
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B*35)
Keywords rate of progression
References Jin *et al.* 2002

- Patients with HLA-B*35 variants B*3502, B*3503, B*3504, and B*5301 tend to proceed to AIDS more quickly than those with B*3501.
- Of 32 patients with HLA-B*35 alleles CD8+ CTL responses were quantified using an intracellular cytokine staining assay – 75% had responses to Pol, 69% to Gag, 50% to Nef, and 41% to Env.
- The overall magnitude of CTL responses did not differ between those bearing B*3501 and the others. A higher percentage of Gag responses was observed in those that had lower RNA levels that carried B*3501, and there was a negative association with viral load and CTL activity. The data is consistent with higher levels of CTL responses contributing to protection in B*3501 individuals, but not in B*3502, B*3503, B*3504, and B*5301 individuals.

HXB2 Location Nef
Author Location Nef
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade NL43 *HIV component:* Nef *Adjuvant:* Bupivacaine
Species (MHC) mouse (H-2^{d})
Assay type CD8 T-cell Elispot - IFNγ
Keywords class I down-regulation by Nef, vaccine antigen design
References Majumder *et al.* 2003

- Non-functional Nef vaccine constructs that do not down-regulate class I or CD4 proteins are shown to be capable of inducing primary and memory T cell immune response after DNA vaccination in BALB/c mice, which makes them good candidates for vaccines.
- The responses to peptide pools suggest the C-terminal region of Nef is more immunogenic (the two most reactive peptide pools spanned positions 126-175, and positions 166-215).

HXB2 Location Nef
Author Location Nef (BRU)
Epitope
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade BRU *HIV component:* Nef
Species (MHC) mouse (H-2D^{d})
References Collings *et al.* 1999

- A comparison of DNA vaccination with HIV-1 Nef expression vectors pBN-CMV-NEF and pBN-RSV-NEF (self-replicating), pCGE2-NEF (non-replicating).
- CTL immune responses were detected using all three expression vectors, while a humoral immune response to Nef was only observed in the self-replicating expression vectors; possibly antibody responses require higher levels of protein expression.

HXB2 Location Nef
Author Location Nef (SIV)
Epitope
Immunogen SIV infection
Species (MHC) macaque (Mamu-A*11, Mamu-B*03, Mamu-B*04, Mamu-B*17)
References Dzuris *et al.* 2000

- Cell binding assays for Mamu molecules were employed to describe the peptide binding motifs for Mamu-A*11, -B*03, -B*03, -B*04, and -B*17 CTL epitopes – a similarity for Mamu-A*11 and -B*03 and human HLA-B*44 and -B*27, respectively, was observed – all epitopes studied were SIV epitopes, so not specifically listed here.

HXB2 Location Nef

Author Location Nef (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression, Th1
References Wasik *et al.* 2000

- HIV+ infants that progressed rapidly to AIDS had lower Th1 responses and decreased production of beta-chemokines and IL-2 relative to other HIV+ infants.
- No HIV+ infants had no demonstrable CTL at birth, but Th1 responses accompanied by CTL responses developed in children with slowly progressive disease, and not in rapid progressors.
- CTLp frequencies were determined by limiting dilution using autologous B cells infected with vaccina/HIV constructs.

HXB2 Location Nef
Author Location Nef
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References De Maria *et al.* 1997

- CD3+ cells that also carry a natural killer cell receptor (NKR+) can exhibit down regulation of T cell function.
- Anti-NKR IgM MAb masked this inhibitory function and increased HIV-1 specific CTL activity in phytohemagglutinin-activated PBMC cultured in the presence of IL-2 from 3/5 patients, and in one other case anti-NKR MAb brought HIV-1 specific CTL activity to detectable levels.

HXB2 Location Nef
Author Location Nef
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Lubaki *et al.* 1999

- Three strategies were used to analyze CTL activity: area under the net HIV-specific lysis curve (ACU), linear regression (LR) of net specific lysis, and the standard method, lytic units (LU20)
- A correlation between low HIV plasma viral load and increased levels of HIV-specific Gag and Nef CTL activity was observed using ACU and LR, but not LU20.

HXB2 Location Nef
Author Location Nef (LAI)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade SF2 *HIV component:* Env, Gag, Nef, Protease
Species (MHC) human
References Gorse *et al.* 1999b

- The vaccine used was rec canarypox expressing HIV-1 env, gag, pol, nef and protease (vCP300) with or without administration of HIV-1 SF-2 rgp120.
- In vitro inducible CTL activity against HIV-1 Env, Gag, Pol, and Nef antigens was observed in 79% (15 of 19) of vaccine recipients.
- The combination of vCP300 and vP1291 together resulted in an overall increase in CTL induction and detection sensitivity.

HXB2 Location Nef
Author Location Nef
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords TCR usage
References Gamberg *et al.* 1999

- 13/13 subjects with advanced HIV infections showed CD8 T cell proliferation and differentiation of CTL *in vitro*, and six individuals showed HIV-specific responses to Gag, Pol, Env or Nef antigens.
- Data suggests that the functional and genetic integrity of the CD8 T cell repertoire (TCR betaV gene intrafamily genetic diversity) remains intact through advanced HIV infection, although HIV-specific CTL activity decreases.

HXB2 Location Nef
Author Location Nef
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Nef, Rev, Tat
Species (MHC) human
Keywords HAART, ART
References Calarota *et al.* 1999

- 9/9 HIV-1 + subjects were given one of three DNA vaccinations for nef, rev or tat, and novel proliferative and CTL responses were generated.
- The nef DNA immunization induced the highest and most consistent CTLp activity, IFN-gamma production, and IL-6 and IgG responses.
- Highly active antiretroviral treatment (HAART) did not induce new HIV-specific CTL responses but reduced viral load, while DNA vaccination induced new immune responses but did not reduce viral load – thus this is a potentially complementary and promising combination.

HXB2 Location Nef
Author Location Nef (LAI)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Buseyne *et al.* 1998a

- This study showed a correlation between strong CTL memory and breadth of response in 7-12 month old infants, and remaining AIDS-free for the first year of life, higher absolute CD4 and CD8 cells, and lower viral load.

HXB2 Location Nef
Author Location Nef (LAI)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Buseyne *et al.* 1998b

- In infants with positive CTL responses, most responses showed cross-clade reactivity with somewhat diminished recognition of epitopes from different subtypes.

HXB2 Location Nef
Author Location Nef (LAI)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: canarypox *HIV component:* Gag, gp120, gp41, Nef, Protease, RT
Species (MHC) human
References Evans *et al.* 1999

- A Canarypox vaccine expressing gp120, gp41, Gag, Protease, Nef and Pol CTL epitopes gave rise to CTL that could be detected in 61% of the volunteers – responses to Gag, Env, Nef and Pol were detected 3-6 months after the last vaccination.

HXB2 Location Nef
Author Location Nef
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References da Silva & Hughes 1998

- CTL dense regions of Nef tend to lie in conserved domains with low non-synonymous substitution per site – authors consider that this may be due to a host adaptation to infection that focuses the CTL response to be directed against conserved functional domains da Silva & Hughes [1998]

HXB2 Location Nef
Author Location Nef (LAI)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Legrand *et al.* 1997

- Seventeen recently infected patients were tested for CTL response to HIV proteins Env, Gag, Pol, Rev, Nef, Vif and Tat.
- An early response (within a month following PI) was noted in 87% of the subjects to Gag, 75% to Env, and 50% to Nef.
- Early responses to Pol, Rev, Vif and Tat were rare.

HXB2 Location Nef
Author Location Nef (LAI)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Zerhouni *et al.* 1997

- CTL responses to Env, Gag, Nef and RT were tested at various phases of disease progression – 10 asymptomatic patients generally had CTL responses to all proteins, 10 ARC patients responded well to all proteins except Nef, and AIDS patients had few responses to any proteins.

HXB2 Location Nef
Author Location Nef
Epitope
Immunogen HIV-1 infection
Species (MHC)
Keywords epitope processing
References Kuiken *et al.* 1999

- A correlation between conserved regions of Nef and CTL epitope density was also noted in Kuiken *et al.* [1999]. The authors suggest that this may be due to biological reasons such as the one described above da Silva & Hughes [1998], or due to epitope processing, or may be an artifact of experimental strategy for epitope definition, such that conserved epitopes would tend to be identified because they are more likely to be cross-reactive with the test reagents.
- Both p17 and Nef show a correlation between epitope density and conserved regions in the protein; in contrast, p24 is a more conserved protein, and known epitopes are evenly distributed across p24.

HXB2 Location Nef
Author Location Nef (BRU)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Aladdin *et al.* 1999

- In vitro measurements of CTL-activity by Cr release assay in bulk culture showed no correlation between CTL-activity (gp120, Gag, Pol and Nef) and disease progression as measured by viral load, CD4 and time to death.

HXB2 Location Nef
Author Location Nef (SF2)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Jin *et al.* 1998a

- CTL precursor frequencies were determined in HIV-1 infected pregnant women, and higher CTLp frequencies to Pol and SF2 Nef, but not IIIB Nef, were found in non-transmitting mothers than in transmitting mothers – Nef CTL responses have been found in uninfected infants born to HIV+ women (Lazuriaga95);

HXB2 Location Nef
Author Location (subtype C)
Epitope
Subtype C
Immunogen
Species (MHC) human
Keywords subtype comparisons, immunodominance
References Novitsky *et al.* 2001

- This study is provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort.
- 37 of 45 subjects (82%) demonstrated Nef specific ELISPOT CTL responses of more than 100 SFC/106 PBMC.
- Two Nef-immunodominant regions were identified, one spanned amino acid positions 67 to 96 using HXB2 numbering system while the second corresponded to amino acid positions 122 to 141.

CTL CD8+

- While there was some subtype B and C cross-reactivity, there was greater breadth and intensity of response if the CTL from HIV-1-infected individuals was probed with ELISPOT using peptides derived from the same subtype (a median of three Nef epitopes recognized within subtype C compared with one Nef epitope recognized from subtype B peptides, and ELISPOT results with a median of 763 SFC/106 PBMC among responses to HIV-1 C, versus a median of 318 SFC/106 PBMC among responses to HIV-1 B.

HXB2 Location Nef
Author Location Nef (subtype A, B, D)
Epitope
Subtype A, B, D
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons
References Cao *et al.* 2000

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in HIV infected Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, Pol, RT or Nef from HIV-1 clades A, B, and D.
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype.

HXB2 Location Nef
Author Location Nef
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *HIV component:* Nef, Rev, Tat *Adjuvant:* CpG immunostimulatory sequence (ISS)
Species (MHC) human
Keywords review
References Calarota & Wahren 2001

- This review discusses the cellular immune response, and comments on the stimulatory role of CpG motifs and how HIV-1 DNA vaccines can boost the CTL and Th proliferative responses in asymptomatic HIV+ individuals.

HXB2 Location Nef
Author Location
Epitope
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission
References De Maria *et al.* 1994; Kuhn *et al.* 2002

- 6/24 HIV uninfected infants (ages 15-50 months) born to HIV+ mothers had HIV-1 specific CTL responses to vaccinia-expressed Nef, Gag/Pol, Env.
- Reviewed in Kuhn *et al.* [2002].

HXB2 Location Nef
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, escape
References Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated, traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.

HXB2 Location Nef
Author Location Nef (HXB)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords epitope processing, vaccine-specific epitope characteristics
References Lu *et al.* 2000a

- Bacillus anthrax lethal toxin (LFn)-HIV fusion proteins are candidate HIV vaccines that are safe in mice, and LFn-V3 region fusion proteins induce CD8 T cells in BALBc mice. LFn causes exogenous protein to be taken up and processed in a class I pathway. Expressed proteins from Gag p24 and nef fragments cloned into the LFn expression plasmid stimulate gag-specific CD4 proliferation and CTL responses in HIV-infected donor PBMCs *in vitro*.

HXB2 Location Nef
Author Location (BRU)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Edwards *et al.* 2002

- 96% (26/27) chronically infected HIV-1 infected patients elicited gamma-IFN CD8+ T-cell responses against Gag.
- Nef and/or Pol CTL responses were detected in 86% of the subjects.
- The magnitude and breadth of Gag and p24 T-cell responses correlated with absolute CD4 counts, and inversely correlated with viral load.
- Pol and Int CTL responses correlated positively with absolute CD4+ T-cell count.

CTL CD8+

- Nef and Env responses did not correlate with either CD4 counts or viral load.

HXB2 Location Nef
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, dendritic cells
References Larsson *et al.* 2002b

- Autologous mature dendritic cells with rec vaccinia expressing Gag, Pol, Nef and Env could amplify CD8+ T-cell Elispot responses 4-38 fold in five HIV+ patients on successful HAART treatment, relative to autologous monocytes. Some weak responses could only be detected using mature dendritic cells as APCs, and this approach could be useful for detection of low frequency memory cells.

HXB2 Location Nef
Author Location (SF2)
Epitope
Subtype B
Immunogen HIV-1 and HCV co-infection
Species (MHC) human
Keywords rate of progression
References Lauer *et al.* 2002

- HIV-1 and HCV immune responses were studied in 22 individuals who were co-infected with HIV-1 and hepatitis C virus (HCV). IFNgamma production was measured in an Elispot assay of CD8+ T-cells using targets expressing either Gag, RT, Env and Nef in a vaccinia construct, or one of seven HCV proteins.
- All 22 patients targeted at least one protein. 20/22 patients recognized RT, 17/22 patients recognized Gag, 13/22 subjects recognized Env and 11/22 patients recognized Nef. Robust CTL activity was independent of disease progression or viral load.
- Despite high HCV viral loads, very few HCV CD8+ T-cell Elispot responses were detected. In a control HCV infected person who did not have HIV-1, strong anti-HCV responses were mounted.
- HIV-specific CD4 proliferative responses were detected in 9/17 coinfected patients, but no HCV responses were detected.

HXB2 Location Nef
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, responses in children
References Scott *et al.* 2001

- CTL responses before and after initiation of ART were studied in 13 HIV-1 vertically infected infants <6 months of age, and 4 that were >6 months of age.
- Before ART 2/13 infants <6 months of age showed IFNgamma Elispot CD8+ T-cell responses, one to Nef and one to Env and Nef, and these responses became undetectable after successful therapy– 3 infants were coinfected with CMV and all 3 had CMV-specific CD8+ T-cell responses.
- One older infant, at 23 months, had CTL responses against all for proteins tested, Gag, Pol, Nef and Env, and had the lowest plasma viremia of the study group. 3/4 infants older than 6 months of age responded to either Nef or Pol.
- Administration of ART over 48 weeks broadened the HIV-1-specific CTL response in 2/4 of the older children that were incomplete responders.

HXB2 Location Nef
Author Location (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, supervised treatment interruptions (STI)
References Ortiz *et al.* 2001

- Immune responses in eight chronically HIV-1 infected patients undergoing HAART therapy structured treatment interruptions (STI) were studied. STI boosted HIV-1 specific CTL responses and elevated CTL responses were maintained up to 22 weeks after the last treatment interruption, but viral load rebound to pretreatment levels and CD4 T-cell count decline was observed. CD8 responses in PBMC were measured by cytokine flow cytometry with gp160, Gag p55, RT-Pol and Nef expressed in vaccinia.

HXB2 Location Nef
Author Location
Epitope
Immunogen vaccine
Vector/Type: adenovirus *HIV component:* Gag-Pol, Nef, Vpr
Species (MHC) mouse
References Muthumani *et al.* 2002

- Vpr can cause cells to go into G2 arrest, and it surpresses immune cell activation and inflammatory cytokine production, so co-immunization of BALB/c mice with recombinant adenovirus expressing Vpr and HIV-1 antigens Nef or Gag/Pol was tested to see if Vpr reduced the immune response to the other HIV antigens.
- Vpr compromised CD8+ T-cell lytic responses and T-helper proliferative responses in mice co-immunized with Vpr and Nef or Gag/Pol.
- In vitro, Vpr reduced T-cell cytokine production of IL-12 and TNFalpha, indicative of Vpr-mediated immune suppression.

HXB2 Location Nef
Author Location Nef
Epitope
Subtype multiple
Immunogen
Species (MHC) human
Assay type Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Currier *et al.* 2003

- CD8-cellular immune responses from 21 HIV-1 infected patients from Kenya infected with subtype A, C, D, and unique recombinants were studied for cross-recognition of Gag, Env, and Nef vaccinia-expressed proteins representing subtypes A-H, including CRF01.

CTL CD8+

- Both subtype-specific and cross-reactive CTL were observed, with a skewing of responses towards the infecting subtype in the nine subjects with full length sequence available. The magnitude of the responses to Gag were the highest, less to Nef, and still less to Env.
- For Gag, 8/21 subjects responded to at least 7/8 different subtype proteins, 7 had a mixed response, recognizing some subtypes but not others, and 6 responded to only one or none of the different subtype proteins. For Env, 4/19 subjects responded to at least 7/8 subtypes, 8 had a mixed response, and 7 responded to one or none. For Nef, 5/19 subjects responded to at least 7/8 subtypes, 8 had a mixed response, and 6 responded to one or none.

HXB2 Location Nef
Author Location Nef (B.AU.AF064676)
Epitope
Subtype B
Immunogen
Species (MHC) human
References

HXB2 Location Nef
Author Location Nef
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords assay standardization/improvement
References Draenert *et al.* 2003

- Six different HIV-1 Nef peptide sets ranging in length from 15-20 amino acids with overlap from 10-11 amino acids derived from either the B clade consensus sequences or the B clade sequence B.AU.AF064676 were used to study the impact of using different peptide design strategies to detect CD4 and CD8 T-cell responses. 20 individuals were tested using the six sets of peptides. 17/20 had CD8 T-cell responses to all peptides sets, and 15 of these 17 had CD4 T-cell responses.
- Although there was a trend in detecting more CD8 T cell responses using the shorter 15-mer peptides, longer 20-mers were best for detecting more CD4 T-cell responses, but neither result was statistically significant. Similar results were seen in the 15 to 20 amino acid range for both IFN gamma Elispot and ICS assays.
- Use of the consensus versus the natural strain identified slightly increased numbers of reactive peptides. Seven reactive peptides were observed with the B consensus peptides but not the B.AU.AF064676 peptides, but on the other hand four reactivites were observed using the B.AU.AF064676 peptides but not the consensus.
- Using an overlap of 10 or 11 amino acids did not make a difference.

HXB2 Location Nef
Author Location (C consensus)
Epitope
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Novitsky *et al.* 2003

- In this study, PBMC from 105 asymptomatic HIV-1 C clade infected patients from Botswana were screened for HIV-1 subtype C specific T-cell responses directed against Gag, Pol, Vif, Vpr, Tat, Rev, Vpu, Env and Nef. Nef-specific T-cell responses positively correlated with plasma viral load. In contrast, HIV-1 Gag and especially Gag p24 showed an inverse correlation with viral load.

HXB2 Location Nef
Author Location (C consensus)
Epitope
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Novitsky *et al.* 2003

- In this study, PBMC from 105 asymptomatic HIV-1 C clade infected patients from Botswana were screened for HIV-1 subtype C specific T-cell responses directed against Gag, Pol, Vif, Vpr, Tat, Rev, Vpu, Env and Nef. Nef-specific T-cell responses positively correlated with plasma viral load. In contrast, HIV-1 Gag and especially Gag p24 showed an inverse correlation with viral load.

HXB2 Location Nef
Author Location Nef
Epitope
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, immunodominance, acute/early infection, early-expressed proteins
References Masemola *et al.* 2004a

- Anti-HIV T-cell responses in subtype C HIV-1 infected individuals in the beginning of the infection target multiple protein regions, but the responses are dominated by Nef, making up almost one-third of the total responses. 97.5% of the Nef epitopes targeted were within a short stretch of 119 amino acids.
- Neither breadth nor magnitude of CD8+ T-cell responses were correlated with control of virus, however hierarchical preferential targeting of Gag was significantly associated with lower viral loads.

HXB2 Location Nef
Author Location Nef (B consensus)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ

CTL CD8+

Keywords HAART, ART, immunodominance, acute/early infection, vaccine antigen design
References Lichterfeld *et al.* 2004b

- HIV-1 specific CD8 T-cell responses in individuals with acute and early HIV-1 infection are preferentially directed against epitopes in the central region of Nef, with 94% of the magnitude of the response in acute infection directed at Nef, and 46% during early infection. In chronic infection, CD8 T-cell immune responses are broadly diversified towards Gag, Env and Pol, and Nef accounts for only 17% of the response.
- The region of Nef that is targeted is the central most conserved region, but relative to other HIV proteins it is still quite variable. However, responses are cross-reactive enough to detect strong acute responses using consensus based peptides, and is an early expressed gene so may have advantages in the context of a vaccine.
- Nef immunodominance was retained in patients that were treated during acute infection, but no treatment and so continuous antigen exposure resulted in rapid diversification of the immune response.

HXB2 Location Nef
Author Location Nef
Epitope
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Keywords subtype comparisons, computational epitope prediction
References Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian subclade. 30 potential epitopes as well as their binding to the 10 most common HLA in India were computationally predicted within these Nef proteins (Table 3).

HXB2 Location Nef
Author Location
Epitope
Immunogen vaccine
Vector/Type: DNA with CMV promotor *Strain:* B clade HXB2, B clade NL43, A clade 92RW020, C clade 97ZA012 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords therapeutic vaccine
References Catanzaro *et al.* 2006

- 14 volunteers uninfected with HIV completed a set of injections with a 6-plasmid DNA vaccine encoding EnvA, EnvB, EnvC, and subtype B Gag, Pol, and Nef. CD4 and CD8 T cell responses to Env and Gag were most frequently detected.
- For Nef, 3/14 subjects showed a positive CD8+ T cell response by ICS.

HXB2 Location Nef
Author Location Nef
Epitope
Subtype B
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords immunotherapy
References Kavanagh *et al.* 2006

- Transfection of antigen-presenting cells with a clade B consensus nef construct bearing lysosomal targeting signals produced rapid and prolonged antigen presentation to CD4+ and CD8+ T cells. Lysosome-targeted antigen drove a significantly greater expansion of Nef-specific CD4+ T cells, compared with cytoplasm-targeted antigen.

II-B-24 HIV-1 CTL/CD8+ epitopes

HXB2 Location HIV-1 (126–11)
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References Frahm *et al.* 2007a

- Toggled peptides with alternative amino acids were used to broaden the detection of CTL immune response to HIV-1 infection by ELISpot. Both CD4 and CD8 T-cell responses were detected more often, and stronger, using this new strategy.
- Previously used consensus B 18-mers overlapping by 10 aa [Frahm et al. J. Virol. 78:2187-2200(2004)] were tailored to form the toggled set. Toggling was restricted to variants found in at least 5% of the database and included mostly biochemically similar substitutions. Flexible aa positions were well dispersed and infrequent in highly conserved proteins like Gag p24 as compared to variable Gag p17.

HXB2 Location HIV-1
Author Location
Epitope
Subtype CRF01_AE
Immunogen vaccine
Species (MHC) human (A11)
Keywords review, vaccine-specific epitope characteristics, escape
References Ariyoshi *et al.* 2002

- This review summarizes a meeting held to discuss options for determining CTL responses to vaccines. Problems are noted: costs for some assays are prohibitive for a Phase III study, Elispot shows interlaboratory variation but could be extended to many samples. HLA-A11 is very common in Thailand – over 30% carry the HLA-A11 allele. Predominant strains may be evolving to evade recognition of A11 restricted epitopes.

CTL CD8+

Few full length CRF01 sequences are available. Epitopes may differ in vaccinees and infected individuals.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human (A11, B40, B8, Cw8)
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords HAART, ART, acute/early infection, early treatment
References Alter *et al.* 2003

- Longitudinal study (24 mo) monitoring T-cell immune responses in 4 patient groups: Group 1 (n=6) consists of subjects who underwent HAART preseroconversion, group 2 (n=11) were HAART treated during early postseroconversion, group 3 (n=5) contained patients who started HAART during late postseroconversion, and group 4 (n= 6) commenced with HAART during chronic HIV-1 infection.
- The experimental strategey was to test for reactivity levels with sets of peptides that each contain epitopes with known HLA-restricting elements, making the peptide selection based on the optimal epitope list in this database. The HLA alleles found in the patients were balanced so that the frequency in the groups were comparable. Peptides spanning parts of Gag, Env, Nef, and RT were used for Elispot, and Gag peptides were used for ICS.
- All group 1 patients, and 5/11 group 2 patients, maintained the breadth and the magnitude of the immune response throughout the study; those in group 2 that maintained response started therapy earlier. The hierarchy of intensity of responses to different peptides was preserved. Individuals in groups 3 and 4 all showed a decline, and after treatment lost responses. Groups 1 and 2 showed HAART-induced suppression of viremia but maintained resposnes. Groups 3 and 4 both showed viral suppression in association with a decreased immune response in breadth and magnitude after HAART. The authors suggest that preservation of HIV CD4+ responses can be maintained even if HAART is first given beyond the acute phase of infection, and a delay may allow a full CD8 response to develop while still allowing CD4 function to be preserved.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen vaccine
Species (MHC) human (B27, B8)
Keywords binding affinity, review, subtype comparisons, epitope processing, escape
References McMichael & Hanke 2002

- CTL response-eliciting vaccines are reviewed. The natural epitope interactions with the HLA class I presenting molecules and T-cell receptors are described, and the impact of breadth of CTL responses and diversity considered in a vaccine context.
- Interesting specific examples are given concerning anchor chain residues. For B27, the B pocket fits Arg (R) but not Lys (K), so even this conservative change is not tolerated. In B8 either R or K can fit in the B pocket, but the substitution will cause conformational shifts in other parts of the epitope.

HXB2 Location HIV-1
Author Location
Epitope
Epitope name KF11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (B57)
Country United States
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Tetramer binding, Intracellular cytokine staining, Chromium-release assay
Keywords TCR usage, characterizing CD8+ T cells, immune dysfunction
References Alter *et al.* 2008

- By studying HIV-1 dysregulation of CTLs at different infection stages induced by inhibitory KIRs (Killer Immunoglobulin-like receptors), it was determined that KIR surface expression on memory T cells correlates with HIV replication. It results in reduced activation, proliferation, cytokine secretion, and killing following TCR stimulation. Since non-TCR-dependent CTL stimulation was unaffected, TCR-mediated stimulation appears to be defective. KIR induced suppression of CTL function was found to be KIR-ligand-independent.
- KF11-specific CTLs had heterogeneous surface expression of KIR. Of these tetramer positive B57-CTLs, only KIR- cells were able to secrete IFN-gamma upon stimulation.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen vaccine
Vector/Type: Listeria monocytogenes *HIV component:* Gag
Species (MHC) mouse (H-2^d)
Keywords review
References Lieberman 2002

- Attenuated Listeria monocytogenes vectors elicit strong persistent CTL responses in vaccinations of BALB/c mice and can protect mice from a vaccinia-gag challenge.

HXB2 Location HIV-1
Author Location gp120 (V3) and p24 (IIIB, MN, BH10)
Epitope
Subtype A, B
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *Strain:* A clade UG5.94UG018, B clade IIIB *HIV component:* Gag, gp120
Species (MHC) mouse (H-2^d)
Assay type Chromium-release assay
Keywords subtype comparisons
References Buonaguro *et al.* 2002

- Different HIV strains were used for different regions: gp120 A clade UG5.94UG018, and B clade IIIB

- BALB/c mice were given intraperitoneal immunization with virus-like particle (VLPs) expressing recombinant subtype A gp120 and Pr55gag in the absence of adjuvants.
- High dose-independent humoral responses against both gp120 and p24 peptides were detected. Antibodies able to elicit 50% neutralization against A clade IIIB and the autologous clade a virus were obtained.
- Recombinant rgp120 (clade B, MN) induced T-cell proliferative responses *in vitro* from vaccinated animals.
- CTL activity was observed against splenocytes expressing Env (clade A) and Gag (clade B, BH10) from a vaccinia construct.

HXB2 Location HIV-1
Author Location
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA, polyepitope *Strain:* A clade, B clade *HIV component:* Env, Gag, Pol *Adjuvant:* IL-12, IL-2, liposome
Species (MHC) mouse (H-2^{d})
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Delayed-type hypersensitivity (DTH), Chromium-release assay
Keywords vaccine-induced epitopes
References Shinoda *et al.* 2004

- Mice immunized with a polyepitope DNA vaccine encoding 20 antigenic epitopes of several HIV-1 clades (hDNA vaccine) showed strong Ab responses, activation of IFN-gamma secretion cells targeting gp120 and synthetic antigenic peptides, and several peptide specific CTL responses. When challenged with recombinant HIV-vaccinia viruses, mice immunized with the hDNA vaccine showed lower viral titers in the ovary.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Schito *et al.* 2001

- Longitudinal analysis (72 weeks) of 15 patients with acute or recent HIV-1 infection implies that HAART treatment alone can not completely conserve CD8+ cell homeostasis and preserve the original T-cell receptor repertoire.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Mackewicz *et al.* 2000

- Non-cytotoxic anti-HIV responses of CD8+ T cells cultured with CD4 infected HIV cells are mediated be blocking expression of viral RNA, and do not influence viral replication steps through integration of provirus.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen vaccine
Species (MHC)
Keywords dynamics
References Altes *et al.* 2002

- This study employs a mathematical model to study the consequences of increasing the T-helper response through a vaccine, which would have counter-balancing effects in a new infection: a more intense response provides more help but also more target cells. The model indicates that if the infecting virus had a low replication rate, then CTLp and CD4 helper cells could control an infection. Only a vaccine that could increase CTL responsiveness could reduce viral set point with observed replication rates.
- A CD4+ T-cell response without maintained CTL response was deleterious in this model.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords assay standardization/improvement
References Currier *et al.* 2002b

- Elispot standardization was sought using a reference peptide pool of 23, 8-11 mer epitopes from Influenza, cytomegalovirus (CMV), and Epstein Bar Virus (EBV) presented by 11 common HLA class I molecules.
- 15/17 (88%) HIV- and 14/20 (70%) HIV+ individuals reacted with this test set and *in vitro* simulation of the PBMC from these individuals were capable of killing cells expressing the target antigen.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human, macaque
Keywords dynamics, HAART, ART
References Wodarz 2002

- Mathematical modeling is used to support the idea that T-helper cell dysfunction results in a compromised ability to maintain an anti-HIV CTL memory response. Models suggest strategies to restore CTL memory through therapy and improve long-term immunological control of the virus.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection, vaccine
Species (MHC) human
Keywords review
References Zinkernagel 2002

- HIV immunity and vaccine strategies are compared with to other pathogens. We do not have a successful vaccine agains TB leprosy, HIV, HCV and most parasites, and the author suggests this is associated with the need for a strong T-cell response to these diseases. Vaccine strategies that achieve a physiological low does infection that is well controlled but persists may be required to alter the immunopathological consequences of infection with HIV.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen vaccine
Species (MHC) human
Keywords review, subtype comparisons, epitope processing
References Gaschen *et al.* 2002

- The concept of using an artificial consensus sequence for vaccine design is discussed, comparing the concepts of a model ancestor sequence or a consensus sequence, with illustrations of the potential advantages of the strategy based on C-clade comparisons.
- See also a comment Nickle *et al.* [2003], and reply Gao *et al.* [2003]

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human, macaque
Keywords review, class I down-regulation by Nef, escape
References Johnson & Desrosiers 2002

- Reviews evidence for CTL escape in HIV epitopes in natural human infections, and in SIV infections of macaque where viral clones with a known time of infection and multiple animals with the same HLA molecules can be tracked.
- Vigorous CTL responses are made despite class I down-regulation by the Nef protein, but it may delay cytolysis of infected cells. Too great a loss of MHC proteins may enhance NK cell killing so the fitness advantage of this function of Nef may be in balance.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection, vaccine
Species (MHC) human
Keywords review, epitope processing, supertype, computational epitope prediction, HIV exposed persistently seronegative (HEPS), supervised treatment interruptions (STI), immunodominance
References Newman *et al.* 2002

- This extensive review covers many aspects of T-cell immunity and natural HIV infections, and considers how this knowledge might be applied to a polyepitope vaccine approach. Strategies concerning ways to avoid the creation of junctional epitopes and use of linkers to enhance processing of such constructs are discussed.
- The C-terminal flanking residue (C1) was found to be associated with immunodominance of epitopes, such that R or K (positive charge) > N or Q (amide) > C, G, A, T, S (small) > F, W, Y (aromatic) > I, L, M, V (aliphatic) > D (negative). As this position is outside and proximal to the epitope, processing and cleavage is the likely reason for this observation.
- Changing the C1 residue from F to K for an HLA-A2 presented epitope from HBV resulted in a change from the epitope being non-immunogenic to strongly immunogenic.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection, vaccine
Species (MHC) human
Keywords review, HIV exposed persistently seronegative (HEPS)
References Johnston & Flores 2001

- Reviews the current state of HIV vaccine approaches, and discusses the role of CTL induced immunity in protection or partial protection in animal studies, likening it to the CTL found in HEPS studies.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords binding affinity, review, escape
References Klenerman *et al.* 2002

- The importance of breadth, or spread, of CTL responses is discussed, as narrowly focused responses can be more readily escaped.
- Some HLA types and specific epitope recognition may be associated with a better disease outcome. Reasons for this are considered, including NK cell activity, epitope affinity, epitope conservation, and class I specific induction of more effective T-cell receptors.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords review, HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission
References Kuhn *et al.* 2002

- Intrauterine exposure of infants to HIV from their mothers results in HIV-1 specific T-helper cell proliferative responses in 1/3 of exposed uninfected babies, and HIV-1 specific CTL in some. Such responses are evident, but it is unknown whether they are associated with lack of infection, but there is some evidence that HIV-1 T-cell responses may reduce transmission in breastfeeding mothers. Summary tables are provided of CD4 and CD8 responses detected in earlier studies.

HXB2 Location HIV-1
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords HIV exposed persistently seronegative (HEPS), mother-to-infant transmission
References Kuhn *et al.* 2002; Levy *et al.* 1998

- A non-HLA-specific, non-chemokine-mediated CD8+ T-cell non-cytotoxic anti-HIV response, measured by suppression of acute viral infection of CD4 cells, was detectable in approximately 16/31 (52%) of uninfected children born of infected mothers, was more commonly detected in those <1 year old, and could reflect a protective response.
- Reviewed in Kuhn *et al.* [2002].

HXB2 Location HIV-1
Author Location
Epitope
Immunogen vaccine
Species (MHC) human
Keywords dynamics
References Altes *et al.* 2001

- Mathematical modeling suggests if the effector CTL vaccine response exceeds the level of response seen in chronic infection, that a memory CTL population is established that can respond very quickly to protect from infection.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen vaccine
Species (MHC) human
Keywords review
References Copeland 2002

- This review summarizes cytokines and chemokines produced by CD8+ T-cells that can interfere with HIV's infection and replication.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen vaccine
Species (MHC)
Keywords review
References Edgeworth *et al.* 2002

- This review summarizes HIV vaccine strategies, adjuvants, current clinical trials and animal models.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen vaccine
Species (MHC)
Keywords review
References Graham 2002

- This review summarizes HIV vaccine approaches and clinical trials.

HXB2 Location HIV-1
Author Location Env (HXB2)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade HXB2 *HIV component:* gp140ΔCFI, gp160 deletions
Species (MHC) guinea pig, mouse
References Chakrabarti *et al.* 2002

- Intramuscular injection of plasmid DNA was used to vaccinate BALB/c or Huntley guinea pigs with a series of codon-optimized modified HIV-1 HXB2 envelopes – modifications included elimination of glycosylation sites, deletions, and exchange of the V3 loop to change from a X4 or R5 phenotype.
- The mutant envelope gp140deltaCFI gave the most promising result, enhancing antibody responses while retaining the ability to stimulate a strong CTL response.
- gp140deltaCFI has deletions in the cleavage site, fusogenic domain and spacing of the heptad repeats, and was designed to mimic a fusion intermediate.

HXB2 Location HIV-1
Author Location Env (gp160) (384–467)
Epitope
Immunogen vaccine
Vector/Type: hepatitis B surface antigen lipoprotein particles (HsBAg) *Strain:* B clade LAI *HIV component:* V3
Species (MHC) macaque, rabbit
References Michel *et al.* 1993

- Immunization with recombinant HIV1 V3/HBsAg hybrid particles into rabbits or macaques elicited and maintained for several months anti-V3 or HIV-1 Env proliferative, CTL and Ab responses.

HXB2 Location HIV-1
Author Location Gag (HXB2)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Garba *et al.* 2002

- CD8+ Tcells from 25% of HIV positive individuals produce TGF-beta1 in response to stimulation with HIV proteins, and this can significantly reduce CD8+ T-cell IFN-gamma induction to HIV and vaccinia proteins.
- Different peptides can preferentially induce TGF-beta1 or IFN-gamma from CD8+ T-clymphocytes from the same individual, and TGF-beta1 non-specifically suppresses HIV-specific immune responses.

HXB2 Location HIV-1
Author Location Pol (HXB2)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Garba *et al.* 2002

- CD8+ Tcells from 25% of HIV positive individuals produce TGF-beta1 in response to stimulation with HIV proteins, and this can significantly reduce CD8+ T-cell IFN-gamma induction to HIV and vaccinia proteins.
- Different peptides can preferentially induce TGF-beta1 or IFN-gamma from CD8+ T-clymphocytes from the same individual, and TGF-beta1 non-specifically suppresses HIV-specific immune responses.

HXB2 Location HIV-1

Author Location Env (MN)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Garba *et al.* 2002

- CD8+ Tcells from 25% of HIV positive individuals produce TGF-beta1 in response to stimulation with HIV proteins, and this can significantly reduce CD8+ T-cell IFN-gamma induction to HIV and vaccinia proteins.
- Different peptides can preferentially induce TGF-beta1 or IFN-gamma from CD8+ T-clymphocytes from the same individual, and TGF-beta1 non-specifically suppresses HIV-specific immune responses.

HXB2 Location HIV-1
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords assay standardization/improvement, acute/early infection
References Altfeld *et al.* 2003

- The frequency of HIV-1 specific T-cell responses was characterized in an Elispot IFN-gamma assay, using 507 overlapping peptides based on the B clade consensus sequence spanning all HIV-1 clade B proteins against PBMC from 57 HIV-1 infected patients at various disease and treatment stages. 63% of the peptides were recognized (range of 1-42 per subject, median=14). More variable peptides were targeted less frequently.
- Autologous virus sequences from six patients in acute infection spanning of HIV-1 p24, Tat and Vpr were used to scan for missed responses due to viral variation when using the consensus for peptides. 12/42 (29%) responses to these peptides were dectected only with autologous peptides, and often these autologous reponses were immunodominant. Responses were also generally higher using autologous peptides.
- A longitudinal analysis (5 yrs) of the T-cell responses in 5 patients showed that the autologous sequence detected stronger T-cell recongition than the HIV-1 clade B consensus sequence.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) chimpanzee
Keywords review
References Balla-Jhagjhoorsingh *et al.* 2003

- This paper reviews HIV-1-specific cell-mediated immune responses in chimpanzees and discusses mechanisms that might control HIV-1 pathogenesis in chimpanzees. During the first decade of the HIV epidemic, more than 200 chimpanzees were experimentally infected with HIV. Among these only one case of declining CD4+ cells has been reported, all others have remained asymptomatic with no loss of immune function , some after 20 years of infection. In contrast to infected humans which have a skewed Th2 response, chimpanzees maintain balanced Th responses and are likely to support a fully mature CD8+ T-cell response.
- Specific HIV epitopes recognized by chimpanzees have been mapped and CTL detected , but overall the responses are at much lower levels than in humans, as viral loads are so low. Gag epitope responses are estimated to be 0.0095 to 0.0025% of the CD8+ T cell population in chimpanzee, and 1-2% in humans.
- The authors argue that the chimpanzee immune response may be effective at controlling virus because it focuses on conserved epitopes, and further speculate that long contact with lentiviruses may have put strong selection pressures on the chimpanzee MHC class I, narrowing the population's ability to respond to only the most conserved, and so useful, epitopes.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, supervised treatment interruptions (STI)
References Fagard *et al.* 2003

- This study monitored the effects of repeated treatment interruptions (STI), in 2-week intervals, in 133 HIV-1 infected, HAART-treated patients. STIs were rarely able to control viremia without continued HAART, and increases in CD8+ T-cell response frequencies did not correlate with the level of control of viral replication. CD8+ T cell responses were measured by gamma IFN Elispot using between 2-32 different optimal HIV epitopes, selected to be appropriate for the patient's HLA type.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen
Species (MHC) human
References

HXB2 Location HIV-1
Author Location HIV-1
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords responses in children
References Feeney *et al.* 2003

- The magnitude and breadth of CD8+ T-cell responses in 18 pediatric (6-17 years) perinatally HIV-1 infected patients was determined using 1) overlapping peptides spanning all HIV-1 proteins and 2) peptides from all predefined appropriately class I HLA-restricted HIV-1 epitopes.
- Perinatally infected children's CD8+ T-cell responses were comparable in magnitude and breadth to adult responses. Many reactive peptides did not overlap with a previously characterized optimal epitope.

- On average 20% of all known pre-defined optimal epitopes presented by appropriate HLAs were recognized in these children. In two patients, autologous sequences spanning unrecognized potential epitopes usually corresponded to the reactive form of the epitope, so epitope variation alone did not account for unrecognized epitopes.
- Children with detectable viremia showed a broader and greater CTL responses than HAART responsive children with undetectable viremia.

HXB2 Location HIV-1
Author Location HIV-1
Epitope
Immunogen
Species (MHC)
References

HXB2 Location HIV-1
Author Location
Epitope
Immunogen vaccine
Species (MHC)
Keywords review
References Hanke 2003

- Review of HIV vaccine development discussing diversity, the merits and difficulties of stimulating different arms of the immune response, and different strategies, including DNA vaccines, viral vectors, CTL epitope based, and protein- or peptide-based vaccines.

HXB2 Location HIV-1
Author Location HIV-1 (HXB2)
Epitope
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords HIV exposed persistently seronegative (HEPS)
References Hladik *et al.* 2003

- Longitudinal study analyzed IFN-γ CD8+ T cell responses in highly exposed, seronegative homosexual men. Overlapping peptides spanning the Gag, Env, Nef and Pol subtype B HXB2 sequence were used to stimulate PBMC from 26 individuals, whose frequency of HIV-1 specific IFN-γ T cell responses were very low.
- CD8+ T cells from 3/15 individuals (EES15, ES29, and ES63) recognized > 3 peptide pools.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Assay type Chromium-release assay
Keywords dynamics
References Kousignian *et al.* 2003

- The diversity of HIV protein (Gag, Pol, Env, Nef, Rev, Tat, Vif) recognition by CTLs was studied longitudinally in a cohort of 152 HIV-infected untreated individuals, and was analyzed by Markov modelling. CTL responses from 152 HIV-1 infected patients in four stages of disease progression were collected for a period of 5 years. Results show that memory CTL responses against HIV-1 proteins are acquired during early HIV-1 infection and subsequently lost. As viral load increased there was an accelerating loss of multiple protein recognition.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: gp120 depleted whole killed virus *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human
References Lederman & Douek 2003; Robbins *et al.* 2003

- Lederman and Douek is an editorial comment referring to the study presented by Robbins *et al.*, in which the authors discuss why an HIV-1 gp120-depleted inactivated HIV vaccine elicits HIV-1 specific T helper responses in 5/5 HIV+ people, but not CD8+ CTL responses. In chronically infected people it appears that stimulating Th responses in and of itself is not enough to restore strong CTL responses.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen vaccine
Adjuvant: E. coli mutant heat labile enterotoxin (LT-R72), CpG immunostimulatory sequence (ISS), HSP70
Species (MHC) human
Keywords review, Th1, Th2, genital and mucosal immunity
References Lehner 2003

- This review discusses the importance of mucosal and innate immunity for future vaccination strategies in HIV infection in humans. Different mucosal adjuvants are compared, and the advantages of a Th1 polarized response.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Onyemelukwe & Musa 2002

- Longitudinal study (1991-1997) of the clinicial presentation of 80 HIV-1 or HIV-II seropositive people in Zaria, Nigeria, who contracted HIV-1 primarily via heterosexual transmission. Main complicating diseases were tuberculosis and bacterial infections including Salmonella, Streptococcus peneumoniae and Stahhylococcus. HIV-1 progression was associated with a decline of not only CD4+ T cells, but CD8+ T cells as well – patients had CD4+ counts < 200 cells/ul, and CD8 counts were 190 cells/ul versus 440 cells/ul for controls.

CTL CD8+

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Onyemelukwe & Musa 2002

- Longitudinal study (1991-1997) of the clinicial presentation of 80 HIV-1 or HIV-II seropositive people in Zaria, Nigeria, who contracted HIV-1 primarily via heterosexual transmission. Main complicating diseases were tuberculosis and bacterial infections including Salmonella, Streptococcus peneumoniae and Stahhylococcus. HIV-1 progression was associated with a decline of not only CD4+ T cells, but CD8+ T cells as well – patients had CD4+ counts < 200 cells/ul, and CD8 counts were 190 cells/ul versus 440 cells/ul for controls.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ
Keywords HAART, ART
References Price *et al.* 2003

- CD4+ and CD8+ T cell responses were analyzed in this longitudinal study (19 mo) of 53 patients with chronic HIV-1 infection receiving continous ART therapy. Three subgroups were compared: one with suppressed viremia and increasing CD4+ T cell counts, one with dectable viral load and declining CD4, and one with detectable viral load with a positive CD4+ T cell slope.
- IFN-γ ELISPOT analysis was performed with peptides spanning RT, Env, Gag (p24), Gag(p17), Nef, Tat and Rev. The IFN-γ analysis showed the greatest CD4+ as well as CD8+ T-cell responses in the group with stable CD4+ T cell responses despite detectable virus over a median time course of 9 months.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen
Species (MHC) human
Assay type Chromium-release assay
Keywords rate of progression
References Sindhu *et al.* 2003a; Sindhu *et al.* 2003b

- In a cross-sectional study of 31 HIV+ people, a correlation was observed between CTL-mediated bystander HLA-unrestricted lysis of primary CD4+ T-cells. γδ CTL are abnormally expanded in HIV+ people, and the Vδ1 subset can deplete bystander CD4+ T-cells and expedite progression. In a set of 13 patients, an inverse correlation was observed between CD8+ T-cell activation markers and viral load, thought to be an indicator of CTL-associated immunopathogenesis in HIV progression.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC)
Keywords review
References Vella & Daniels 2003

- This article reviews the CD8+ T-cell antiviral factor (CAF). CAF contributes to MHC restricted, CD8+ T-cell mediated non-cytolytic suppression of HIV in infected individuals.

HXB2 Location HIV-1
Author Location
Epitope
Subtype A, B, C
Immunogen vaccine
Vector/Type: DNA, polyepitope *HIV component:* gp120, gp41, Nef, p17 Gag, p24 Gag, Pol *Adjuvant:* concavalin A-immobilized polystyrene nanospheres
Species (MHC) mouse
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords vaccine-induced epitopes
References Bazhan *et al.* 2004

- A synthetic T cell polyepitope immunogen containing 80 overlapping Env, Gag, Pol and Nef epitopes was used to immunize mice. It induced both humoral and cellular responses which increased upon reimmunization.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen
Species (MHC)
Keywords review, class I down-regulation by Nef, early-expressed proteins, immune evasion
References Collins 2004

- There are a number of factors that combined make HIV-infected cells resistant to CTLs. HLA-associations with disease progression are reviewed. Nef down-regulation of HLA class I A and B molecules is one important mechanism of HIV immune evasion. Rev allows late viral proteins to be expressed, enabling CTL specific for epitopes in these proteins to recognize infected cells. It is suggested that blocking the activity of Nef and Rev would reduce production of viral variants and enhance the ability of CTLs to combat HIV.

HXB2 Location HIV-1
Author Location (SIV)
Epitope
Immunogen SIV infection
Species (MHC) macaque
Keywords escape, viral fitness and reversion
References Friedrich *et al.* 2004

- SIV CTL escape variants revert to wild-type epitopes after transmission to new hosts with disparate MHC class I alleles. Thus mutations in CTL epitopes may have moderate to severe negative effects on viral replicative fitness although some escape variants are shown to accumulate substitutions in flanking regions of the epitope that help compensate for fitness loss.

HXB2 Location HIV-1
Author Location

Epitope
Immunogen
Species (MHC) human
Keywords dynamics, HAART, ART
References Ganusov 2003

- The rate of virus decline after initiation of HAART is shown by a mathematical model, to depend on whether the virus is controlled by the CTL response via lytic or non-lytic mechanisms.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords review, class I down-regulation by Nef, escape, dendritic cells, TCR usage, memory cells, immune dysfunction
References Gulzar & Copeland 2004

- HIV has developed numerous strategies to evade CD8+ T-cell response that are reviewed in this paper, including escape mutations in CD8+ T-cell recognition, down-regulation of MHC-I surface expression, alternating cytokine production, disruption of proper CD8+ T-cell signaling resulting in anergy, and disruption of the function of CD4+ T-cells and APCs required for CD8+ T-cell maturation.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen in vitro stimulation or selection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Kitchen *et al.* 2004

- This paper characterizes a population of cells that are CD3+, CD8+, and CD4+. These cells are mature and highly activated. The CD4 molecule expressed by these CD8+ T-cells plays an important role in expression of IFN-gamma and Fas ligand and cytotoxic responses. HIV infection of CD8+CD4+ T-cells results in Nef independent down-regulation of CD4 and dysregulation of IFN-gamma and Fas ligand, and provides an additional resevoire for the virus.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen
Species (MHC) human
Keywords review, characterizing CD8+ T cells
References Petrovas *et al.* 2004

- This review discusses the attributes of HIV-specific CTLs that contribute to their inability to control HIV infection, with an emphasis on the susceptibility of HIV-specific CTL to CD95/Fas induced apoptosis upon binding target cells. Furthermore, Nef may inhibit apoptosis by blocking CD95/Fas signaling on infected cells.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country United Kingdom
Assay type proliferation, CD8 T-cell Elispot - IFNγ, T-cell Elispot, Flow cytometric T-cell cytokine assay
Keywords HAART, ART, immune dysfunction
References Pires *et al.* 2004

- Daily administration of rec human growth hormone (rhGH) induced an increase in the numbers of naive CD4 T-cells and effector CD8 T-cells. Also, a rise in HIV-1 antigen-specific CD4 and CD8 T-cell responses was observed. The function of specific effector CD8 T-cells was perserved despite an eventual decrease of specific CD4 T-cell responses.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection, vaccine
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords review, supervised treatment interruptions (STI), vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization
References Robinson 2003

- This paper is a commentary on Altfeld et al, Nature 420:434 2002. The patient AC-06 was superinfected with a second strain of HIV-1 after STI despite 12 of 25 recognized CD8+ T-cell epitopes maintaining strong cross-reactive immunity measured by gamma IFN EliSpot against the second strain. While vaccine trials in macaques have given optimistic results, this patient's superinfection in spite of a strong cross-reactive CD8+ T-cell immune response suggests that vaccine strategies may have to be re-examined.

HXB2 Location HIV-1
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Spain
Assay type Flow cytometric T-cell cytokine assay
Keywords rate of progression
References Rodés *et al.* 2004

- A complex set viral or host factors has been found to be associated with the absence of disease progression among long-term non-progressors (LTNP). 19 LTNP were followed for six years; 12 were non-progressors over this period, 7 showed a slow progressive CD4 depletion. Their virus replicative capacity was shown to be reduced and T-cell activation was low. Pooled peptide CD8+ T-cell gamma IFN responses did not differ between non-progressors, slow progressors, or a group of HIV progressors.

HXB2 Location HIV-1
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with recombinant protein boost *Strain:* B clade SF2 *HIV component:* Env, Gag, Protease
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References Russell *et al.* 2003

- IFN-γ Elispot assay is shown to be a good initial screening method for measurment of CD8+ T-cell responses in both vaccination and natural HIV-1 infection. Responses were detected using peptides at low concentrations (1-2 µg/mL) and an increase in detection of HIV-1 specific CD8+T-cells by using 15-mers rather than 20-mer peptides for cell activation was observed. More responses were detected using smaller pools (10 or 2 peptides) than larger pools (25 or 50 peptides), so smaller pools may be needed to detect low frequency responses. Responses to natural infection were more than a log higher than to the vaccine.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection, SIV infection
Species (MHC) human, macaque
Keywords review, escape, viral fitness and reversion
References Smith 2004

- This paper reviews several studies which track HIV and SIV CTL escape mutations after transmission into a new host, and reversion rates and fitness costs of CTL escape. Some escape mutants have a cost to viral fitness. The author suggests that CTL based HIV-1 vaccine should therefore not only increase cellular responses against viral epitopes but also favor epitopes where escape mutations result in significant decrease in viral fitness.

HXB2 Location HIV-1
Author Location
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade *HIV component:* gp140, gp160 *Adjuvant:* reovirus alpha 1 protein
Species (MHC) mouse
Donor MHC H-2d
Assay type Cytokine production, Chromium-release assay
Keywords adjuvant comparison
References Wang *et al.* 2003

- M cells are found in the follical-associated epithelium in mucosal inductive tissues, and reovirus are able to attach to these cells via the alpha 1 protein. Respiratory mucosal sites were targeted with a reovirus protein alpha 1 protein delivered with a DNA vaccine administerd i.n. in BALB/c mice. The naked gp160 DNA vaccine did not elicit CD8+ T cell reponses, but when delived with alpha 1 protein, CTL responses were observed in the lungs, spleens and lymph nodes. gp160 was shown to be most immunogenic compared to a cytoplasmic gp140 and secreted gp140. The vaccinated animals had reduced vaccinia virus when challeneged with a vaccinia-env recombinant.

HXB2 Location HIV-1
Author Location Gag
Epitope
Immunogen vaccine
Vector/Type: DNA with CMV promotor, fowlpoxvirus *Strain:* SIV *HIV component:* Env, Gag, Pol, Rev, Tat, Vpu *Adjuvant:* IFNγ, CpG immunostimulatory sequence (ISS)
Species (MHC) macaque
Assay type proliferation, T-cell Elispot, Intracellular cytokine staining
Keywords adjuvant comparison, vaccine antigen design
References Dale *et al.* 2004

- Macaques immunized with DNA and fowlpox vaccines showed high levels of CD4 and CD8 T-cell immune responses to Gag. Single DNA priming vaccination or coexpressed IFN-gamma with the fowlpox virus boost were shown to be less immunogenic and less protective than sequental DNA and fowlpox virus vaccination. Partial protective immunity was observed following a high dose, virulent SHIV challenge, for the DNA fowlpox prime boost, as well as the DNA vaccination alone, even though standard assays failed to detect a strong immune respsonse with DNA alone.

HXB2 Location HIV-1
Author Location (IIIB, Thai B', Chinese CB)
Epitope
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human
Country China
Assay type Intracellular cytokine staining, Chromium-release assay
Keywords subtype comparisons, characterizing CD8+ T cells
References François-Bongarcon *et al.* 2004

- The ability of circulating T-cells from 7 North American and 4 Chinese HIV+ donors to produce IFN-gamma and/or lyse autologous primary cells infected with HIVIIIB, B' (Thai B) or C/B recombinant form was tested. The results showed cross-clade CD8 T-cell responses to the Cinese viruses among North American donors and to HIVIIIB in Chinese donors, suggesting that many of the T-cell responses to clade B virus epitopes are conserved across clades. Lysis of cells by N. American donor CD8+ T cells infected with IIIB or a Thai B' strain were comparable, while lysis infected with the Chinese BC recombinant was somewhat reduced, although the reduction was not statistically significant.

HXB2 Location HIV-1
Author Location

CTL CD8+

Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country Canada
Assay type Cytokine production, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords TCR usage, memory cells, characterizing CD8+ T cells, immune dysfunction
References Gamberg *et al.* 2004b

- A relationship was found between the proportion of HIV-specific CTLs expressing CD28 and CD4+ T-cell counts, viral load and disease progression. This association cannot be linked to disease related degeneration of CD8+CD28- T-cells in terms of their TCRbetaV family repertoire diversity or ability to produce cytokines. This suggests that effective immune responses contain CD8+CD28+ T-cell populations that shift to CD8+CD28- in ineffective responses.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen
Species (MHC)
Keywords review, epitope processing, vaccine-specific epitope characteristics, rate of progression, immunodominance, escape, acute/early infection, early-expressed proteins, TCR usage, viral fitness and reversion
References Goulder & Watkins 2004

- CTLs have a central role in the control of HIV infection. Emergence of escape variants to CTLs is one of the major obstacles to vaccine development. Factors that should be considered for the development of an HIV vaccine are CTLs that are specific for epitopes recognized during the acute phase of infection, CTLs that are able to efficiently control viral replication, and epitopes from regions of the viral genome that are highly conserved or where variation results in loss of viral fitness.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 exposed seronegative
Species (MHC) human
Country Kenya
Assay type Chromium-release assay
Keywords HIV exposed persistently seronegative (HEPS), characterizing CD8+ T cells
References Kaul *et al.* 2004

- HIV-1 specific CTL responses found in HIV exposed persistently seronegative Kenyan female sex workers were shown to be associated with age and recent HIV-1 exposure, but not with protection against HIV-1 infection. The authors note that CTL may be the result of a non-productive HIV infection, but not mediate protection; alternatively, the low incidence, possibly due to behavioral interventions, may not give adequate sampling to detect the response.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country France
Keywords HAART, ART, characterizing CD8+ T cells, immune dysfunction
References Kryworuchko *et al.* 2004

- A subset of HIV-1 infected untreated patients had CD8+ T-cells that were unable to respond to IL-2 by activating STAT5a and b proteins. This was correlated with an impaired activation of the upstream kinase Jak-3. 6 months of HAART was shown to restore Jak/STAT signalling in those patients and their CD8+ T-cell response to IL-2. This suggests another mechanism for immune dysfunction in HIV infected patients.

HXB2 Location HIV-1
Author Location
Epitope
Subtype A, B, C, D, F, G, U
Immunogen computer prediction
Species (MHC) human
Keywords vaccine antigen design
References Maksyutov *et al.* 2004

- Every HIV protein was shown to have some regions that were highly similar to the regions of human proteins. Most of those regions contained T-cell or/and B-cell epitopes. The epitopes shared by HIV and its host may have immunopathogenic potential through stimulating autoimmunity and should possibly be excluded from HIV vaccines. All HIV proteins from the sequence of BH10 were compared to human proteins, as well as many HIV-1 V3 variants.

HXB2 Location HIV-1
Author Location (ELI)
Epitope
Immunogen in vitro stimulation or selection
Species (MHC) human
Assay type Cytokine production, proliferation, Chromium-release assay, Flow cytometric T-cell cytokine assay
Keywords class I down-regulation by Nef, rate of progression, dendritic cells, immune dysfunction
References Quaranta *et al.* 2004

- Exogenous Nef protein activates immature DCs and inhibits the capacity of DCs to prime CD8+ T-cell responses by down-regulating their proliferation and function capacities. Nef induces CD8+ T-cell apoptosis by up-regulating TNF-alpha and FasL production by DCs, while DCs are protected from apoptosis themselves. These mechanisms, as well as by down regulation of the HLA class I proteins, can contribute to HIV-triggered immune dysfunction.

HXB2 Location HIV-1
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Switzerland

Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ
Keywords rate of progression
References Oxenius *et al.* 2004a

- In untreated, HIV-1 chronically infected patients, CD4+ T-cell responses and, to a lesser extent, CD8+ T-cell responses, were found to inversely correlate with disease progression rate. Polymorphisms in CCR genes, HLA genotype and GB virus C coinfection were not found to be related to slower disease progression.

HXB2 Location HIV-1
Author Location (B clade)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Canada
Assay type CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords genital and mucosal immunity, characterizing CD8+ T cells
References Sheth *et al.* 2004

- HIV viral load in semen is found to be 10-fold lower than in blood. No correlation was found between viral load in either semen or blood and systemic HIV-specific CD8 T-cell responses, in 20 samples.

HXB2 Location HIV-1
Author Location
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA with CMV promotor, virus-like particle (VLP), modified vaccinia Ankara (MVA) *Strain:* B clade *HIV component:* Env, Gag, Pol, Protease, RT
Species (MHC) macaque
Assay type T-cell Elispot, Intracellular cytokine staining
Keywords vaccine antigen design
References Smith *et al.* 2004

- Macaques were immunized with codon-optimized Gag DNA and non-codon-optimized Gag-Pol-Env DNA vaccines, expressed as VLPs as aggregates, followed by an MVA boost. There was no significant difference in anti-Gag T-cell responses and anti-Env Ab responses between the different vaccines. A second MVA boost did not increase T-cell responses but it increased anti-Env Ab titers by 40- to 90-fold.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen
Species (MHC) human
Keywords review, epitope processing, rate of progression, escape, early-expressed proteins, vaccine antigen design
References Yang 2004

- This review considers CTL biology in HIV infection in the context of vaccine design principles. Since HIV-1 infection damages immunity through depletion of CD4+ T-cells, which in turn results in diminished capacity of the immune system to produce new and functional CTL responses, maximizing the breadth of CTL responses might not be enough for an HIV-1 vaccine. CTLs recognizing early proteins might be more prone to epitope escape mutation, while those recognizing more conserved structural proteins might be more likely to persist, so focusing on more conserved proteins those might be a good strategy to produce an attenuating vaccine.
- Original antigenic sin is discussed, the initial responses to an antigen that persist even after escape occurs, blunting the later immune response. If the goal is to prevent disease, focusing on conserved late expressed proteins might be the best target, where the fitness cost is greatest for escape; if the goal is to prevent infection, focusing the vaccine on the more variable early expressed proteins that elicit the first responses, Tat and Nef, might be best.

HXB2 Location HIV-1
Author Location p24 (HIV-2 ROD, HIV-1 IIIB)
Epitope
Subtype B, HIV-2
Immunogen HIV-1 or HIV-2 infection
Species (MHC) human
Country Gambia
Assay type Cytokine production, proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression, HIV-2
References Jaye *et al.* 2004

- A comparison of T cell responses in HIV-1 and HIV-2 infected asymptomatic patients with CD4+ cell counts 20% showed no significant difference between groups. Viral loads were roughly 20 times greater in HIV-1 positive patients than HIV-2 positive patients.
- 10/20 (50%) of HIV-1 infected patients demonstrated proliferative responses with SI greater than 1.4 to gp120, and 11/20 to p24. 8/29 (29%) of HIV-2 infected patients recognized gp105, and 8/29 (29%) p26. Cytokine responses in both groups did not differ.
- 9/21 (43%) of HIV-1 + and 15/30 (50%) of HIV-2 + patients had cytotoxic T cell responses to Gag, and 3/21 (14%) HIV-1 + and 8/30 (27%) HIV-2 + responded to Pol.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country Spain
Assay type proliferation, Intracellular cytokine staining
Keywords HAART, ART
References López *et al.* 2004

- A clinical trial compared chronically HIV-1 infected patients who had replaced HAART with didanosine (ddI) and hyroxyurea (HU) were followed for 12 months to an untreated HIV+ group and a group that continued on HAART.

- Approximately 20% of the patients treated with ddI-HU had detectable CD4+ T-cell proliferative responses to Gag and Env in contrast to drug-naive and HAART treated HIV-infected patients, who had few or no responses.
- HIV-specific CD8+ T-cell responses were higher in ddI-HU treated patients than HAART treated patients, even in individuals that maintained undetectable viral loads.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen
Species (MHC)
Keywords review, adjuvant comparison
References Mitchison & Sattentau 2005

- Review summarizes mechanisms of immunoregulation relevant for new vaccine development, with a brief summary of adjuvant triggering innate immunity through Toll-like receptors (TLRs), Nod molecules, and other activators. DNA encoded adjuvants that have been tested in DNA vaccines are summarized. The balance between Th1 (CTL activating) and Th2 (B cell activating) responses is discussed, and it is noted that BALB/c mice are predominately Th2 responders, C57BL Th1.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords escape
References Piontkivska & Hughes 2006

- Greatest amino acid diversity is found in sites in the HIV genome that are spanned by antibody epitopes. Sites spanned by CTL epitopes, but not by antibody epitopes, showed reduced amino acid diversity, even in comparison to non-epitope sites. However, mutations within CTL epitopes were more likely to be convergent than mutations within antibody epitopes. These patterns were consistent both in Gag and in Env.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ, CD8 T-cell RecycleSpot - IFNγ
Keywords assay standardization/improvement, optimal epitope
References Bihl *et al.* 2005

- This study describes a novel approach to achieve maximal information from an extensive set of antigens (HIV, EBV, CMV, HCV, and HBV) to determine the magnitude of T-cell responses while requiring minimal cell numbers. Large sets of peptides based on optimally defined epitopes from each pathogen are used. It is shown that, when compared to ex vivo cell preparations, antigen-unspecific in vitro T-cell expansion maintains the breadth of detectable T-cell responses. Also, harvesting cells from negative ELISpot wells for re-use (RecycleSpot) maximizes the use of available cells.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ
Keywords genital and mucosal immunity, characterizing CD8+ T cells
References Ibarrondo *et al.* 2005

- The breadth and magnitude of HIV-1-specific CTL responses in blood and sigmoid colon mucosa were assessed in 16 patients. The magnitude of pool-specific CTL responses in blood and mucosa was correlated within each individual and across all individuals. CTL targeting was also found to correlate between these 2 compartments, with Nef being the most highly targeted region, followed by Gag. No correlation between the magnitude and breadth of CTL responses and viremia and blood CD4 levels was found in any of the compartments. Concordant peptide pool responses were found in the blood and mucosa 85%; pools that differed were near the threshold of detection.
- This study suggests that HIV-1-specific CTL responses in the blood mirror those in the mucosa during chronic infection.

HXB2 Location HIV-1
Author Location (Z321)
Epitope
Subtype A, B, C, G
Immunogen vaccine
Vector/Type: gp120 depleted whole killed virus *Strain:* AG recombinant HZ321 *HIV component:* gp120 depleted virus *Adjuvant:* CpG immunostimulatory sequence (ISS)
Species (MHC) mouse
Assay type Cytokine production, proliferation, CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons, genital and mucosal immunity, adjuvant comparison, vaccine antigen design, characterizing CD8+ T cells
References Jiang *et al.* 2005

- Mice were given intranasal immunization with inactivated gp120-depleted HIV-1 antigen plus a CpG ODN adjuvant and examined for local immune responses in the genital tract. Mice immunized with HIV Ag plus CpG produced significantly higher levels of IFN-gamma and beta-chemokines than mice immunized with Ag alone, and their lymphocytes showed significant HIV-specific proliferation. CD8 T-cells were increased in the genital tracts of mice immunized with HIV Ag plus CpG.
- The vaccine antigen Z321 is clade G in Gag. Cross-clade protection against an intravaginal challenge was observed for clades A, C, and G, but not clade B.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen computer prediction
Species (MHC) human

CTL CD8+

Assay type Other
Keywords assay standardization/improvement, computational epitope prediction
References Larsen *et al.* 2005

- A computational epitope identification method integrating predictions of MHC class I binding affinity, TAP transport efficiency and C-terminal proteasomal cleavage was compared to two already existing computational epitope identification tools. It was shown that the new ANN method performed better, reducing the number of nonamers needed to be tested in order to identify 85% of the epitopes from 9-10% to only 7%.

HXB2 Location HIV-1
Author Location (A, B, and C consensus)
Epitope
Subtype A, B, C
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords subtype comparisons
References Yu *et al.* 2005

- HIV-specific T-cell responses to peptide from A, B, and C clade spanning the entire HIV proteome were assessed in clade B infected individuals. Many cross-reactive responses were observed against clade A, B, and C consensus sequences, preferentially recognized in conserved regions with low intra-clade diversity and high inter-clade homology.
- At the individual peptide level, within clade responses to B clade peptides were more frequent. 194 responses were detected with only one peptide, of these 105 recognized B clade, 55 C clade , and 34 A clade. 125 responses recognized peptides from two clades, and 110 of these were with B plus either A or C. 166 responses were cross-reactive with all three clades.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen computer prediction
Species (MHC)
Keywords escape, viral fitness and reversion
References Ganusov & De Boer 2006

- A simple mathematical model is used to estimate costs of CTL escape mutations and killing rate of CTLs. Using in vivo data, it is shown that minimal estimates of the fitness cost of the escape mutations and minimal estimates of the average killing rate can be obtained. This general model may be used for both acute and chronic phases of SIV/HIV infection.
- Fitness cost is found to be proportional to the rate of replacement of the mutant by wild-type rather than the time taken for this to happen. Exponential growth of the virus is assumed during such reversion experiments. However, no virus growth is assumed during escape experiments to gauge the minimum average rate at which the CTL response clears one viral epitope.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords review, escape
References Frahm & Brander 2007

- This report characterizes HIV epitope variants with a view to guiding vaccine design. It discusses immune correlates of controlled HIV infection, HIV escape from cellular immunity and the effects of sequence diversity on T-cell recognition.
- In controlled infections it is noted that diversity of HIV-specific cells is associated with better control of infection than magnitude of HIV-specific response. The specific epitopic region targeted by host immune cells is a determinant in controlling infection too. However, high avidity responses are effective in virus control and epitope recognition despite a limited T-cell receptor repertoire. While HLA-B alleles mediate most CTL cellular immunity, subdominant responses are key in effective immune control. On the other hand, uncontrolled virus replication is linked to high expression of PD-1, low IL-7R, fewer early and intermediate differentiated cells, absence of CD4 T-cell help and reduced proliferation.
- HIV escape can occur on several fronts - viruses may develop compensatory changes to restore fitness; transmission between individuals with different HLA types allows virus reversion; certain epitopes may disappear from circulating viral populations if there is a high population frequency of specific HLA and specific epitope variants can even act as antagonists or partial agonists either silencing total epitopic T-cell responses or inducing immune responses even with only partial functionality.
- Sequence diversity is greatly increased by the spread of unique recombinant forms of HIV in individuals. The authors advise the use of detailed single-peptied-based analyses in addition to using peptide pools. They also suggest 3 approaches to incorporating sequence diversity in vaccine studies.

HXB2 Location HIV-1
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*01, A*02, B*08, B*40, Cw*03, Cw*07; A*01, A*31, B*08, B*35, Cw*04, Cw*07; A*02, A*24
Country Australia
Assay type Other
Keywords acute/early infection, immune evasion, viral fitness and reversion
References Li *et al.* 2007a

- To address the role of reversions in early HIV-1 evolution, the authors studied 7 acute infected AIDS patients longitudinally. Their findings show that most forward mutations in HIV-1 were significantly likely to occur within and including "neighboring" CTL epitope residues restricted by the host's HLA type. 62% of early/fast mutations arising within 6 months of infection were reversions to consensus sequences while 73% of forward mutations occurred as late/slow mutations. Almost 30% of reversions were found in CTL epitopes not restricted by the current host. Reversions themselves occurred faster in conserved residues as well as more conserved proteins like

Gag and Pol; however slow reversions were seen more frequently in Env and non-structural proteins like Vif, Tat and Nef. The authors suggest that fitness cost and structural constraints may be the underlying cause for high and early reversion rates.

HXB2 Location HIV-1
Author Location
Epitope
Subtype B, C
Immunogen vaccine
Strain: A clade, B clade *HIV component:* Env, Gag, gp120, Nef, Pol, Rev, Tat, Vif, Vpr, Vpu
Species (MHC) human
Assay type Other
Keywords vaccine antigen design
References Fischer *et al.* 2007

- In order to work towards a global vaccine covering multiple variable and conserved epitopes, the authors have designed a method for generating polyvalent vaccines optimized against HIV-1 M group viruses. 4 mosaic proteins were produced by in silico recombination natural sequences, including common, and excluding rare potential 9-mer epitopes. Total coverage was assessed by tracking exact and partial 9-mer matches. Such mosaic, polyvalent multi-antigens that resemble a native protein would also allow more natural delivery and eptiope processing in vivo.

HXB2 Location HIV-1
Author Location (HXB2)
Epitope
Subtype B
Immunogen HIV-1 infection, SIV infection, SHIV infection
Species (MHC) human, macaque
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords assay standardization/improvement, escape, immune evasion, viral fitness and reversion
References Asquith & McLean 2007

- By using a method developed recently [Asquith et al., PLOS Biology. Vol:4, Issue: 4. pp. 583-592 (2006)] for estimating the in vivo rate at which CTLs kill HIV-1-productively infected cells, the authors compare previously determined human CTL control of HIV-1 infection with macaque CTL control of SHIV/SIV infection. Quantitatively, it was shown that macaque CTLs kill infected cells significantly faster than human. Also, in most cases for both species, the outgrowth of escape variants was too rapid to put anything but a lower bound on the escape rate. There was also no significant difference in virus escape rate between macaque chronic or acute infection.
- Inspite of the fact that CTL response in macaques is faster than in humans, CTL-induced viral escape variants appeared more rapidly in macaques than in humans. However, macaque escape variants also had a higher fitness cost, as evidenced by their higher rate of reversion upon transfer of viral variant to macaques that did not present the HLA restricting the epitope under study. Taken together, it was determined that immunodeficient virus-infected cells were killed almost 10 times more rapidly in macaques than in humans.

HXB2 Location HIV-1
Author Location (HXB2)
Epitope
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA, adenovirus type 5 (Ad5), DNA prime with Ad5 boost *Strain:* B clade *HIV component:* Gag, Nef, Pol
Species (MHC) human
Country Brazil, Botswana, Cameroon, Malawi, United States, South Africa
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement
References Dubey *et al.* 2007

- To evaluate the immunogenicity of various vaccine modalities the IFN-gamma ELISpot assay is optimized and validated here across vaccine recipients and regimens, using 9-, 15- or 20-mer peptide pools. An empirical method to establish positivity criteria with a <1% false-positive rate was established at >=55 spots/10^6 PBMCs and >=4-fold over mock negative control. Moreover, 15-mer peptides had greater sensitivity than 20-mers as well as a greater specificity; i.e. ability to stimulate CD4 and CD8 T cells with fewer false-positives and cross-reactive responses, than 9-mers.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, immunodominance
References Fu *et al.* 2007

- Using IFN-gamma ELISpot analyses and peptide pools, the authors studied a cohort of 54 chronically infected HIV-positive individuals to evaluate CTL responses against HIV-1. 2 criteria were established to score an ELISpot as positive - a reading of > 55 SFC/10^6 PBMC and an antigen response at least 4-fold higher than that of mock antigen. By performing T subset depletion the contribution of CTL responses to cellular immunity was proven. These CTL immune responses were mounted mostly against Gag, Pol and Nef peptide pools, and to a lower extent versus Rev and Tat peptides. Without antiviral therapy, host CTL responses correlate directly with plasma viral loads during chronic infection.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type Intracellular cytokine staining
Keywords assay standardization/improvement
References Meddows-Taylor *et al.* 2007

CTL CD8+

- A whole blood peptide mapping intracellular cytokine staining assay was developed, that allows the direct comparison, at individual peptide level, of CD4+ and CD8+ T cell responses. This assay also allows to monitor the responding cell type in the same reaction and requires considerably less blood than would be necessary if PBMC were first isolated prior to peptide stimulation.
- 396 overlapping peptides across Gag, Pol, Nef, Env, Tat, Rev, Vif, Vpu, Vpr were tested. CD8+ responses were higher in magnitude and in frequency than CD4+ responses in HIV patients screened by this method.

HXB2 Location HIV-1
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: lipopeptide *Strain:* B clade consensus, B clade LAI *HIV component:* Gag, gp120, Nef
Species (MHC) human
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords vaccine-induced epitopes, therapeutic vaccine
References Gahery *et al.* 2006

- This study describes CD4+ and CD8+ T cell responses detected before and after immunization with a mixture of lipopeptides in chronically infected patients treated by HAART. Lipopeptides induces multiple new responses and thus could be used a new immunotherapy strategy.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Assay type Other
Keywords immunodominance, escape, immune evasion, viral fitness and reversion
References Rolland *et al.* 2007a

- This correspondence is in response to an article by Arien et al. (2007) Nature Reviews Microbiology 5(2):141-51. Here the authors claim that in silico studies demonstrate HIV follows "survival of the flattest" effects. They propose that HIV-1 shifts to robust population characters that protect it from niche perturbations and increase its survival at the expense of replicative fitness. The balance between intra-host replication and inter-host transmission is suggested to be held by circulating viruses going from high fitness and low mutational support to lower fitness and high mutations. They maintain that lower fitness does not equal virus attenuation as discussed by Arien et al.

HXB2 Location HIV-1
Author Location
Epitope
Subtype B, C
Immunogen HIV-1 infection
Species (MHC) human
Keywords vaccine-specific epitope characteristics, immunodominance, escape, vaccine antigen design, immune evasion, neutralization
References Rolland *et al.* 2007c

- To sidestep the issue that in vaccine design against AIDS, providing protection against global diversity may be an insurmountable problem, a prototype conserved elements (CE) vaccine comprising 45 8-residue long HIV segments is described. Therefore the authors seek to cope with HIV-1 diversity by avoiding it altogether. Stringent conservation criteria are followed to find CEs devoid of mutable segments across M group viral proteomes. Most CE were identified in Pol, Gag, Env, Vif and Rev.
- Even though most CE peptides were identified in Pol, these are rarely targeted in natural infections probably because of the much lower ratio of Pol proteins produced compared to Gag. Therefore Pol CE were used here in contrast to most other vaccines.
- Nef was not used and fewer Env CE peptides were used in this vaccine, even though they are usually found in other vaccines.
- Many CE segments contained known CTL epitopes and are implicated with LTNPs. One crucial advantage of this strategy is that a single global CE vaccine should work against all circulating HIV-1 M strains.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen
Species (MHC)
Keywords review
References Mullins & Jensen 2006

- This is a review discussing HIV mutational potential and perspective for effective vaccines.

HXB2 Location HIV-1
Author Location Rev (B clade consensus)
Epitope
Subtype B
Immunogen HIV-1 infection, SHIV infection
Species (MHC) macaque
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords assay standardization/improvement
References Chea *et al.* 2005

- The study describes a novel in vivo killing (IVK) assay using overlapping peptide pools pulsed onto autologous fluorescently labeled PBMC. Analysis of SIV/HIV specific immnunity in several weeks following JVK assays showed a marked enhancement of virus-specific CD8 and CD4 T-cell immunity.

HXB2 Location HIV-1
Author Location Env (MN)
Epitope
Subtype B
Immunogen HIV-1 infection, SHIV infection
Species (MHC) macaque
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining

Keywords assay standardization/improvement
References Chea *et al.* 2005

- The study describes a novel in vivo killing (IVK) assay using overlapping peptide pools pulsed onto autologous fluorescently labeled PBMC. Analysis of SIV/HIV specific immnunity in several weeks following JVK assays showed a marked enhancement of virus-specific CD8 and CD4 T-cell immunity.

HXB2 Location HIV-1
Author Location
Epitope
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country Malawi, South Africa, Zambia, Zimbabwe
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords subtype comparisons, escape, optimal epitope, HLA associated polymorphism
References Ngandu *et al.* 2007

- For HIV-1 subtype C, it is found that Nef and p24 peptides recognized by CTL response are usually conserved but p17 epitopes are highly variable. Also, database information for subtype C epitopes is severely lacking in comparison with subtype B.

HXB2 Location HIV-1
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human
Assay type Other
Keywords vaccine antigen design, immune evasion, optimal epitope
References Nickle *et al.* 2007

- To develop vaccines that include antigens versus circulating variation in consensus sequences as well as versus mutations, a computational method was developed to reconstruct ancestral sequence at the center of phylogenetic tree using 169 subjects' sequences. Also, to compass sufficient antigenicity, more antigenic sequences would be required, but to avoid large, full-length antigens, short protein sequences present at high frequencies in HIV-1 populations were used in constructs. In this study, 3 constructs were directed against highly variable Nef and immunologically important but conserved Gag. 82% 9-mer coverage for Gag and 62% for Nef were achieved.

HXB2 Location HIV-1
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Canada
Assay type CD8 T-cell Elispot - IFNγ
Keywords rate of progression, escape, HLA associated polymorphism
References Brumme *et al.* 2007

- Using a viral lineage-corrected analytical method, HLA class-I associated mutations were studied in HIV protease, RT, Vpr and Nef in chronically infected ART-naive patients. 478 unique viral polymorphisms were organized into 'escape maps', helping discriminate between virus active immune selection and founder effects as disease progressed.
- Immune escape pathways were predictable, based on host HLA Class I. Epitope anchor residues were not preferred as escape mutation sites.
- Nef had the greatest immune imprinting, revealing differential contributions of HIV genes to escape.
- An inverse correlation was found between disease stage and HLA-associated escape.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection, HIV-2 infection
Species (MHC) human
Assay type T-cell Elispot, Other
Keywords review
References Rowland-Jones 2008

- In this letter "quality" over "quantity" of cellular immune response is reviewed as the key to controlling viral replication. Responses to Gag protein are the only significant immunity in both HIV-1 and -2 (in particular a 15 residue peptide in HIV-2 Gag). Reasons cited are the great fitness cost for Gag escape mutations and early post-infection Gag processing, that gives gag-specific CTL an early advantage in controlling viral replication.
- Other aspects of CTL "quality" mentioned are polyfunctionality, high avidity and replacement of exhausted T cells with new clones. Varying selection pressures between HIV-1 genes, viral founder effects versus actual T-cell selection pressure and mechanisms of antibody anti-viral activity are new discoveries to be considered in vaccine studies.

HXB2 Location HIV-1
Author Location
Epitope `TSTLQEQIAW`
Immunogen
Species (MHC) human
Keywords review, immunodominance, escape, immune evasion, viral fitness and reversion, compensatory mutation
References Allen & Altfeld 2008

- This commentary on Goepfert et al. J. Exp. Med. 205:1009-17 (2008) and other papers discusses the efficacy of HIV-1 control by immune response-driven mutations in the conserved region of Gag.
- As with drug-induced selection pressure, CTL-induced pressures for epitopes like Gag-TW10 (TSTLQEQIAW) in HLA-B57 patients result in immune escape. Viral load, however, remains controlled by reduced replicative fitness as suggested by reduced replication in vitro; rapid reversion upon transmission to B57- hosts; secondary partially restoring compensatory mutations; and an inverse correlation between number of epitope mutations and viral load.

- Transmitted Gag but not Nef accumulated mutations associate with reduced viral load, especially for HLA-B restricted epitopes.
- Immune selection history within the highly conserved 100-amino acid stretch of Gag is most indicative of early, sustained viral control in both HIV-1 and SIV, as well as in HLA-B57 and -27 hosts.
- The higher the number of sequence variations in Gag, the greater viral control.
- The commentary concludes that to reduce and avoid competition between virus-specific CTLs generated against different epitopes, variable regions of Gag should be excluded from vaccine constructs.

HXB2 Location HIV-1
Author Location HIV-1
Epitope
Immunogen computer prediction
Species (MHC) human
Assay type Other
Keywords escape
References Althaus & De Boer 2008

- A computational model of HIV/SIV infection follows immune escape dynamics longitudinally. Several CTL clones recognizing epitopes are used in this model. Escape may be early during acute infection or late and can be sequential too. Early escapes arise rapidly, mostly from immunodominant clones. Escapes could be selected later despite their presence early in virus populations as sub-dominant clones increase.
- Low escape rates do not necessarily mean low killing rates. Escape rates decelerate due to fitness costs for replication. Also, if killing follows Michaelis-Menten rather than mass action kinetics, escape rates lower.
- Immunodominant clones induce strong selection pressure to escape, which though it results in increased numbers of infected cells, also reduces viral replicative capacity.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, acute/early infection
References Rowland-Jones & de Silva 2008

- Comments on Streeck et al. PLOS Medicine 5:5 (2008) along with reference to the literature suggest that starting ART in acute infection and following structured treatment interruptions may best contain mucosal-associated lymphoid tissue damage and preserve epitope-specific CTL polyfunction and proliferative capacity by suppressing HIV-1 replication early and efficiently.

HXB2 Location HIV-1
Author Location
Epitope
Subtype B
Immunogen computer prediction
Species (MHC) human
Assay type Other
Keywords vaccine antigen design
References Thurmond *et al.* 2008

- Bioinformatic tools are made available online at `http://hiv.lanl.gov/content/sequence/MOSAIC/` to (1) design candidate mosaic vaccine proteins and (2) assess their antigen potential. Tools were the Mosaic Vaccine Designer Tool for design; Epicover and Posicover for assessment of potential T-cell epitopes as 9-12mers. Features are graphical output and user control. Tools were tested by designing Gag, Pol and Env mosaic protein sets and comparing them to Merck V520 trial sets. Mosaic antigens showed better coverage.

HXB2 Location HIV-1
Author Location
Epitope
Subtype B, C, M
Immunogen HIV-1 infection
Species (MHC) human
Country Barbados, Peru, United States, South Africa
Assay type CD8 T-cell Elispot - IFNγ, Other
Keywords assay standardization/improvement
References Frahm *et al.* 2008

- Peptides from 3 computationally designed centralized sequences (consensus, ancestor and center-of-tree (COT)) of HIV clades B,C and group M were compared for their ability to be targeted in gamma-interferon ELISPot detection assays. Consensus sets used were ConB'01, ConB'02, ConC and ConM; ancestral were AncB and AncM; and COT, COTB and COTM. No one peptide set was a more sensitive detector, but combination of the sets were significantly more potent at CTL response detection.
- Genetic distance between local patient HIV sequence and peptide test set was inversely related to response rate. Inter-clade C peptide sets were more robust detectors of C-clade infection than intra-clade (B); however group M peptide responses were comparable to within-clade C ones. Thus for HIV-C infections, combining group M, all clade B and clade C sets was significantly better than detection by ConC alone. This was not true of Clade-B intra-clade responses.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen vaccine
Species (MHC) human
Keywords assay standardization/improvement, review, variant cross-recognition or cross-neutralization
References D'Souza & Altfeld 2008

- This commentary on the 3 tiers of assays used in the HIV Vaccine Trials Network, evaluates T-cell responses to exogenous antigen. The addition of assays assessing antiviral activity is one upgrade that is suggested.
- Bennett et al. JID 197:337-339 (2008), use a viral inhibition assay with serial dilutions that is recommended. Its possible limitations however include (1) long-term in vitro maintained cultures (2) use of single TCR on the clone surface (3) labor-intensive separation of CD4 and CD8 T cells (4) culture conditions can affect cell-killing ability (5) in vitro virus replication depends on input virus and T cell activation (6) complex standardization of assay.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen computer prediction
Species (MHC) human, mouse
Keywords computational epitope prediction
References Lundegaard *et al.* 2008b

- A new algorithm that may be used for HIV or other viruses to predict MHC I peptide or epitope binding is implemented at `http://www.cbs.dtu.dk/services/NetMHC-3.0` (NetMHC-3.0) and `http://www.cbs.dtu.dk/services/NetMHCpan-1.1` (NetMHCpan-1.1). Here 8-, 10- and 11-mer peptide affinities can be predicted in addition to the standard 9-mers'. It is validated as comparable or better than methods trained on peptide length identical to predicted epitopes.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen computer prediction
Species (MHC) human, mouse
Assay type Other
Keywords computational epitope prediction
References Lundegaard *et al.* 2008a

- For rational and effective CTL epitope discovery, an algorithm, NetMHC-3.0 (`http://www.cbs.dtu.dk/services/NetMHC`) based on artificial neural networks and trained on data from 55 human and non-human MHC alleles as well as position-specific scoring matrices for 67 alleles is made available. This method has been used for HIV and can generate MHC affinities for peptides of length 8-11. It is validated using newly published experimental data that does not overlap those used in the training set for the algorithm.

HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype CRF02_AG
Immunogen HIV-1 infection, HIV-2 infection
Species (MHC) human
Country Gambia
Assay type Cytokine production, Flow cytometric T-cell cytokine assay
Keywords characterizing CD8+ T cells
References Duvall *et al.* 2008

- HIV-1 and HIV-2 infections were compared for polyfunctionality of helper and CTL response. Both CD4+ and CD8+ cells were more polyfunctional in HIV-2 infections, producing more IFN-gamma and TNF-alpha than monofunctional T cells. No association was found between CTL phenotype tested and function.
- Patient T cells were stimulated using pools of either HIV-2 Gag 15-mer peptides from a consensus of 5 patient isolates, or HIV-1 Clade A Gag consensus 15-mer peptides.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection, vaccine
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords review
References Yang 2008b

- In evaluating failure of the STEP rÅd5 HIV-1 vaccine, several suggestions for initial the overestimation of its efficacy are given. The primary use of IFN-gamma ELISpot to assay immunity is faulty as it does not correlate clearly with immune control. CTL polyfunctionality via ICS is important, but may not be enough.
- Rather than mostly peripheral blood CTL, tissue-based CTL in particular early, gut compartment CTL, should be evaluated.
- HIV-1 sequence variability is confounding due to possible vaccine-virus sequence mismatches since even a point mutation can develop into an escape. Rather than focus on which protein, stretches of highly conserved sequences or epitopes to include in the vaccine should be determined.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: adenovirus type 5 (Ad5)
Species (MHC) human
Assay type Other
Keywords vaccine-specific epitope characteristics, vaccine antigen design
References Yang 2008a

- This opinion article discusses CTL failure and suggests HIV vaccine antigens. Early immunodominance against variable epitopes; and CTL mis-targeting leading to escaping immunodominant epitopes, 'original antigenic sin', depletion of CD4+ T cells that aid memory and long term T-cell function, abnormal CTL activation and differentiation are reasons for multifactorial CTL failure in chronic infection.
- Subverting immunodominance against poorly conserved epitopes could interrupt events causing CTL failure. Suggested viral sequences for vaccine inclusion are (i) epitopes from relatively conserved regions less prone to escape, (ii) administered before natural infection, in order to set CTL memory to avoid immunodominance. This, however, would diminish breadth of response as well as cross-clade immunogenecity.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords review, HIV exposed persistently seronegative (HEPS)
References Piacentini *et al.* 2008

- Several possible protection mechanisms against HIV infection are discussed for exposed seronegative cohorts, including aspects of cellular, humoral and innate immune responses. One reason for an infection-controlling cellular response is the presence of CTLs recognizing different, separate epitopes than those in infected patients. These epitopes are restricted by HLA I alleles associated with resistance to infection.

CTL CD8+

HXB2 Location HIV-1
Author Location HIV-1
Epitope
Immunogen
Species (MHC) human
Keywords rate of progression, escape
References Asquith 2008

- This theoretical study quantified the contribution of viral escape from CTL to the HLA-associated rate of progression to AIDS. Three datasets were analyzed: (i) all (21) detailed longitudinal escape events reported in the literature; (ii) published functional CTL response data in 150 HIV-1 infected individuals (Frahm et al, 2004); (iii) sequence variation in the clade B sequences from Los Alamos HIV database.
- Epitopes restricted by protective HLA class I alleles tended to have escape variants with a weak evolutionary selective advantage, were less likely to contain sequence variation, and the escapes occurred infrequently.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords assay standardization/improvement
References Precopio *et al.* 2008

- The study describes and tests an optimized method for configuration of peptide pool matrices encompassing hundreds of overlapping peptides and the method of epitope deconvolution.
- 4 matrices of pools of peptides (15-mers overlapping by 11) were constructed and tested in 3 HIV-positive individuals.
- It was found that the peptide configuration requiring the least amount of blood sample depends on the predicted number of positive peptides in the set.
- In the 3 patients tested, 74 reactive peptides were identified altogether, with minimum 53 potential epitopes taking overlaps into account. Many of the peptides have been previously identified as CTL or helper epitopes.

HXB2 Location HIV-1
Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Jamaica
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords responses in children
References Huang *et al.* 2008a

- CD8+ and CD4+ T cell responses were studied in 76 pediatric patients using overlapping peptides spanning B clade consensus.
- T cell responses were present in the majority of infected infants, but there was a gualitative difference in responses in young infants and older children.
- Targeting of Gag was associated with significantly lower plasma HIV-1 RNA levels, but Gag-specific responses were less commonly detected in infants than in children older than 12 months. CD8 T cells exhibiting multiple effector functions (IFN-γ, TNF-α and degranulation) were detected less frequently in younger infants. CD4 T cell responses were of very low magnitude in nearly all pediatric patients and absent in the youngest infants.

CTL CD8+

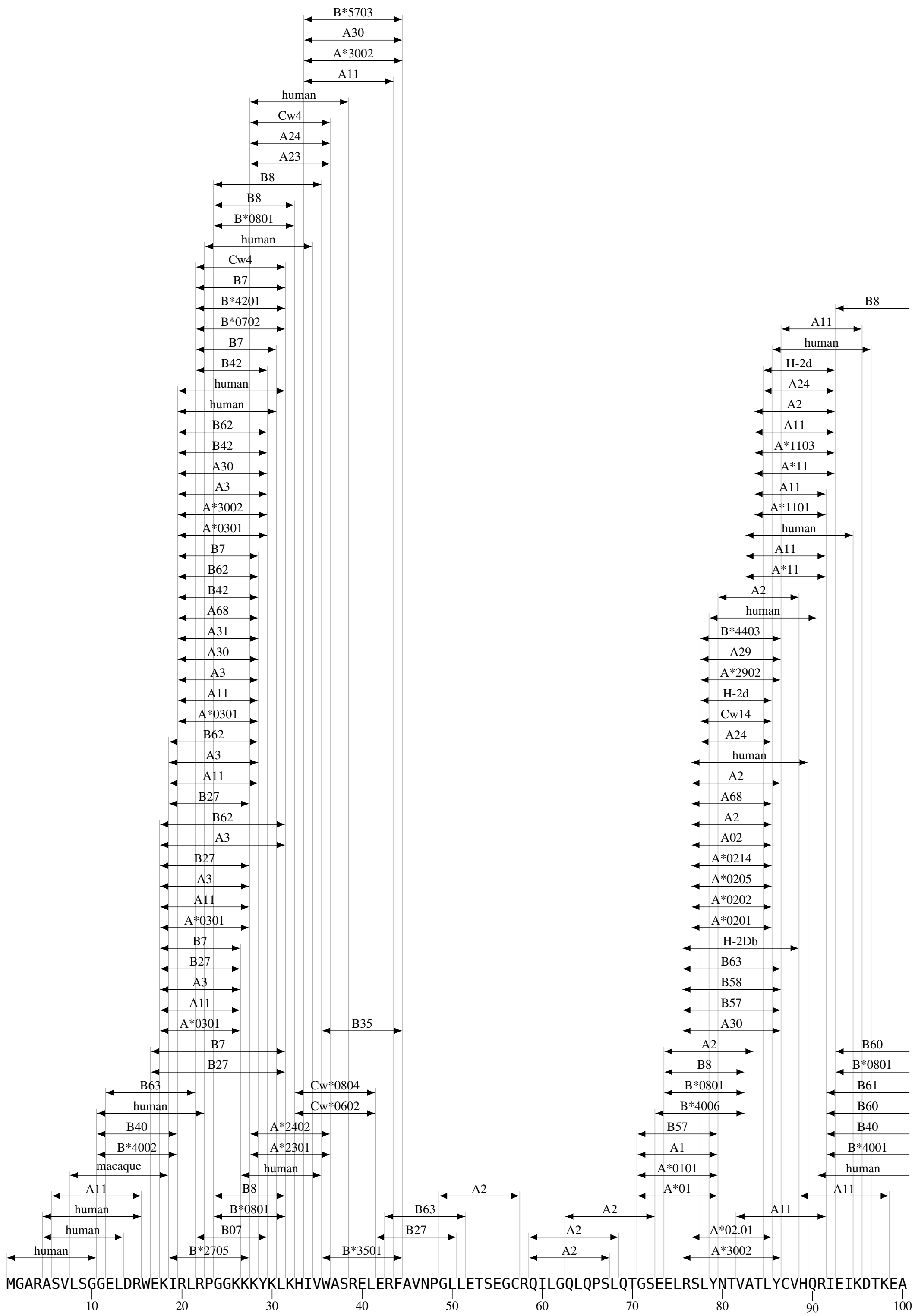
II-C

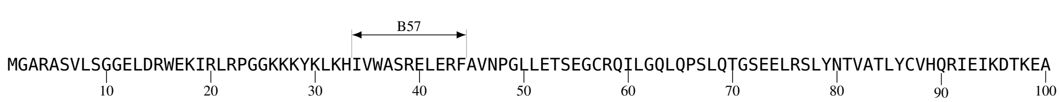
Maps of CTL/CD8+ Epitope Locations Plotted by Protein

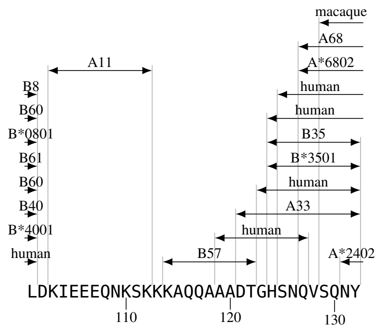
Linear CTL epitopes mapped to within a region of 14 amino acids or less are shown.

CTL CD8+

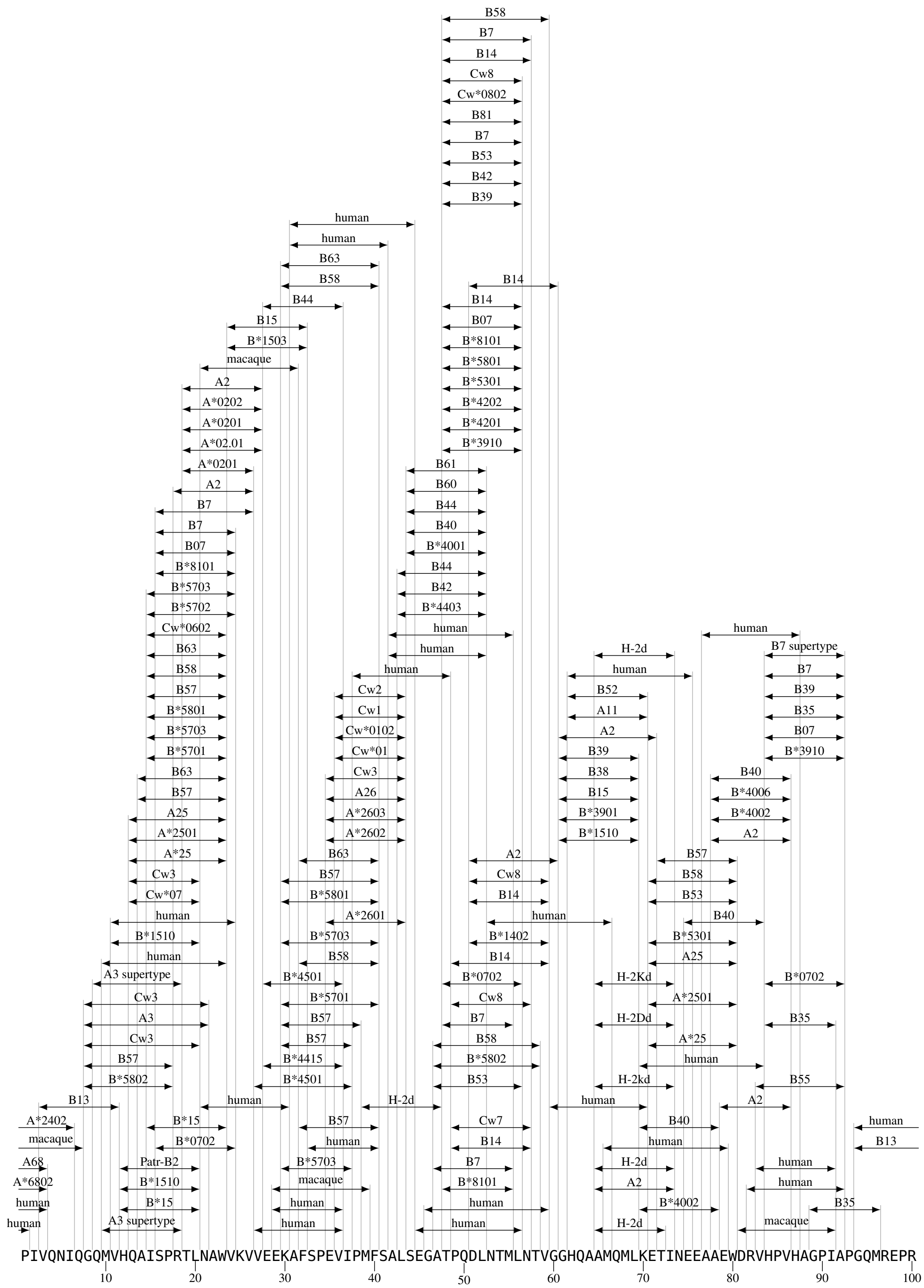
II-C-1 p17 CTL/CD8+ Epitope Map



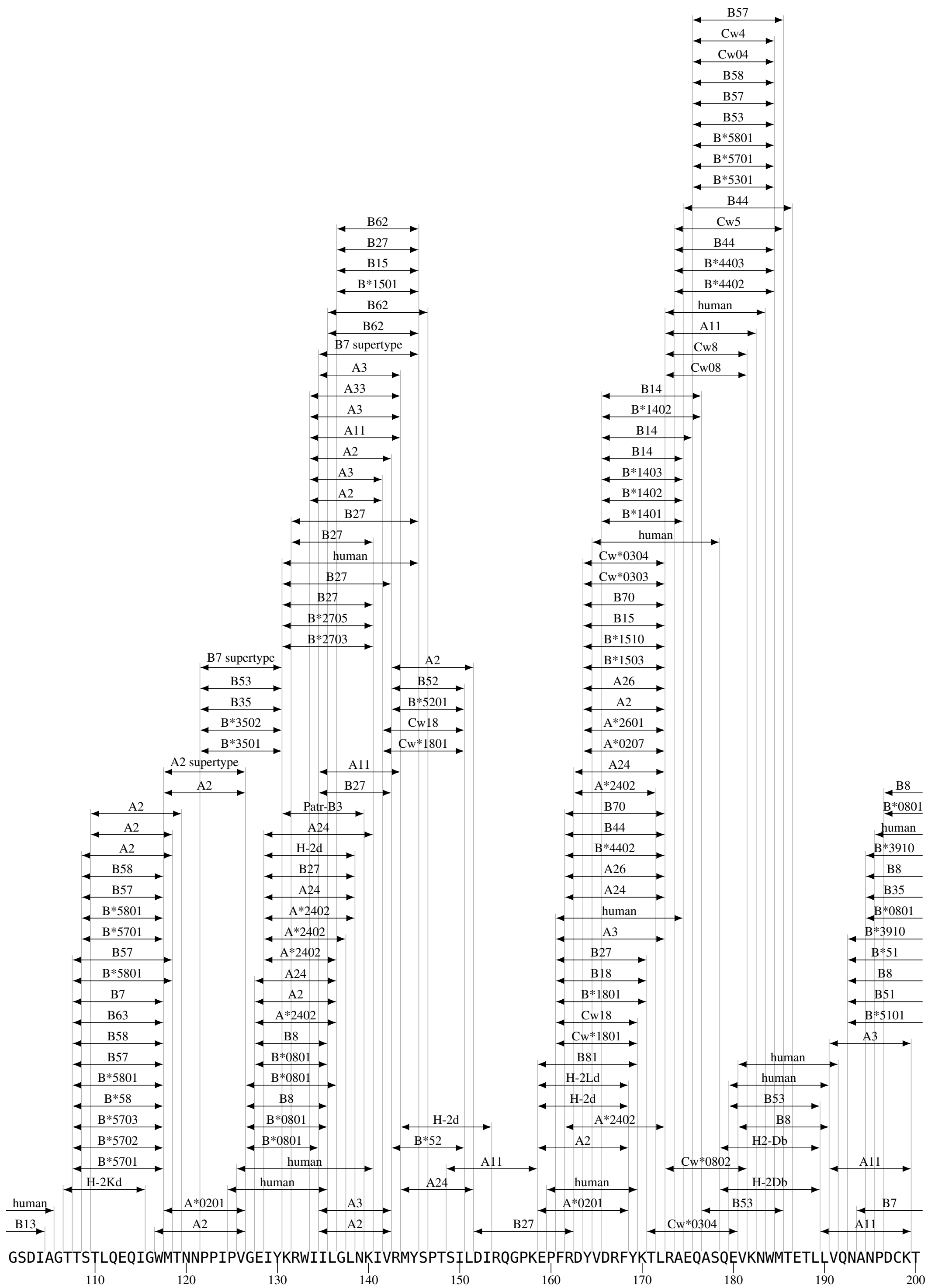



macaque
A68
A*6802
A11
human
B8
human
B60
B35
B*0801
B*3501
B61
human
B60
A33
B40
human
B*4001
B57
A*2402
human
LDKIEEEQNKSKKKAQQAAADTGHSNQVSQNY
110
120
130

II-C-2 p24 CTL/CD8 + Epitope Map



CTL CD8+


GSDIAGTTSTLQEQIGWMTNNPPIPVGEIYKRWIILGLNKIVRMYSPTSILDIRQGPKEPFRDYVDRFYKTLRAEQASQEVKNWMTETLLVQNANPDCKT
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130
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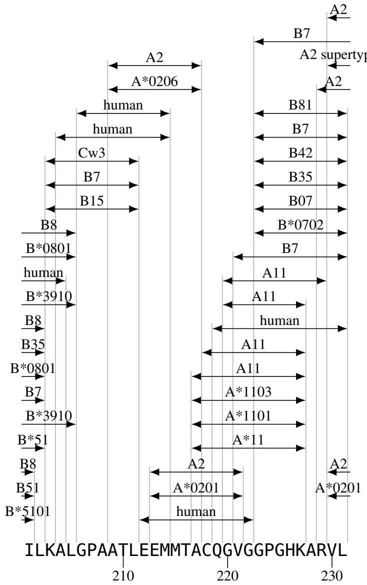
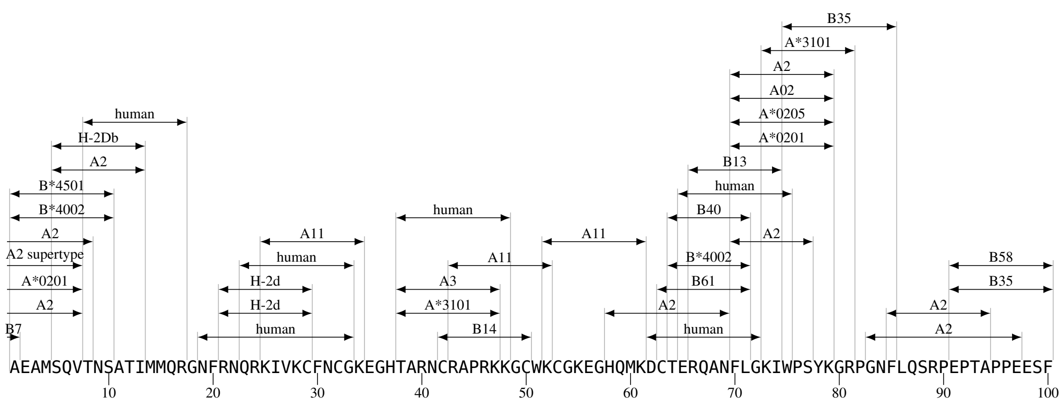
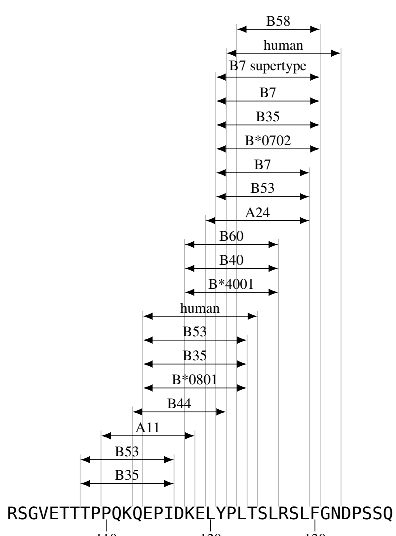
180
190
200

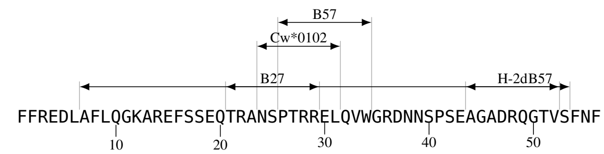


II-C-3 p2p7p1p6 CTL/CD8+ Epitope Map

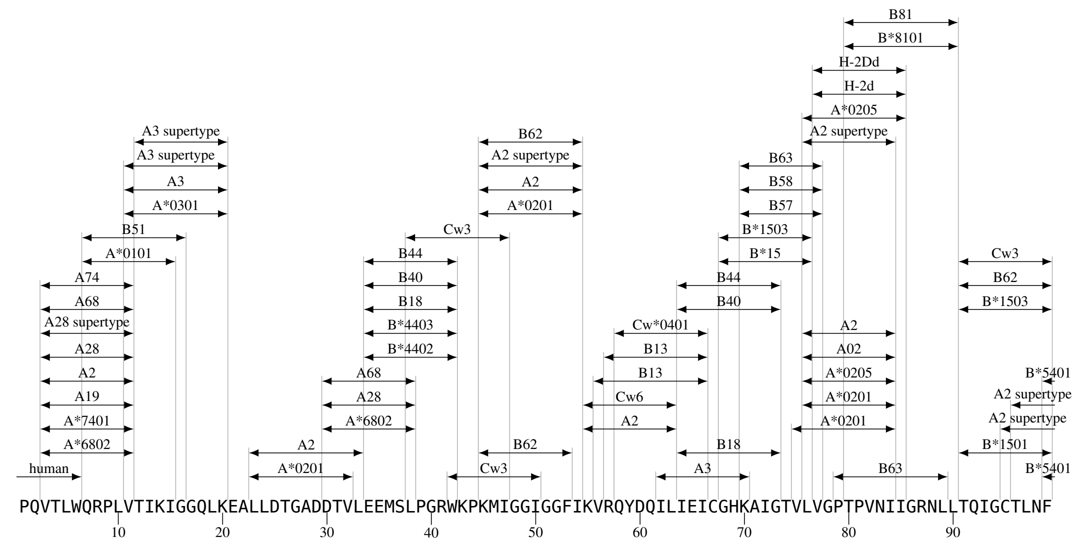




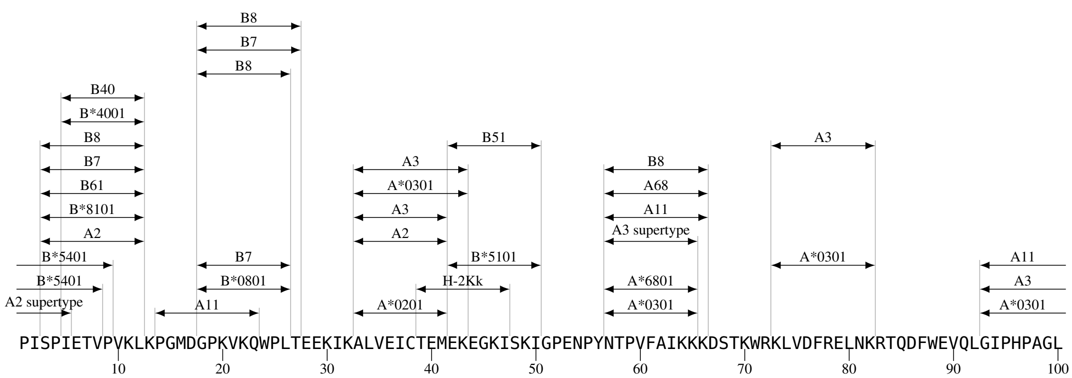
II-C-4 Gag/Pol TF CTL/CD8+ Epitope Map



II-C-5 Protease CTL/CD8+ Epitope Map

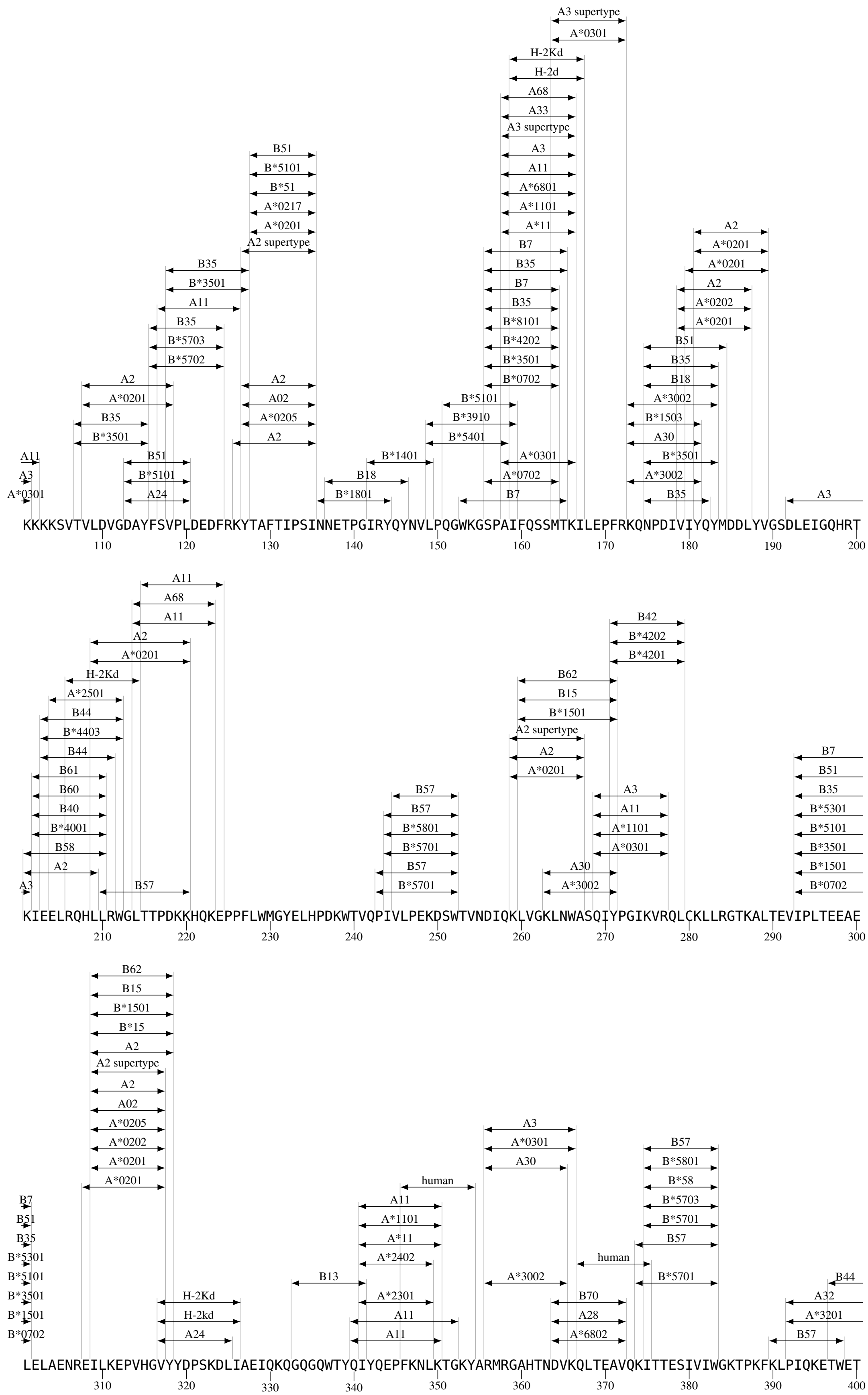


II-C-6 RT CTL/CD8+ Epitope Map



CTL CD8+

CTL CD8+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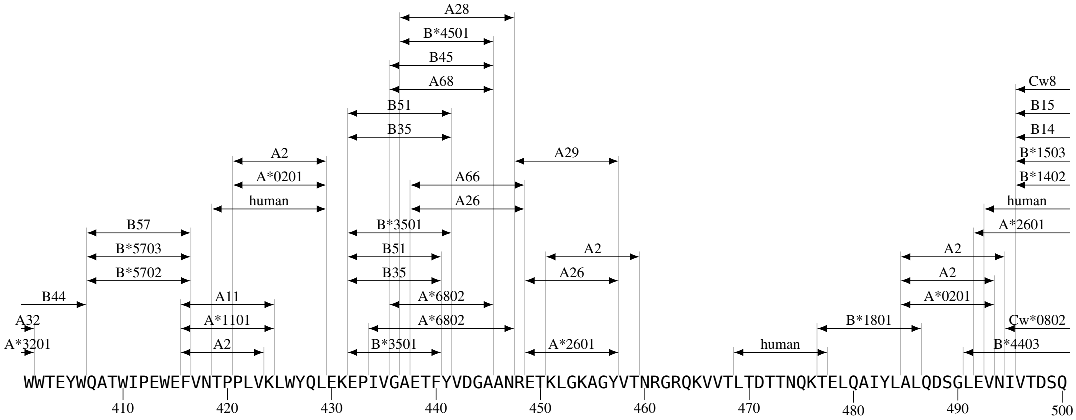
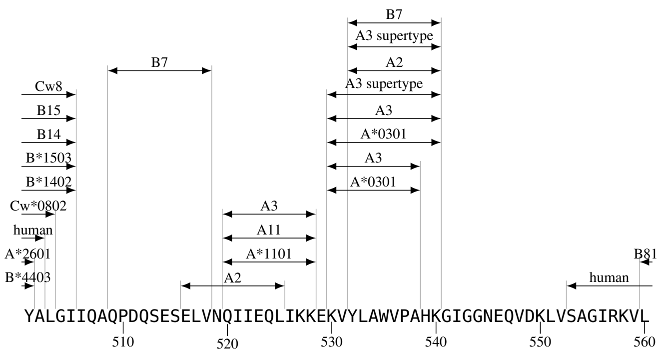
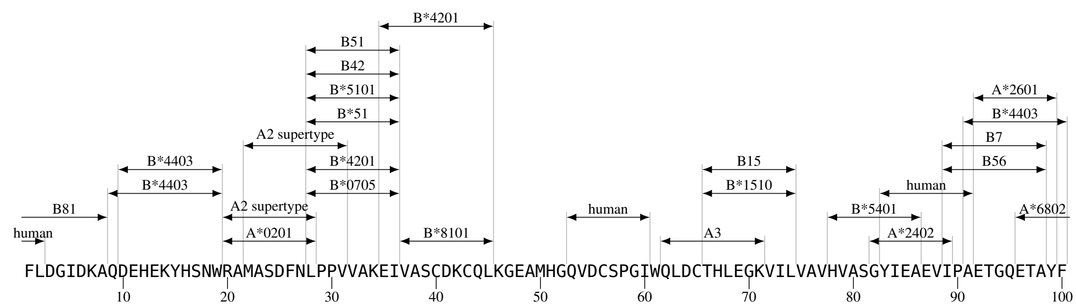
H-2Kd
H-2d
A68
A33
A3 supertype
A3
A11
A*6801
A*1101
A*11
B51
B*5101
B*51
A*0217
A*0201
A2 supertype
A2
A*0201
A*0201
B7
B35
B7
B35
B*8101
B*4202
B*3501
B*0702
B35
B*3501
A11
B35
B*5703
B*5702
A2
A*0202
A*0201
B51
B35
B18
A2
A*0201
B35
B*3501
A2
A02
A*0205
A2
B*5101
B*3910
B*5401
A*3002
B*1503
A30
A11
A3
A*0301
B51
B*5101
A24
B*1401
B18
B*1801
A*0301
A*0702
B7
B*3501
A*3002
B35
A3
KKKKSVTVLDVGDAYFSVPLDEDFRKYTAFTIPSINNETPGIRYQYNVLPQGWKGSPAIFQSSMTKILEPFRKQNPDIVIYQYMDDLYVGSDLEIGQHRT
110 120 130 140 150 160 170 180 190 200
A11
A68
A11
A2
A*0201
H-2Kd
A*2501
B44
B*4403
B44
B61
B60
B40
B*4001
B58
A2
A3
B57
B42
B*4202
B*4201
B62
B15
B*1501
A2 supertype
A2
A*0201
B57
B57
B*5801
B*5701
B57
B*5701
A3
A11
A*1101
A*0301
A30
A*3002
B7
B51
B35
B*5301
B*5101
B*3501
B*1501
B*0702
KIEELRQHLLRWGLTTPDKKHQKEPPFLWMGYELHPDKWTVQPIVLPEKDSWTVNDIQKLVGKLNWASQIYPGIKVRQLCKLLRGTKALTEVIPLTEEAE
210 220 230 240 250 260 270 280 290 300
B62
B15
B*1501
B*15
A2
A2 supertype
A2
A02
A*0205
A*0202
A*0201
A*0201
B7
B51
B35
B*5301
B*5101
B*3501
B*1501
B*0702
H-2Kd
H-2kd
A24
B13
human
A11
A*1101
A*11
A*2402
A*2301
A11
A11
A3
A*0301
A30
A*3002
human
B70
A28
A*6802
B57
B*5801
B*58
B*5703
B*5701
B57
B*5701
B44
A32
A*3201
B57
LELAENREILKEPVHGVYYDPSKDLIAEIQKQGQGQWTYQIYQEPFKNLKTGKYARMRGAHTNDVKQLTEAVQKITTESIVIWGKTPKFKLPIQKETWET
310 320 330 340 350 360 370 380 390 400

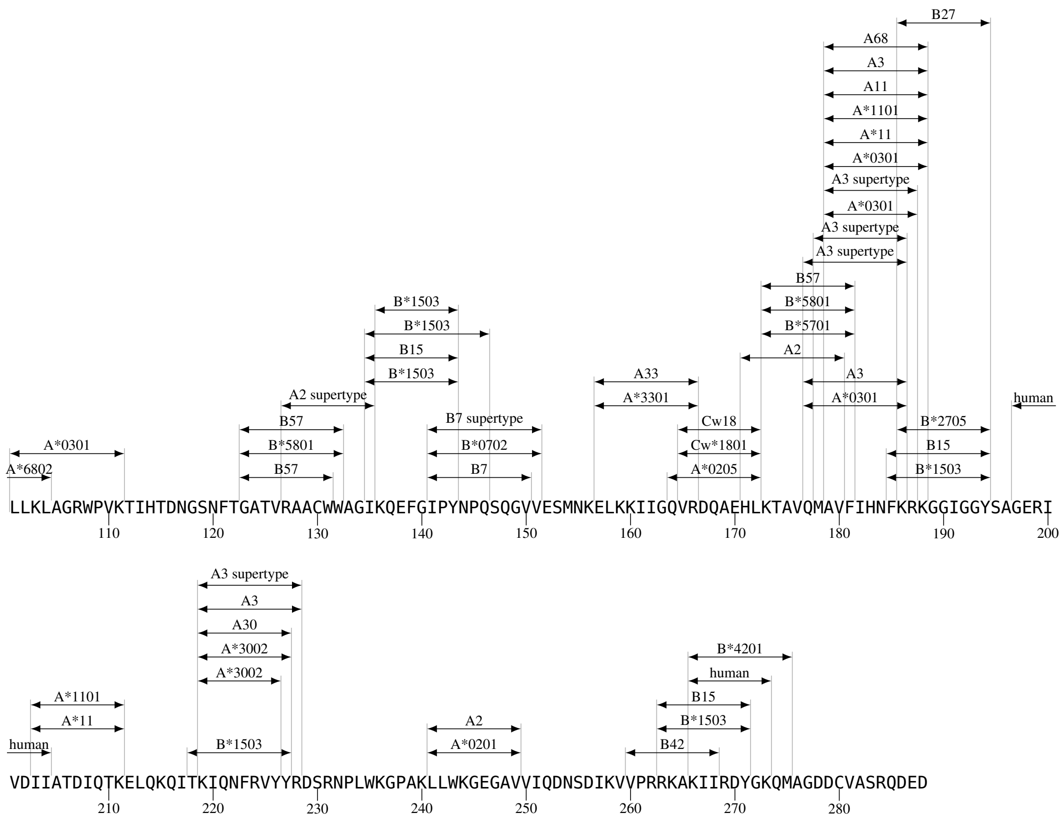




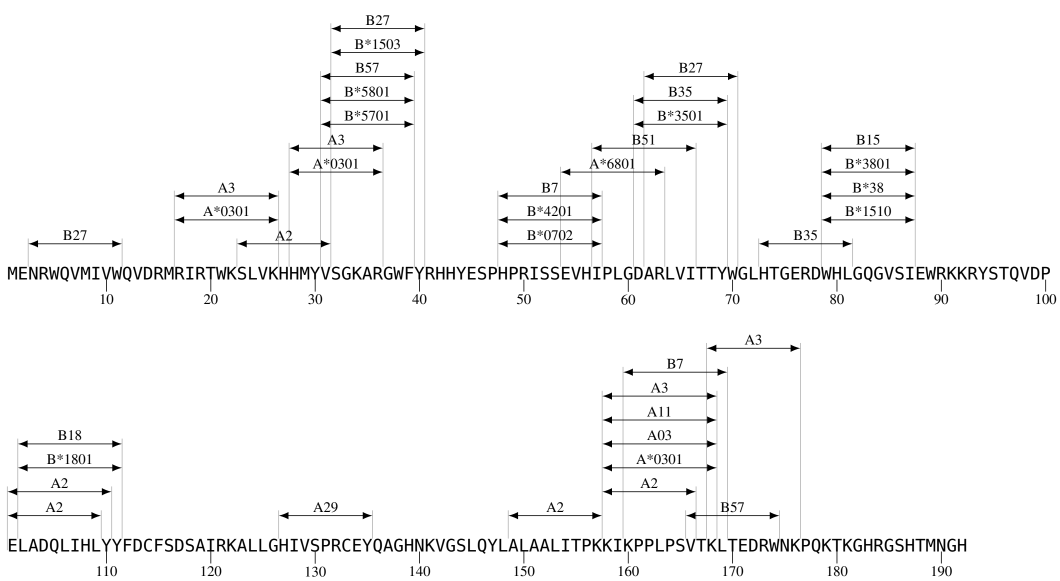
II-C-7 Integrase CTL/CD8+ Epitope Map



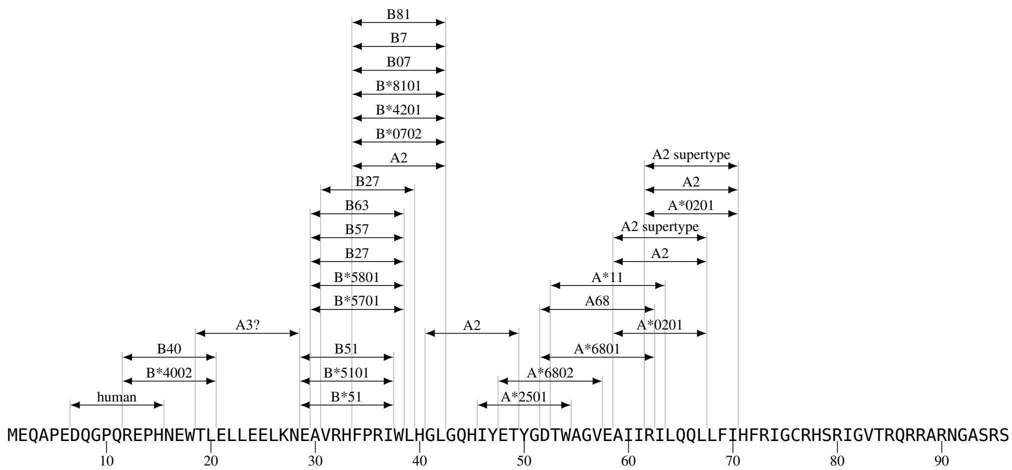
CTL CD8+



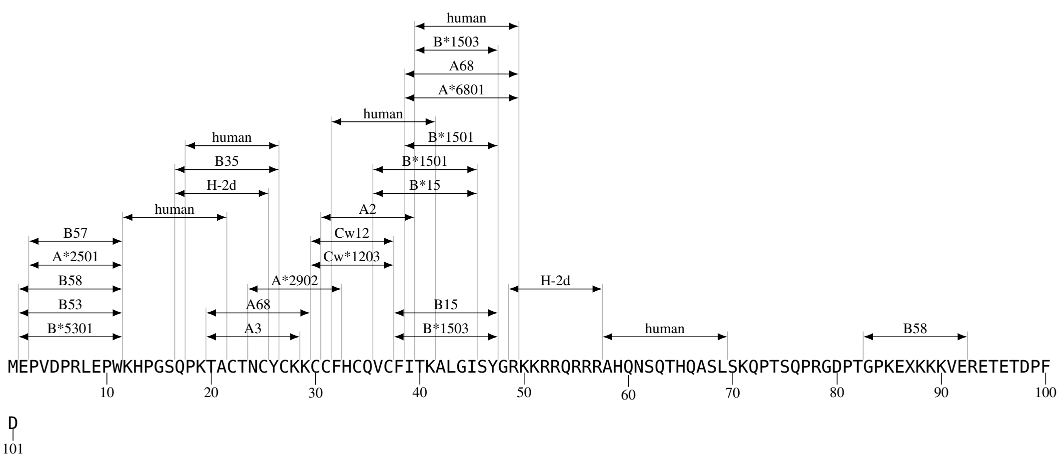
II-C-8 Vif CTL/CD8+ Epitope Map



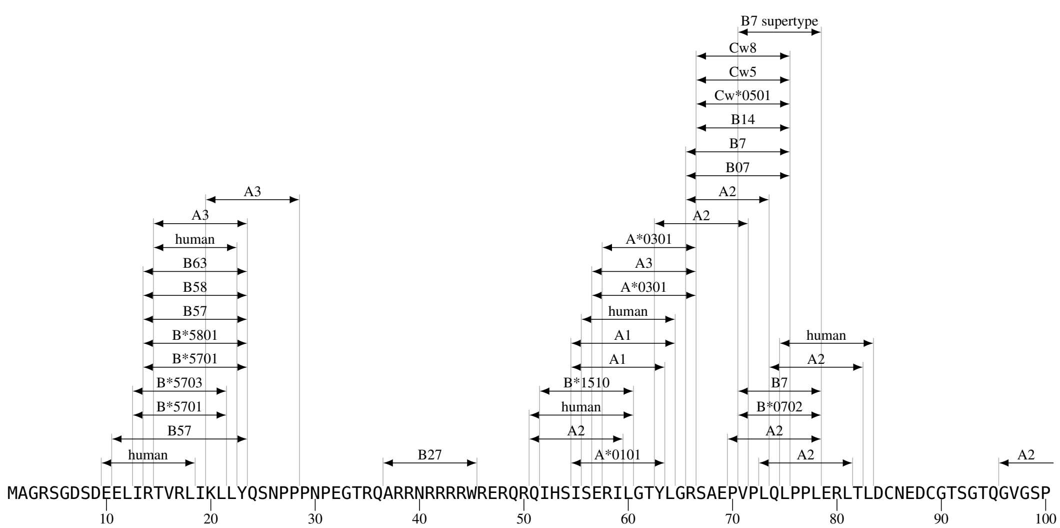
II-C-9 Vpr CTL/CD8+ Epitope Map



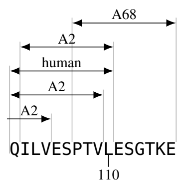
II-C-10 Tat CTL/CD8+ Epitope Map



II-C-11 Rev CTL/CD8+ Epitope Map

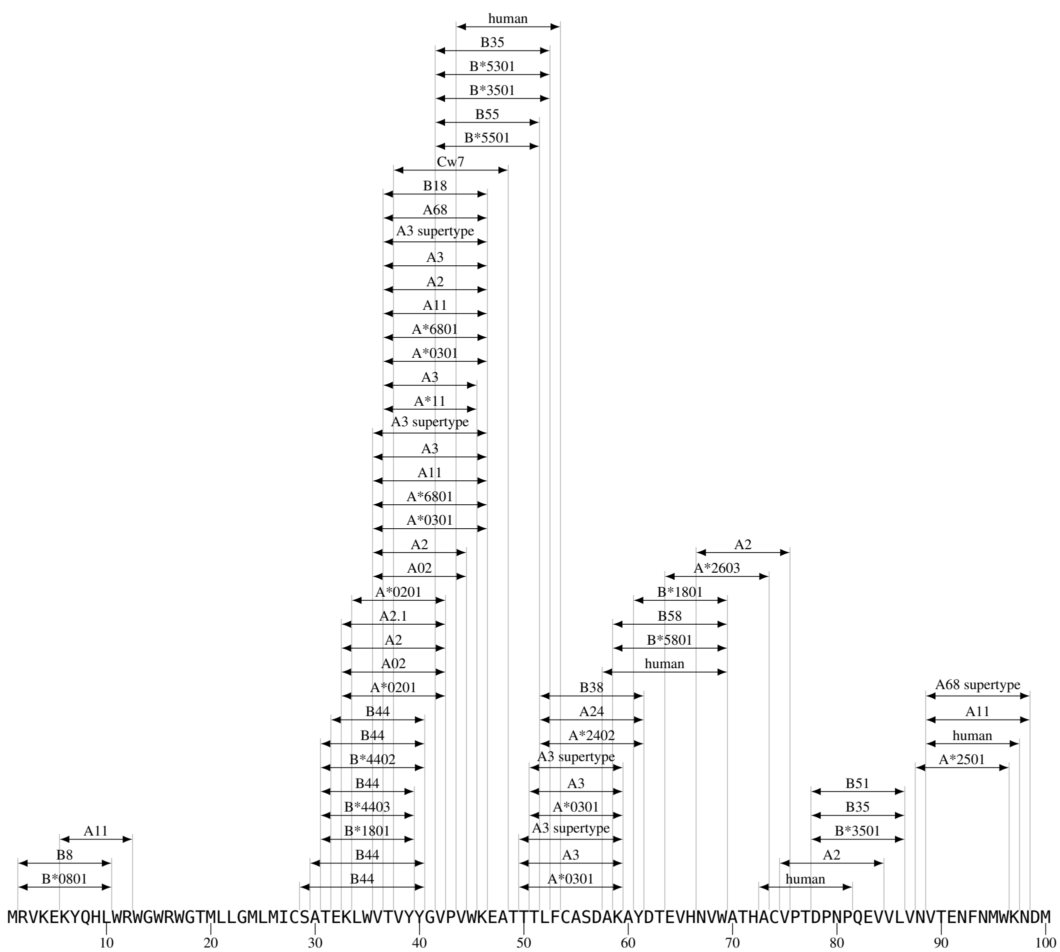


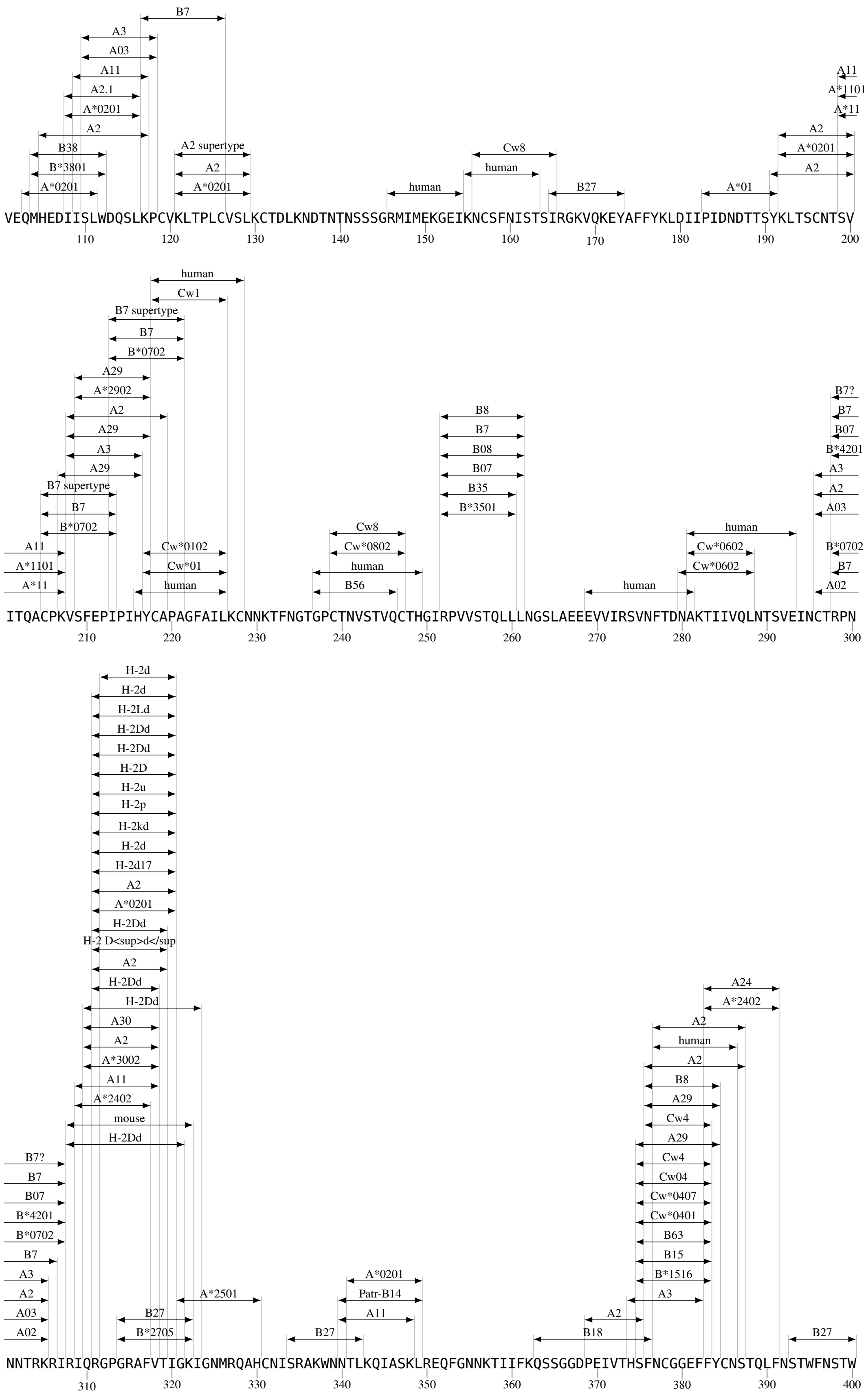
CTL CD8+



II-C-12 Vpu CTL/CD8+ Epitope Map

II-C-13 gp160 CTL/CD8+ Epitope Map

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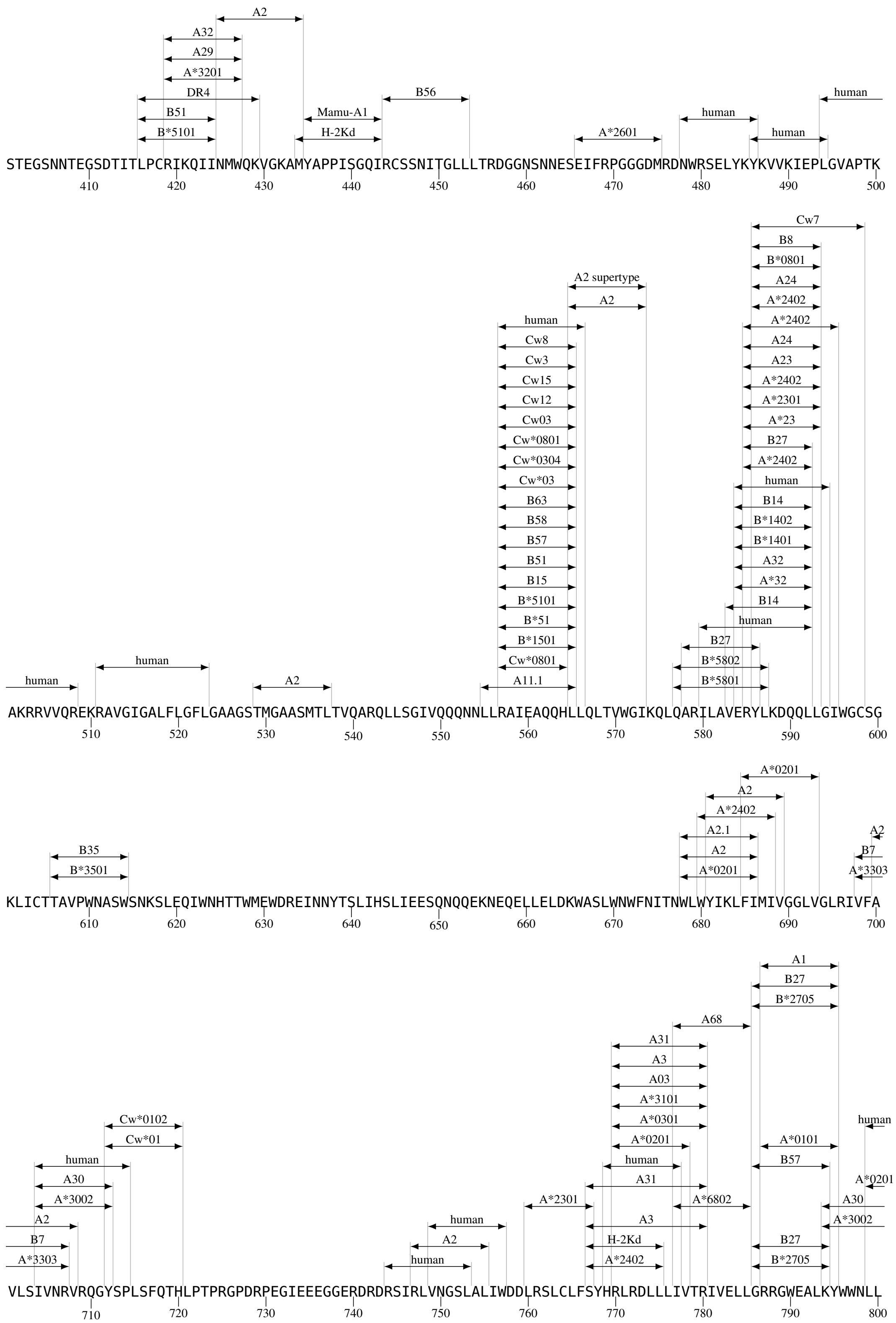
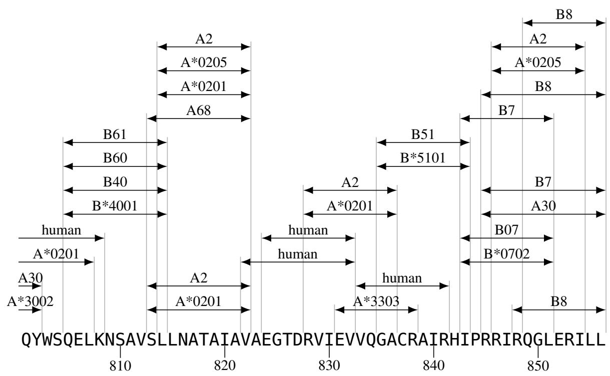
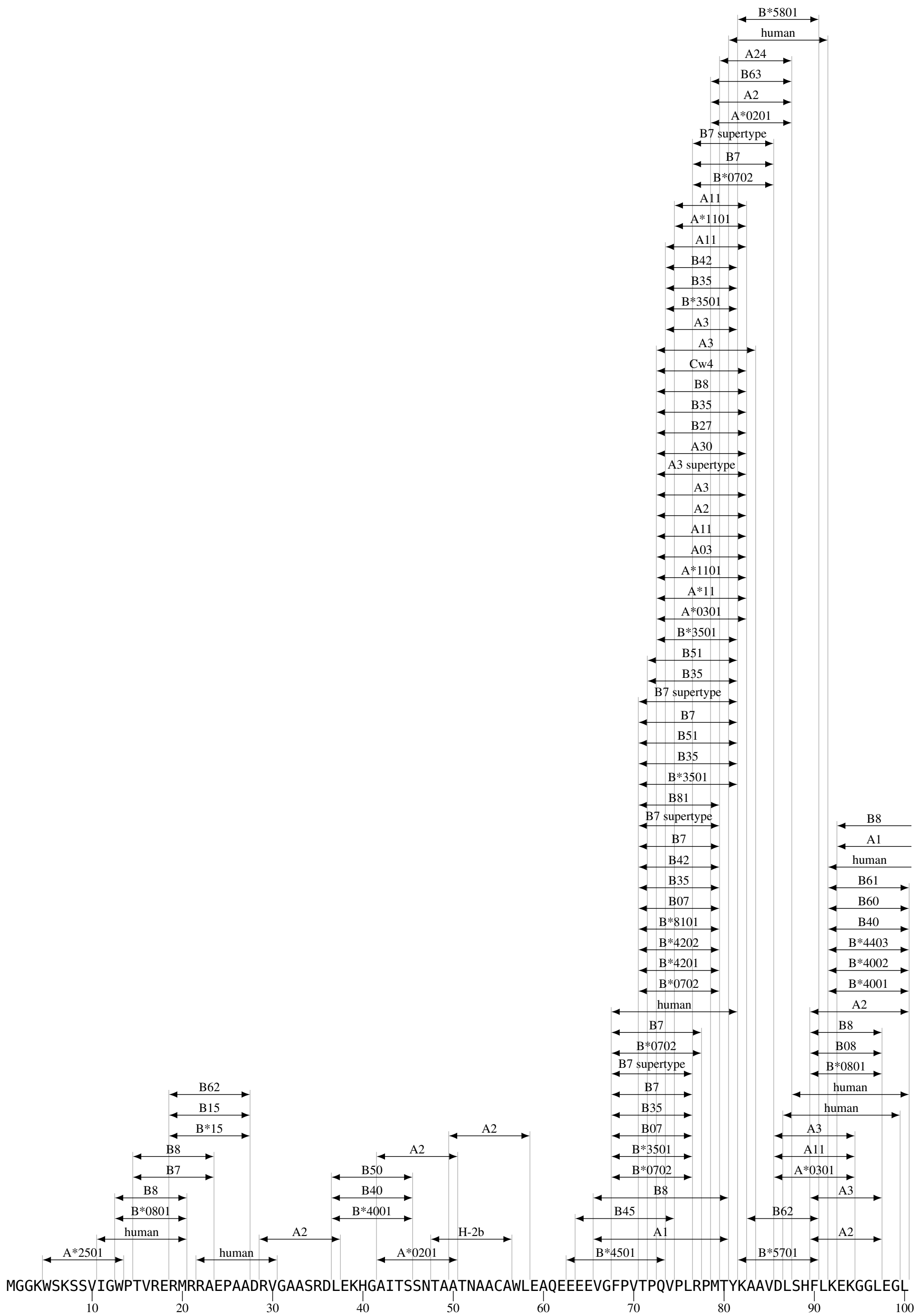
A03
A11
A2.1
A*0201
A2
B38
A2 supertype
Cw8
B*3801
A2
human
A*0201
human
B27
A*01
A11
A*1101
A*11
A2
A*0201
A2
VEQMHEDIISLWDQSLKPCVKLTPLCVSLKCTDLKNDTNTNSSSGRMIMEKGEIKNCSFNISTSIRGKVQKEYAFFYKLDIIPIDNDTTSYKLTSCNTSV
110 120 130 140 150 160 170 180 190 200
human
Cw1
B7 supertype
B7
B*0702
A29
A*2902
A2
A29
A3
A29
B7 supertype
B7
B*0702
A11
A*1101
A*11
Cw*0102
Cw*01
human
Cw8
Cw*0802
human
B56
B8
B7
B08
B07
B35
B*3501
human
human
Cw*0602
Cw*0602
B7?
B7
B07
B*4201
A3
A2
A03
B*0702
B7
A02
ITQACPKVSFEPIPIHYCAPAGFAILKCNNKTFNGTGPCTNVSTVQCTHGIRPVVSTQLLLNGSLAEEEVVIRSVNFTDNAKTIIVQLNTSVEINCTRPN
210 220 230 240 250 260 270 280 290 300
H-2d
H-2d
H-2Ld
H-2Dd
H-2Dd
H-2D
H-2u
H-2p
H-2kd
H-2d
H-2d17
A2
A*0201
H-2Dd
H-2 D<sup>d</sup
A2
H-2Dd
H-2Dd
A30
A2
A*3002
A11
A*2402
mouse
H-2Dd
B7?
B7
B07
B*4201
B*0702
B7
A3
A2
A03
A02
B27
B*2705
A*2501
B27
A*0201
Patr-B14
A11
A24
A*2402
A2
human
A2
B8
A29
Cw4
A29
Cw4
Cw04
Cw*0407
Cw*0401
B63
B15
B*1516
A3
A2
B18
B27
NNTRKRIRIQRGPGRAFVTIGKIGNMRQAHCNISRAKWNNTLKQIASKLREQFGNNKTIIFKQSSGGDPEIVTHSFNCGGEFFYCNSTQLFNSTWFNSTW
310 320 330 340 350 360 370 380 390 400

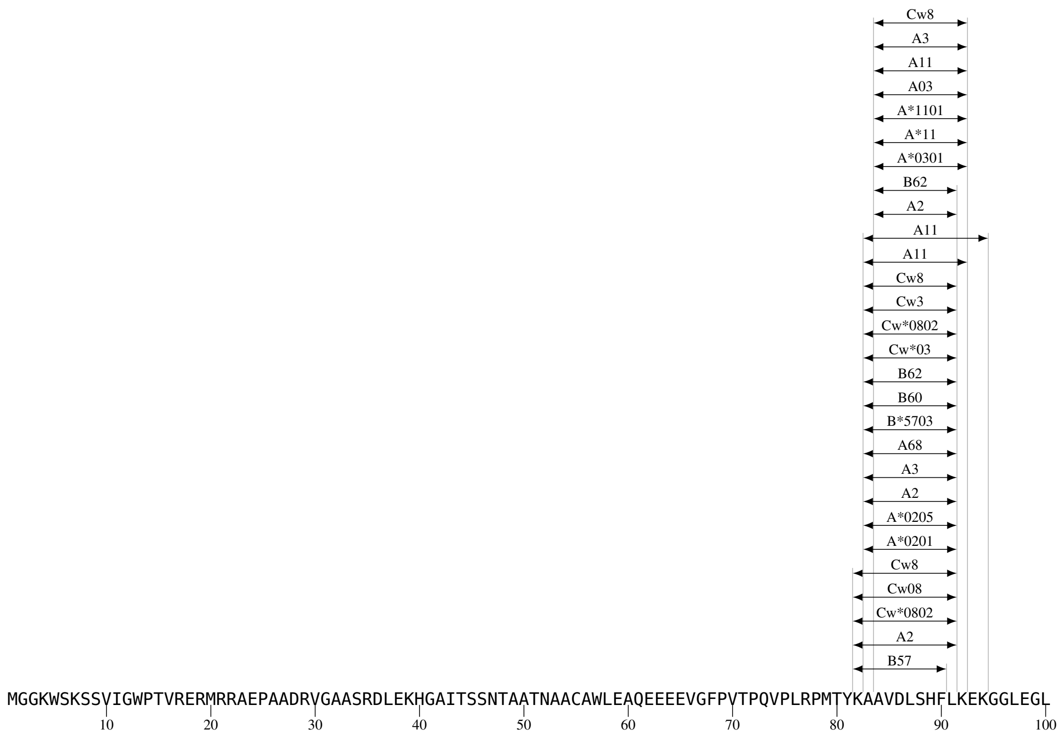
CTL CD8+


A2
A32
A29
A*3201
DR4
B51
B*5101
Mamu-A1
H-2Kd
B56
A*2601
human
human
human
STEGSNNTEGSDTITLPCRIKQIINMWQKVGKAMYAPPISGQIRCSSNITGLLLTRDGGNSNNESEIFRPGGGDMRDNWRSELYKYKVVKIEPLGVAPTK
410 420 430 440 450 460 470 480 490 500
Cw7
B8
B*0801
A2 supertype
A24
A2
A*2402
human
A*2402
Cw8
A24
Cw3
A23
Cw15
A*2402
Cw12
A*2301
Cw03
A*23
Cw*0801
B27
Cw*0304
A*2402
Cw*03
human
B63
B14
B58
B*1402
B57
B*1401
B51
A32
B15
A*32
B*5101
B14
B*51
human
B*1501
B27
Cw*0801
B*5802
human
human
A2
A11.1
B*5801
AKRRVVQREKRAVGIGALFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQLLGIWGCSG
510 520 530 540 550 560 570 580 590 600
A*0201
A2
A*2402
A2.1
A2
B35
A2
B7
B*3501
A*0201
A*3303
KLICTTAVPWNASWSNKSLEQIWNHTTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNITNWLWYIKLFIMIVGGLVGLRIVFA
610 620 630 640 650 660 670 680 690 700
A1
B27
B*2705
A68
A31
A3
A03
A*3101
A*0301
Cw*0102
human
Cw*01
A*0201
A*0101
human
human
B57
A30
A31
A*0201
A*3002
A*2301
A*6802
A30
A2
human
A3
A*3002
B7
A2
H-2Kd
B27
A*3303
human
A*2402
B*2705
VLSIVNRVRQGYSPLSFQTHLPTPRGPDRPEGIEEEGGERDRDRSIRLVNGSLALIWDDLRSLCLFSYHRLRDLLLIVTRIVELLGRRGWEALKYWWNLL
710 720 730 740 750 760 770 780 790 800


B8
A2
A2
A*0205
A*0205
A*0201
B8
A68
B7
B61
B51
B60
B*5101
B40
A2
B7
B*4001
A*0201
A30
human
human
B07
A*0201
human
B*0702
A30
A2
human
A*3002
A*0201
A*3303
B8
QYWSQELKNSAVSLLNATAIAVAEGTDRVIEVVQGACRAIRHIPRRIRQGLERILL
810
820
830
840
850

II-C-14 Nef CTL/CD8+ Epitope Map




Cw8
A3
A11
A03
A*1101
A*11
A*0301
B62
A2
A11
A11
Cw8
Cw3
Cw*0802
Cw*03
B62
B60
B*5703
A68
A3
A2
A*0205
A*0201
Cw8
Cw08
Cw*0802
A2
B57
MGGKWSKSSVIGWPTVRERMRRAEPAADRVGAASRDLEKHGAITSSNTAATNAACAWLEAQEEEEVGFPVTPQVPLRPMTYKAAVDLSHFLKEKGGLEGL
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30
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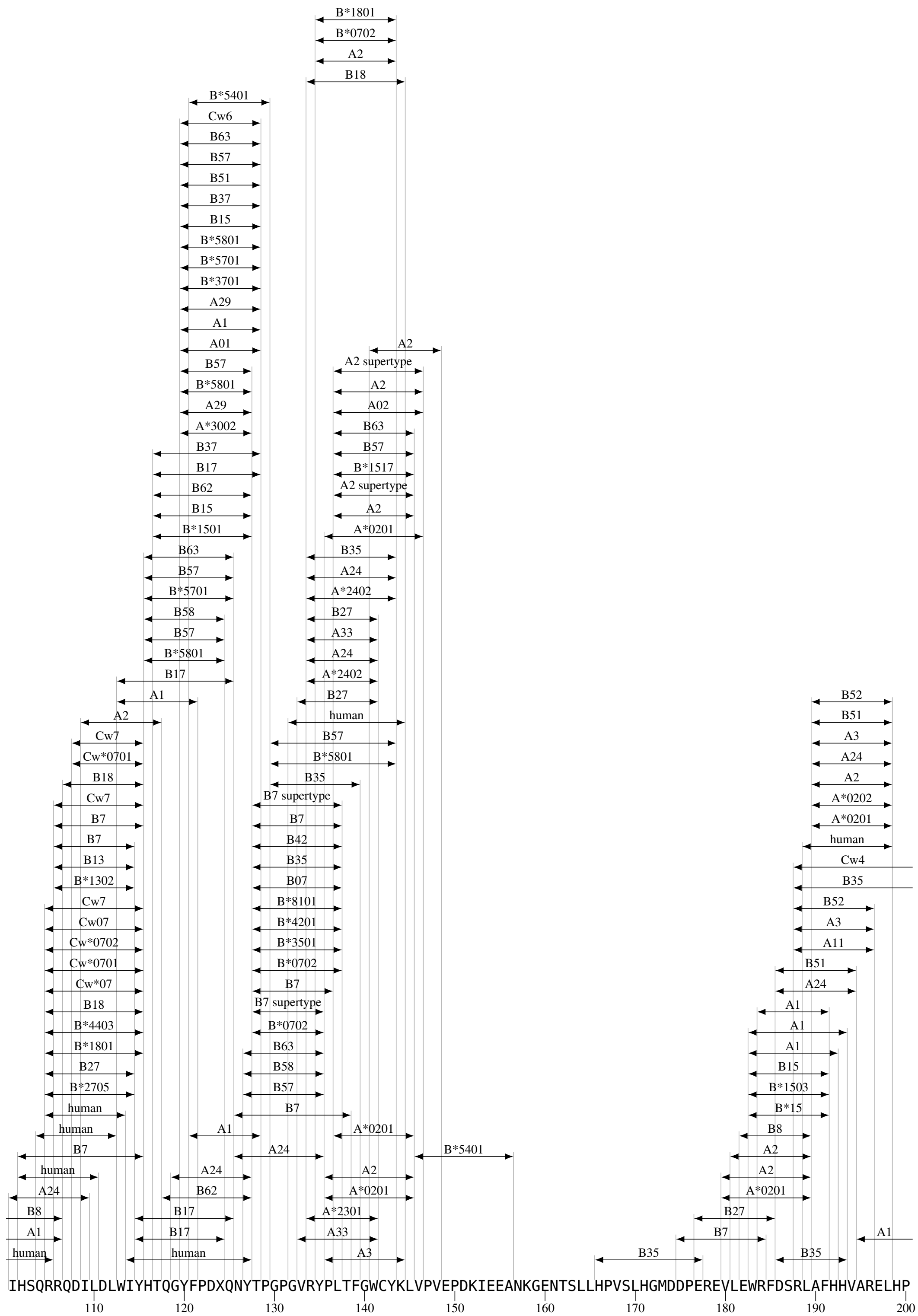
50
60
70
80
90
100


B*1801
B*0702
A2
B18
B*5401
Cw6
B63
B57
B51
B37
B15
B*5801
B*5701
B*3701
A29
A1
A2
A01
A2 supertype
B57
A2
B*5801
A02
A29
B63
A*3002
B57
B37
B*1517
B17
A2 supertype
B62
A2
B15
A*0201
B*1501
B63
B35
B57
A24
B*5701
A*2402
B58
B27
B57
A33
B*5801
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A*2402
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A2
human
B51
Cw7
B57
A3
Cw*0701
B*5801
A24
B18
B35
A2
Cw7
B7 supertype
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B7
A*0201
B7
B42
human
B13
B35
Cw4
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B07
B35
Cw7
B*8101
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Cw07
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A3
Cw*0702
B*3501
A11
Cw*0701
B*0702
B51
Cw*07
B7
A24
B18
B7 supertype
A1
B*4403
B*0702
A1
B*1801
B63
A1
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B58
B15
B*2705
B57
B*1503
human
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A2
A24
B62
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A*0201
B8
B17
A*2301
B27
A1
B17
A33
B7
A1
human
human
A3
B35
B35
IHSQRRQDILDLWIYHTQGYFPDXQNYTPGPGVRYPLTFGWCYKLVPVEPDKIEEANKGENTSLLHPVSLHGMDDPEREVLEWRFDSRLAFHHVARELHP
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120
130
140
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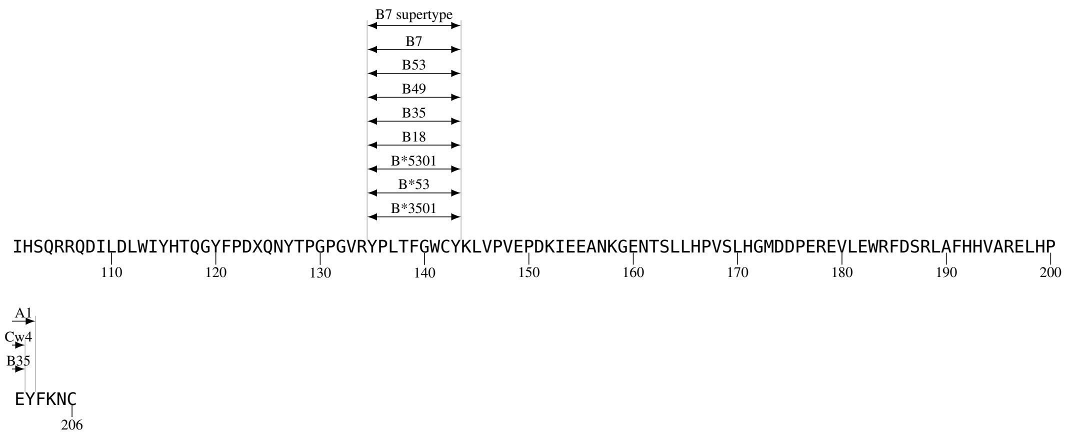
160
170
180
190
200


B7 supertype
B7
B53
B49
B35
B18
B*5301
B*53
B*3501
IHSQRRQDILDLWIYHTQGYFPDXQNYTPGPGVRYPLTFGWCYKLVPVEPDKIEEANKGENTSLLHPVSLHGMDDPEREVLEWRFDSRLAFHHVARELHP
110
120
130
140
150
160
170
180
190
200
A1
Cw4
B35
EYFKNC
206

Part III

HIV Helper/CD4+ T-Cell Epitopes

III-A

Summary

This part includes tables, maps, and associated references of HIV-specific helper T-cell (Th) epitopes from the literature arranged sequentially according to the location of the proteins in the HIV-1 genome. We attempted to make this part as comprehensive as possible, requiring that the epitope be contained within a defined region of a maximum of 30 amino acids, but not that the optimal boundaries be defined. Studies that were based on the analysis of whole proteins are described at the end of each protein section. The same epitope can have multiple entries, as each entry represents a single publication in this part of the database. HLA specificity is usually not determined for Th epitopes. For more recent updates, epitope sequence alignments, and useful search capabilities, please see our web site: `http://www.hiv.lanl.gov/content/immunology`. Helper T-cell responses to proteins with no defined epitopes are listed at the end of each protein section.

Recent studies utilize multiple functions attributed to T cells to define responses, and the simple distinctions of cytotoxic T cells and helper T cells have become blurred as more is learned about the range of responses triggered in CD4 and CD8 positive T cells responding to antigenic stimulus. When adding the most recent studies to the database, we have tried to place T cell responses in a reasonable manner into our traditional helper T cell and CTL parts, and to specify the assay used to measure the response in each study.

III-A-1 Epitope tables

Each T-helper epitope has a multi-part basic entry:

HXB2 location: The viral strain HXB2 (GenBank Accession Number K03455) is used as a reference strain throughout this publication. The position of the defined epitope location relative to the sequence of the HXB2 protein is indicated. The numbering in this table corresponds to the protein maps. Because of HIV-1 variation the epitope may not actually be present in HXB2; rather, the position in HXB2 indicates the position aligned to the epitope. HXB2 was selected as the reference strain because so many studies use HXB2, and because crystal structures for HXB2-related proteins are often available. The precise positions of an epitope on the HXB2 reference strain can be readily obtained using the interactive position locator at our web site: `http://www.hiv.lanl.gov/content/sequence/LOCATE/locate.html`.

Author location: The amino acid positions of the epitope boundaries and the reference sequence are listed as given in the primary publication. Frequently, these positions as published are imprecise, and do not truly correspond to the numbering of the sequence, but they provide a reasonable guide to the peptide's approximate location in the protein. Also, in many cases the reference sequence identification was not provided, and in such cases it is not possible to use these numbers to specify precise locations.

Epitope: The amino acid sequence of the epitope of interest as defined in the reference, based on the reference strain used in the study defining the epitope. On occasions when only the position numbers and not the actual peptide sequence were specified in the original publication, we tried to fill in the peptide sequence based on the position numbers and reference strain. If the sequences were numbered inaccurately by the primary authors, or if we made a mistake in this process, we may have misrepresented the binding site's amino acid sequence. Because of this uncertainty, epitopes that were not explicitly written in the primary publication, that we determined by looking up the reference strain and the numbered location, are followed by a question mark in the table.

Epitope name: If the epitope has a name attributed by the publication, it is recorded here, e.g. "SL9".

Subtype: The subtype under study, if specified in the primary publication; this is generally not specified for B subtype.

Immunogen: The antigenic stimulus of the Th response. Often this is an HIV-1 infection. If a vaccine was used as the original antigenic stimulation, not a natural infection, this is noted separately, and additional information about the vaccine antigen is provided as available.

Species (MHC): The species responding and MHC or HLA specificity of the epitope.

Donor MHC: The HLA genotype of the individual that responded to the epitope.

Country: The country where the samples were obtained; this is generally not specified if the study was conducted in the United States.

Assay type: Assay used to characterize the response.

Keywords: Keywords are a searchable field for the web interface that is included in the T-cell sections of the printed version to help identify entries of particular interest.

Reference: The primary reference (sometimes two or more directly related studies are included). Details for some of the earlier references are in Part V.

Following the entry for a given Th epitope brief comments explain the context in which the epitope was studied and what was learned about the epitope in a given study.

III-A-2 HIV protein epitope maps

All HIV Th epitopes mapped to within a region of 18 amino acids or less are indicated on the HIV protein epitope maps. The location and HLA restriction elements of Th epitopes are indicated on protein sequences of HXB2. These maps are meant to provide the relative location of defined epitopes on a given protein, but the HXB2 sequence may not actually carry the epitope of interest, as it may vary relative to the sequence for which the epitope was defined. Epitopes with identical boundaries and HLA fields are included in the maps only once. If one laboratory determines HLA presenting molecules at the serotype level (example: A2) and another at the genotype level (example: A*0201) both will be included in the map. MHC specificities are indicative of the host species; when no MHC presenting molecule is defined, the host species is noted.

III-A-3 Alignments

To conserve space, no epitope alignments are provided in this book, but they can be generated using the Th epitope search tool at `http://www.hiv.lanl.gov/content/immunology`. The master alignment files from which the epitope alignments were created are available at our web site at `http://www.hiv.lanl.gov/content/sequence/NEWALIGN/align.html`.

III-B

HIV Helper/CD4 + T-Cell Epitope Tables

All HIV Helper/CD4+ T-Cell epitopes are arranged by protein position. The table entries are sorted in a nested way—first by protein, then by HXB2 start location within the protein, and finally by HLA presenting molecule. Epitopes for which the HXB2 location is unknown appear at the end of the listing of the protein in which they are located.

III-B-1 Gag p17 Helper/CD4 + T-cell epitopes

HXB2 Location p17 (1–18)
Author Location p17 (1–18 B consensus)
Epitope MGARASVLSGGELDRWEK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This epitope was recognized by 14% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p17 (5–16)
Author Location Gag (5–15)
Epitope ASILRGGKLDKW
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was not detectable.

HXB2 Location p17 (7–17)
Author Location Gag (7–17)
Epitope VLSGGELDRWE
Epitope name Gag 1.2
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade *HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu
Species (MHC) macaque
Assay type T-cell Elispot, Intracellular cytokine staining
Keywords subtype comparisons, memory cells
References Amara *et al.* 2005

- Clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02_AG consensus Gag in macaques. The activity was better-conserved for CD8 than CD4 T cells.
- 3/5 CD8 epitopes and 2/8 CD4 epitopes were conserved across multiple HIV-1 clades. All 5 CD8, and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation. VLSGGELDRWE was not reported for human infections.
- The response elicited to the B clade epitope VLSGGELDRWE does not cross-react with the CRF02_AG form VLtGGELDsWE. The forms VLSGG[e/k]LD[r/ak]WE are prevalent among M group clades.

HXB2 Location p17 (9–26)
Author Location p17 (9–26 B consensus)
Epitope SGGELDRWEKIRLRPGGK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding

T-Helper CD4 +

Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 22% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p17 (10–24)
Author Location p17 (242–256)
Epitope `GGKLDAWEKIRLRPG`
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag
Species (MHC) human
Assay type proliferation, CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords vaccine antigen design
References Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.
- 2/8 subjects responded to this epitope.

HXB2 Location p17 (13–23)
Author Location Gag (13–23)
Epitope `LDRWEKIRLRP`
Epitope name Gag 1.3
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade *HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu
Species (MHC) macaque
Assay type T-cell Elispot, Intracellular cytokine staining
Keywords subtype comparisons, memory cells
References Amara *et al.* 2005

- Clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02_AG consensus Gag in macaques. The activity was better-conserved for CD8 than CD4 T cells.
- 3/5 CD8 epitopes and 2/8 CD4 epitopes were conserved across multiple HIV-1 clades. All 5 CD8, and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation.
- LDRWEKIRLRP was not reported for human infections.
- The response elicited to the B clade epitope LDRWEKIRLRP does not cross-react with the CRF02_AG form LDsWEKIRLRP. Other clades most commonly carry an A in this position, and C clade consensus carries K (LD[r/ak]WEKIRLRP).

HXB2 Location p17 (17–31)
Author Location Gag (17–31 HXB-2)
Epitope `EKIRLRPGGKKKYKL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DQB1*0301, DQB1*0601, DRB1*1303, DRB1*1502, DRB3*0101, DRB5*0102
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

HXB2 Location p17 (17–34)
Author Location p17 (17–34 B consensus)
Epitope `EKIRLRPGGKKKYKLKHI`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 14% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.

- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p17 (17–34)
Author Location p17 (17–34)
Epitope EKIRLRPGGKKKYKLHKI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Netherlands
Assay type Cytokine production
References Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. EKIRLRPGGKKKYKLHKI had fixation of 1 mutation (EKIRLRPGGKK[k/r]YKLHKI) in 1 of the patients.

HXB2 Location p17 (18–42)
Author Location p17 (18–42 PV22)
Epitope KIRLRPGGKKKYKLKHIVWASRELE
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*13)
Donor MHC A29, A30, B35, B8, DRB1*03, DRB1*13
Keywords HAART, ART, Th1, Th2
References Lotti *et al.* 2002

- 10/49 chronically HIV-1 infected patients had low p55-Gag-specific CD4+ T cell responses prior to therapy, and these responses remained unchanged 3 and 6 months after initiation of HAART. There was no difference in level of response in those with or without a detectable p55 response.
- For one individual, patient F45 CDC stage A2, CD4+ p55 responding clones were generated. Her response was consistently strong and heterogeneous in terms of HLA restriction and Vβ usage, and some clones had a Th1 cytokine secretion profile (high IFNgamma production) while some had a Th2 profile (high IL-4 and IL-5 production). 5/10 CD4+ clones could also induce cytotoxicity.
- 4/10 clones from patient F45 had their epitopes mapped using overlapping peptides. Clone 6 recognized this peptide sequence restricted by DRB1*13. This clone had a high SI (27.1 to p55, 90.6 to peptide) secreted IFNgamma, indicative of a Th1 response, as well as TNFalpha. Clone 6 was highly cytotoxic, through a perforin-mediated pathway.

HXB2 Location p17 (20–30)
Author Location Gag (25–35)
Epitope RLRPGGKKHYM
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was detectable.

HXB2 Location p17 (21–35)
Author Location p17 (21–35 SF2)
Epitope LRPGGKKKYKLKHIV
Immunogen HIV-1 infection
Species (MHC) human (DR13.02)
Keywords escape
References Harcourt *et al.* 1998

- 43 asymptomatic HIV+ individuals were screened for proliferative responses to HIV – 12 showed a response, and dominant epitopes were mapped for two individuals, one in p24 and one in p17.
- Patient 024's naturally occurring variant LRPGGKKKYQLKHIV also elicited a strong proliferative response.
- Naturally occurring variants of this epitope were found within the individual who made this response – several did not stimulate the CD4+ T-cell line that recognized the index peptide, suggestive of immune escape.

HXB2 Location p17 (21–35)
Author Location p17 (21–35)
Epitope LRPGGKKKYKLKHIV
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human (DR13.02)
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.

T-Helper CD4+

- LRPGGKKKYKLKHIV is a previously known epitope that is a part of TCI fragment KIRLRPGGKKKYKLKHIVWAS-RELERFAVN in this vaccine construct.

HXB2 Location p17 (22–29)
Author Location p17 (22–29 LAI)
Epitope RPGGKKKY?
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.
- Schrier lists this peptide as p24(22-29), but it appears to be in p17.

HXB2 Location p17 (28–38)
Author Location Gag (32–43)
Epitope HYMLKHLVWAS
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was not detectable.

HXB2 Location p17 (29–43)
Author Location Gag (29–43 HXB-2)
Epitope YKLKHIVWASRELER
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DQB1*0301, DQB1*0601, DRB1*1303, DRB1*1502, DRB3*0101, DRB5*0102
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

HXB2 Location p17 (32–46)
Author Location p17 (32–46 B Consensus)
Epitope KHIVWASRELERFAV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p17 (32–46)
Author Location p17 (32–46)
Epitope KHIVWASRELERFAV
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- KHIVWASRELERFAV is a previously known epitope that is a part of TCI fragment KIRLRPGGKKKYKLKHIVWASREL-ERFAVN in this vaccine construct.

HXB2 Location p17 (33–47)
Author Location p17 (33–47 IIIB, B10)
Epitope HIVWASRELERFAVN?
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- Peptides were identified that commonly evoke T-cell responses – 57% of 90 HIV+ people had a T-cell response to this peptide.

HXB2 Location p17 (33–47)
Author Location Gag (33–47 HXB-2)
Epitope HIVWASRELERFAVN
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DQB1*0301, DQB1*0601, DRB1*1303, DRB1*1502, DRB3*0101, DRB5*0102
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

HXB2 Location p17 (35–59)
Author Location p17 (35–49 PV22)
Epitope VWASRELERFAVNPGLLETSEGCRQ
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*13)
Donor MHC A29, A30, B35, B8, DRB1*03, DRB1*13
Keywords HAART, ART, Th1, Th2, TCR usage
References Lotti *et al.* 2002

- 10/49 chronically HIV-1 infected patients had low p55-Gag-specific CD4+ T cell responses prior to therapy, and these responses remained unchanged 3 and 6 months after initiation of HAART. There was no difference in level of response in those with or without a detectable p55 response.
- For one individual, patient F45 CDC stage A2, CD4+ p55 responding clones were generated. Her response was consistently strong and heterogeneous in terms of HLA restriction and Vβ usage, and some clones had a Th1 cytokine secretion profile (high IFNgamma production) while some had a Th2 profile (high IL-4 and IL-5 production). 5/10 CD4+ clones could also induce cytotoxicity.
- 4/10 clones from patient F45 had their epitopes mapped using overlapping peptides. Clone 25 recognized this peptide sequence restricted by DRB1*13 using TCR Vβ 5.1. This clone had a SI of 4.9 to p55, 13.7 to peptide, secreted low levels of IFNgamma, indicative of a Th1 response. Clone 25 had cytotoxic activity, mediated through both a perforin and a Fas-based pathway.

HXB2 Location p17 (37–51)
Author Location p17 (37–51 B consensus)
Epitope ASRELERFAVNPGLL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101, DRB1*0401, DRB1*0405, DRB1*0701, DRB1*1302, DRB1*1501)
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This peptide was recognized by 36% of the study group.
- The peptides that were recognized by the most people were able to bind broadly to multiple HLA-DR molecules. This peptide showed high cross-reactive binding capacity and bound to 6/8 common HLA-DR molecules.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p17 (38–53)
Author Location p17 (270–284)
Epitope SRELERFALNPSLLEE
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag
Species (MHC) human
Assay type proliferation, CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords vaccine antigen design
References Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.
- 4/8 subjects responded to this epitope.

HXB2 Location p17 (39–47)
Author Location p17 (B consensus)
Epitope RELERFAVN
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*1302)
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding

T-Helper CD4+

Keywords supervised treatment interruptions (STI), immunodominance
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This epitope was in the overlap between 2 highly reactive peptides; it was fine mapped and found to be presented by DRB*1302.

HXB2 Location p17 (39–47)
Author Location p17 (39–47)
Epitope RELERFAVN
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human (DRB1*1302)
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- RELERFAVN is a previously known epitope that is a part of TCI fragment KIRLRPGGKKKYKLKHIVWASRELERFAVN in this vaccine construct.

HXB2 Location p17 (41–51)
Author Location p17 (41–51 B consensus)
Epitope LERFAVNPGLL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*1302)
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This core epitope, LERFAVNPGLL, was found to bind to 1/8 HLA-DR proteins tested, DRB*1302.

HXB2 Location p17 (41–55)
Author Location Gag (41–55 HXB-2)
Epitope LERFAVNPGLLETSE
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DQB1*0301, DQB1*0601, DRB1*1303, DRB1*1502, DRB3*0101, DRB5*0102
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

HXB2 Location p17 (42–51)
Author Location p17 (B consensus)
Epitope ERFAVNPGLL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB3*0202, DRB3*0301)
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), immunodominance
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This epitope was in the overlap between 2 highly reactive peptides, and was fine mapped; 2 different presenting alleles for 2 different clones were determined, and found to be DRB3*0202, DRB3*0301.

HXB2 Location p17 (42–56)
Author Location p17 (274–289)
Epitope ERFALNPSLLETAEG

T-Helper CD4+

Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag
Species (MHC) human
Assay type proliferation, CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords vaccine antigen design
References Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.
- 4/8 subjects responded to this epitope.

HXB2 Location p17 (42–58)
Author Location p17 (42–58 B consensus)
Epitope `ERFAVNPGLLETSEGCR`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101, DRB1*0405, DRB1*1101, DRB1*1302)
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), immunodominance
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 28% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The peptides that were recognized by the most people were able to bind broadly to multiple HLA-DR molecules. This peptide showed high cross-reactive binding capacity and bound to 4/8 tested HLA-DR molecules.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p17 (48–58)
Author Location Gag (53–63)
Epitope `PGLLETSEGCK`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was not detectable.

HXB2 Location p17 (70–86)
Author Location p17 (70–86 B Consensus)
Epitope `TGSEELRSLYNTVATLY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p17 (71–85)
Author Location p17 (302–316)
Epitope `TSEELKSLFVTVATL`
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag
Species (MHC) human
Assay type proliferation, CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords vaccine antigen design
References Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.
- 2/8 subjects responded to this epitope.

HXB2 Location p17 (73–83)
Author Location Gag (73–83)
Epitope EELRSLYNTVA
Epitope name Gag 4.3
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade *HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu
Species (MHC) macaque
Assay type T-cell Elispot, Intracellular cytokine staining
Keywords subtype comparisons, memory cells
References Amara *et al.* 2005

- Clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02_AG consensus Gag in macaques. The activity was better-conserved for CD8 than CD4 T cells.
- 3/5 CD8 epitopes and 2/8 CD4 epitopes were conserved across multiple HIV-1 clades. All 5 CD8, and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation.
- EELRSLYNTVA was not reported for human infections.
- The response elicited to the B clade epitope EELRSLYNTVA does not cross-react with the CRF02_AG form EEfkSLYNiVA. The epitope is however conserved across clades A,B,C,D,F.

HXB2 Location p17 (73–89)
Author Location p17 (73–89 clade B consensus)
Epitope EELRSLYNTVATLYCVH
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (DRB1*0101, DRB1*0401, DRB1*0405, DRB1*0701, DRB1*1101, DRB1*1302, DRB1*1501)
Country Brazil
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 brazilian HIV-1 chronically infected individuals.
- While the reacting peptide is EELRSLYNTVATLYCVH, shorter LRSLYNTVATLYC is the predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

HXB2 Location p17 (75–89)
Author Location p17 (306–320)
Epitope LKSLFNTVATLYCVH
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag
Species (MHC) human
Assay type proliferation, CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords vaccine antigen design
References Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.
- 2/8 subjects responded to this epitope.

HXB2 Location p17 (77–91)
Author Location Gag (77–91 HXB-2)
Epitope SLNTVATLYCVHQR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

HXB2 Location p17 (77–94)
Author Location p17 (77–94 B consensus)
Epitope SLYNTVATLYCVHQRIEV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101, DRB1*0401, DRB1*0405, DRB1*0701, DRB1*1302, DRB5*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

T-Helper CD4+

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This peptide was recognized by 25% of the study group.
- The peptides that were recognized by the most people were able to bind broadly to multiple HLA-DR molecules. This peptide showed high cross-reactive binding capacity and bound to 6/8 common HLA-DR molecules.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p17 (77–94)
Author Location p17 (77–94)
Epitope SLYNTVATLYCVHQRIEV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Netherlands
Assay type Cytokine production
References Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. SLYNTVATLYCVHQRIEV had fixation of 1 mutation (SLYNT[v/i]ATLYCVHQRIEV) in 1 of the patients.

HXB2 Location p17 (82–92)
Author Location Gag (87–97)
Epitope VATLYCVHAGI
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was detectable.

HXB2 Location p17 (93–107)
Author Location p17 (93–107 IIIB, B10)
Epitope EIKDTKEALDKIEEE
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location p17 (118–132)
Author Location p17 (118–132 IIIB, B10)
Epitope AAADTGHSSQVSQNY
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

III-B-2 Gag p17-p24 Helper/CD4+ T-cell epitopes

HXB2 Location p17-p24 (131–18)
Author Location Gag (131–150 LAI)
Epitope NYPIVQNIQGQMVHQAISPR
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other
Species (MHC) transgenic mouse (DR1)
Country France
Assay type proliferation, CD4 T-cell Elispot - IFNγ, Chromium-release assay
Keywords computational epitope prediction, Th1
References Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQNANPDCKTILKALGPA, KTILKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTILKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQNANPDCKTILKALGPA, NKIVRMYSPTSILDIRQGPK.

HXB2 Location p17-p24 (131–18)
Author Location Gag (131–150 HXB2)
Epitope NYPIVQNIQGQMVHQAISPR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human

T-Helper CD4+

Donor MHC DRB1*1302, DRB1*1503; DRB1*0701, DRB1*1601
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 20-mer peptides were compared with autologous sequences in 9 chronic unteated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.

III-B-3 Gag p24 Helper/CD4+ T-cell epitopes

HXB2 Location p24 (1–9)
Author Location p24 (133–141 HXB2)
Epitope `PIVQNIQGQ`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101)
Donor MHC DQ1, DQ5, DR51, DRB1*0101, DRB1*1501
Assay type proliferation, T-cell Elispot, Intracellular cytokine staining
Keywords HAART, ART
References Boritz *et al.* 2003

- HIV infected individuals with advanced disease often have only weak or undetectable HIV specific Th responses, and HAART can sometimes restore Th HIV recognition in such cases. The repertoire of Th responses to p24 in an individual who responded to HAART after having a CD4+ T-cell count of 0 cells ul was determined. Eleven clonotypes were found among 13 clones, recognizing eight distinct epitopes, with a range of MHC affinities and functional avidities. Multiple Gag p24 peptides were also recognized using CD4 Elispot assays based on samples from six additional HAART-treated CD4 T-cell-reconstituted subjects.
- The TCR that recognized this epitope used Vβ5.1.

HXB2 Location p24 (1–11)
Author Location p24 (1–11 SF2)
Epitope `PIVQNLQGQMV`
Immunogen HIV-1 infection
Species (MHC) human (DR1)
Keywords escape
References Harcourt *et al.* 1998

- 43 asymptomatic HIV+ individuals were screened for proliferative responses to HIV – 12 showed a response, and dominant epitopes were mapped for two individuals, one in p24 and one in p17.
- Out of five truncated versions of peptide PIVQNLQGQMVHQAISPRTL, only p24(1-11) elicited a proliferative response.
- Nine naturally occurring variants of this epitope were found within the individual who made this response – all bound to HLA-DR1, but three did not stimulate the CD4+ T-cell line that recognized the index peptide, suggestive of immune escape.

HXB2 Location p24 (1–15)
Author Location p24 (133–147 IIIB, B10)
Epitope `PIVQNIQGQMVHQAI`
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- Peptides were identified that commonly evoke T-cell responses – 62% of 90 HIV+ people had a T-cell response to this peptide.

HXB2 Location p24 (1–22)
Author Location p24 (133–154 SF2)
Epitope `PIVQNIQGQMVHQAISPRTLNA`
Immunogen HIV-1 infection
Species (MHC) human
References Rosenberg *et al.* 1997

- While anti-HIV CD4 Th responses are characteristically undetectable in chronic infections, strong p24-specific proliferative responses were inversely correlated with low viral load in 10 chronically infected people.
- The dominant proliferative response in one of two long term survivors was to this peptide.

HXB2 Location p24 (7–21)
Author Location Gag (171–185)
Epitope `QGQMVHQAISPRTLN`
Epitope name Gag 171
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Keywords subtype comparisons
References Wilson *et al.* 2001

- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
- This epitope binds to nine HLA-DR alleles: DRB1*0101, DRB1*1501, DRB1*0401, DRBI*0405, DRB1*1302, DRB1*0701, DRB1*0901, DRB5*0101 and DRB4*0101 with an IC_{50} threshold below 1,000 nM.
- This epitope sequence is conserved in 52% of clade B isolates.
- 7/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

HXB2 Location p24 (7–21)
Author Location p24 (171–185)
Epitope `QGQMVHQAISPRTLN`
Epitope name Gag1
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Country United Kingdom
Assay type proliferation, Intracellular cytokine staining
Keywords supertype, rate of progression

T-Helper CD4+

References Boaz *et al.* 2003

- Proliferative and cytokine (IFNgamma and Il-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNPs (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive.
- Gag-specific CD4+ T cells in LTNPs showed increased numbers of IFN gamma and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFNgamma, levels were correlated with proliferation.
- Gag1 was 1 of 3 peptides that had a negative correlation between absolute number of responding cells and viral load.

HXB2 Location p24 (7–21)
Author Location Gag (171–185)
Epitope QGQMVHQAISPRTLN
Epitope name Gag 171
Immunogen vaccine
Vector/Type: DNA with CMV promotor, peptide *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (DR, I-A^{b})
Donor MHC H-2b
Keywords vaccine-specific epitope characteristics, immunodominance
References Livingston *et al.* 2002

- 4 Th HIV epitopes presented by HLA-DR molecules were identified that also could be presented by murine class II molecule I-Ab, enabling testing of vaccine strategies in H-2b mice.
- Responses to pooled peptides, polyepitope peptides in a linear construct or in a branched MAP construct, and a DNA polyepitope construct with a CMV promoter were compared. A linear arrangement in polyepitope construct created a junctional epitope that could be disrupted with the addition of GPGPG spacers. The linear polyepitope construct with the GPGPG spacer worked well in terms of eliciting responses to all 4 peptides, using either DNA or protein for the vaccination.

HXB2 Location p24 (9–26)
Author Location p24 (9–26 B Consensus)
Epitope QMVHQAISPRTLNAWVKV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p24 (11–26)
Author Location p24 (143–157)
Epitope VHQAISPRTLNAWVKC
Immunogen in vitro stimulation or selection
Species (MHC) human
References Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.
- Matches 3/3 anchor residues for HLA DR: **V**HQA**I**SPR**T**

HXB2 Location p24 (11–30)
Author Location Gag (143–152 SF2)
Epitope VHQAISPRTLNAWVKVVEEK
Immunogen vaccine
Vector/Type: Listeria monocytogenes *Strain:* B clade SF2 *HIV component:* p24 Gag
Species (MHC) mouse (H-2^{b}, H-2^{d})
Keywords immunodominance, Th1
References Mata & Paterson 1999

- *Listeria monocytogenes* is an intracellular bacterium that lives in the cytoplasm and generates a cell-mediated immune response.
- *L. monocytogenes* vaccine expressing HIV-1 p24 protein (Lm-Gag) was used to stimulate gag-specific CD4+ T cell proliferative responses in BALB/c(H-2d) and C57BL/6(H-2b) mice.
- 2/3 reactive p24 peptides (out of 22 overlapping peptides that span p24) were recognized by both murine strains; this epitope is immunodominant in C57BL/6 mice and also can stimulate a BALB/c response.
- The proliferative response is due to CD4+ IFN-γ-producing cells, a Th1 response.

HXB2 Location p24 (11–30)
Author Location p24 (143–162 HXB2)
Epitope VHQAISPRTLNAWVKVVEEK
Subtype B
Immunogen vaccine
Vector/Type: Listeria monocytogenes *Strain:* B clade HXB2 *HIV component:* Gag
Species (MHC) mouse (H-2^{b}, H-2^{d})

References Mata & Paterson 1999

- BALB/c and C57BL/6 mice were immunized with *Listeria monocytogenes* (Lm-Gag) expressing HIV-1 HXB2 Gag.
- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm; secreted *L. monocytogenes* antigens are processed and presented by both class I and class II pathways.
- The class II Th response was probed using 20mer peptides that overlapped by 10; the peptides VHQAISPRTL-NAWVKVVEEK and FRDYVDRFYKTLRAEQASQD were recognized in H-2^b and H-2^d mice.

HXB2 Location p24 (19–38)
Author Location Gag (151–170 HXB2)
Epitope TLNAWVKVVEEKAFSPEVIP
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DRB1*0405, DRB1*0701; DRB1*1302, DRB1*1503; DRB1*0701, DRB1*1601
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic unteated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.
- 1/3 responding patients had autologous sequence exactly matching this peptide.

HXB2 Location p24 (21–35)
Author Location Gag (153–167 SF2)
Epitope NAWVKVVEEKAFSPE
Epitope name Peptide 39
Subtype B
Immunogen vaccine
Vector/Type: protein-Ab complex *Strain:* B clade IIIB *HIV component:* Gag, Tat *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse (H-2^d)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes
References Cellini *et al.* 2008

- In order to increase the known number of epitopes in Gag protein so that they can be assayed for reactivity in vaccine studies, BALB/c mice were inoculated with Gag or Gag+Tat. OLPs were used to elicit T-cell immune responses from mouse splenocytes, tested for by cytotoxicity or ELISpot assays. 5 novel predicted optimal CTL epitopes, 2 novel predicted CD4 epitopes and 2 immune response eliciting peptides were found.
- Peptide NAWVKVVEEKAFSPE contains a Gag CD4 epitope.

HXB2 Location p24 (21–35)
Author Location Gag (153–167)
Epitope NAWVKVVEEKAFSPE
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Mice immunized with Gag and Tat responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- This peptide epitope was recognized by mice co-immunized with Gag and Tat, but not by mice immunized with Gag alone.

HXB2 Location p24 (21–36)
Author Location p24 (153–167)
Epitope NAWVKVVEEKAFSPEC
Immunogen in vitro stimulation or selection
Species (MHC) human
References Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.

HXB2 Location p24 (22–36)
Author Location p24 (22–36)
Epitope AWVKVIEEKAFSPEV
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag
Species (MHC) human
Assay type proliferation, CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords vaccine antigen design
References Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.
- 2/8 subjects responded to this epitope.

HXB2 Location p24 (23–40)
Author Location p24 (23–40 B Consensus)
Epitope WVKVVEEKAFSPEVIPMF
Subtype B
Immunogen HIV-1 infection

Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p24 (23–40)
Author Location p24 (23–40)
Epitope `WKVVEEKAFSPEVIPMF`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Netherlands
Assay type Cytokine production
References Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. WKVVEEKAFSPEVIPMF had fixation of 2 mutations WKV[v/i]EEKAF[s/n]PEVIPMF in 1 of the patients.

HXB2 Location p24 (25–39)
Author Location
Epitope `KVVEEKAFSPEVIPM`
Epitope name G040
Immunogen HIV-1 infection
Species (MHC) human
Country Canada
Assay type proliferation, Flow cytometric T-cell cytokine assay
Keywords memory cells
References Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN-γ, but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN-γ only-producing cells are short lived.

HXB2 Location p24 (28–36)
Author Location p24 (160–168 HXB2)
Epitope `EEKAFSPEV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101)
Donor MHC DQ1, DQ5, DR51, DRB1*0101, DRB1*1501
Assay type proliferation, T-cell Elispot, Intracellular cytokine staining
Keywords HAART, ART
References Boritz *et al.* 2003

- HIV infected individuals with advanced disease often have only weak or undetectable HIV specific Th responses, and HAART can sometimes restore Th HIV recognition in such cases. The repertoire of Th responses to p24 in an individual who responded to HAART after having a CD4+ T-cell count of 0 cells ul was determined. Eleven clonotypes were found among 13 clones, recognizing eight distinct epitopes, with a range of MHC affinities and functional avidities. Multiple Gag p24 peptides were also recognized using CD4 Elispot assays based on samples from six additional HAART-treated CD4 T-cell-reconstituted subjects.
- The TCR that recognized this epitope used Vβ2.

HXB2 Location p24 (28–38)
Author Location p24 (HXB2)
Epitope `EEKAFSPEVIP`
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DQ5)
Assay type CD4 T-cell Elispot - IFNγ
Keywords epitope processing, vaccine antigen design
References SenGupta *et al.* 2004

- Multiple HLA calss I-restricted and class II-restricted T-cell epitopes were shown to be processed and presented from an exogenously added HIV-1 gag-p24 peptide complexed to a heat shock protein. T-cell recognition of the complex was shown to be inhibited by brefeldin A indicating an endoplasmic reticulum-dependent pathway.

HXB2 Location p24 (28–38)
Author Location p24 (161–171 NY-5)
Epitope `EEKAFSPEVIP`
Epitope name EP11
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DQ5)
Donor MHC DQ3, DQ5, DR11, DR14, Drw52
Country United States

T-Helper CD4+

Assay type proliferation, CD4 T-cell Elispot - IFNγ, Chromium-release assay
Keywords subtype comparisons, rate of progression, acute/early infection, early treatment, variant cross-recognition or cross-neutralization
References Norris *et al.* 2004

- 5 CD4-T cell epitopes in Gag-p24 were studied, and a minimum epitope length of 6-16 amino acids was found to be required for CD4+ T cell proliferation. Cross-clade recognition was found to be impaired in 17/32 variants tested.
- Patient AC-01, who was infected with HIV-1 in 1997, recognized this epitope and epitope EPRGSDIAGT during acute infection, and 19 months post-initiation of ART therapy started during primary infection.
- The epitope EEKAFSPEVIP is highly conserved in B clade. Common variants from other clades were tested and all had markedly diminished responses, including eeRafspevip, eekaLspevip, and eDkafspevip (all found in clade A); eekGfspevip, eekGfNpevip (clades A and CRF01_AE); eekafspeIip (clade C); eekafNpevip (clade D).
- Minimum length peptides for the epitopes studied were not particularly optimal, and peptides longer than the minimum, up to 22 amino acids, were often as potent, in marked contrast to CD8+ T-cell responses.

HXB2 Location p24 (29–48)
Author Location Gag (161–180 HXB2)
Epitope `EKAFSPEVIPMFSALSEGAT`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DRB1*0701, DRB1*1601
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic unteated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.
- Responding patient had autologous sequence exactly matching this peptide.

HXB2 Location p24 (31–41)
Author Location Gag (171–181)
Epitope `AFSPEVIPMFT`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was detectable.

HXB2 Location p24 (31–46)
Author Location p24 (163–177)
Epitope `AFSPEVIPMFSALSEC`
Immunogen in vitro stimulation or selection
Species (MHC) human
References Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.
- Peptide contains a CTL epitope identified in HIV-positive patients.
- Peptide binds to HLA A*0201 and causes regulation of class I expression on T2 cells.
- Matches 3/3 anchor residues for HLA DR: **V**IPMF**S**AL**S**

HXB2 Location p24 (31–47)
Author Location p24 (31–47 B Consensus)
Epitope `AFSPEVIPMFSALSEGA`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p24 (31–48)
Author Location p24 (31–48)
Epitope `AFSPEVIPMFSALSEGAT`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Netherlands
Assay type Cytokine production
References Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. AFSPEVIPMFSALSEGAT had fixation of 2 mutations (AF[s/n]PEVIPMF[s/t]ALSEGAT) in 1 of the patients.

HXB2 Location p24 (31–50)
Author Location Gag (164–183)
Epitope `AFSPEVIPMFSALSEGATPQ`
Epitope name p24.4
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0401)
Assay type Tetramer binding
Keywords assay standardization/improvement
References Scriba *et al.* 2005a

- Conditions required for optimal HLA class II tetramer staining of DR1- and DR4-restricted CD4+ T cells were studied. Staining was rapid and efficient and did not require internalization. Ultrasensitive detection of rare CD4+ T cells was performed by combining tetramer staining with magnetic bead enrichment, and level of detection was much higher than by standard flow-cytometric techniques.

HXB2 Location p24 (31–52)
Author Location p24 (163–184 SF2)
Epitope `AFSPEVIPMFSALSEGATPQDL`
Immunogen HIV-1 infection
Species (MHC) human
References Rosenberg *et al.* 1997

- Low viral load correlated with strong HIV-1-specific proliferative response.
- A proliferative response to this epitope was detected in two long term survivors.

HXB2 Location p24 (33–45)
Author Location p24 (33–45 clade B consensus)
Epitope `SPEVIPMFSALSE`
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (DRB1*0101, DRB1*0301, DRB1*0401, DRB1*0405, DRB1*1101, DRB1*1501)
Country Brazil
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 brazilian HIV-1 chronically infected individuals.
- While the reacting peptide is SPEVIPMFSALSE, shorter VIPMFSALSE was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

HXB2 Location p24 (34–49)
Author Location p24 (HXB2)
Epitope `PEVIPMFSALSEGATP`
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DR1)
Assay type CD4 T-cell Elispot - IFNγ
Keywords epitope processing, vaccine antigen design, characterizing CD8+ T cells
References SenGupta *et al.* 2004

- Multiple HLA class I-restricted and class II-restricted T-cell epitopes were shown to be processed and presented from an exogenously added HIV-1 gag-p24 peptide complexed to a heat shock protein. T-cell recognition of the complex was shown to be inhibited by brefeldin A indicating an endoplasmic reticulum-dependent pathway.

HXB2 Location p24 (34–49)
Author Location p24 (168–177 NY-5)
Epitope `PEVIPMFSALSEGATP`
Epitope name PP16
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DR1)
Donor MHC DQ5, DQ7, DR1, DR11, DRw52
Country United States
Assay type proliferation, CD4 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression, acute/early infection, early treatment, variant cross-recognition or cross-neutralization
References Norris *et al.* 2004

- 5 CD4-T cell epitopes in Gag-p24 were studied, and a minimum epitope length of 6-16 amino acids was found to be required for CD4+ T-cell proliferation. Cross-clade recognition was studied and found to be impaired in 17/32 variants tested.
- Patient AC-25 was an acute seroconvertor at the time of sampling, infected with HIV-1 in 1998, and given ARVs during primary infection. The study subject was resampled 18 months after initiation of therapy.
- Natural variants of the epitope PEVIPMFSALSEGATP diminished the level of the response, including pevipmfPalsegStp and pevipmfsalsegStp, found in CRF01_AE; peIipmfTalsegatp, clade C; pevipmfsalSegatp, clade B; pevipmfTalsegatp, clades A, B and C; and pevipVfsalsegatp, clade A.
- Minimum length peptides for the epitopes studies were not particularly optimal, and peptides longer than the minimum, up to 22 amino acids, were often as potent, in marked contrast to CD8+ T-cell responses.

HXB2 Location p24 (34–49)
Author Location p24
Epitope `PEVIPMFSALSEGATP`
Epitope name PP16
Immunogen HIV-1 infection

T-Helper CD4+

Species (MHC) human (DR1)
Assay type proliferation, Tetramer binding, CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords binding affinity, escape, optimal epitope, antagonism
References Norris *et al.* 2006

- This study demonstrates a mechanism of antagonism by a peptide shorter than the minimum length epitope for an HIV p24-specific CD4+ T-cell clone.
- Truncation of the peptide from PEVIPMFSALSEGATP (PP16) to PEVIPMFSALSEG (PG13) rendered the peptide unable to elicit proliferation, IFN-γ release, or serine esterase release, even though it retained strong binding to MHC.
- Although both the original and truncated peptide-MHC complexes bound TCR clone, PEVIPMFSALSEGATP-DR1 tetramer bound with higher avidity than PEVIPMFSALSEG-DR1 tetramer, suggesting that tighter association of the peptide-MHC complex with the TCR is associated with the extent of T-cell activation.
- G/P substitution in the original full-length peptide (PEVIPMFSALSE[g/p]ATP) led to complete loss of agonist activity, and PEVIPMFSALSEpATP became antagonistic.

HXB2 Location p24 (35–44)
Author Location p24 (HXB2)
Epitope `EVIPMFSALS`
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DR4)
Assay type CD4 T-cell Elispot - IFNγ
Keywords epitope processing, vaccine antigen design, characterizing CD8+ T cells
References SenGupta *et al.* 2004

- Multiple HLA calss I-restricted and class II-restricted T-cell epitopes were shown to be processed and presented from an exogenously added HIV-1 gag-p24 peptide complexed to a heat shock protein. T-cell recognition of the complex was shown to be inhibited by brefeldin A indicating an endoplasmic reticulum-dependent pathway.

HXB2 Location p24 (35–44)
Author Location p24 (168–177 NY-5)
Epitope `EVIPMFSALS`
Epitope name ES10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DR4)
Donor MHC DQ3, DQ6, DR15, DR4, DRw51, DRw53
Country United States
Assay type proliferation, CD4 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression, acute/early infection, early treatment, variant cross-recognition or cross-neutralization
References Norris *et al.* 2004

- 5 CD4-T cell epitopes in Gag-p24 were studied, and a minimum epitope length of 6-16 amino acids was found to be required for CD4+ T-cell proliferation. Cross-clade recognition was studied and found to be impaired in 17/32 variants tested.
- Patient 161J, infected with HIV-1 in the mid 1980s, was 1 of the 2 LTNPs examined. 161J was ART naive.
- Natural variants of the epitope EVIPMFSALS gave diminished responses including evipmfTals, common in clades A, B and C; and evipVfsals, clade A; evipmfsalA, a clade B variant; and eIipmfTals, clade C. The exception was the CRF01_AE variant evipmfPals, which was as reactive as the original peptide tested.
- Minimum length peptides for the epitopes studies were not particularly optimal, and peptides longer than the minimum, up to 22 amino acids, were often as potent, in marked contrast to CD8+ T-cell responses.

HXB2 Location p24 (35–44)
Author Location p24 (167–176 HXB2)
Epitope `EVIPMFSALS`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101)
Donor MHC DQ1, DQ5, DR51, DRB1*0101, DRB1*1501
Assay type proliferation, T-cell Elispot, Intracellular cytokine staining
Keywords HAART, ART
References Boritz *et al.* 2003

- HIV infected individuals with advanced disease often have only weak or undetectable HIV specific Th responses, and HAART can sometimes restore Th HIV recognition in such cases. The repertoire of Th responses to p24 in an individual who responded to HAART after having a CD4+ T-cell count of 0 cells ul was determined. Eleven clonotypes were found among 13 clones, recognizing eight distinct epitopes, with a range of MHC affinities and functional avidities. Multiple Gag p24 peptides were also recognized using CD4 Elispot assays based on samples from six additional HAART-treated CD4 T-cell-reconstituted subjects.

HXB2 Location p24 (38–48)
Author Location Gag (178–188)
Epitope `PMFTALSEGAT`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was not detectable.

HXB2 Location p24 (39–58)
Author Location Gag (171–190 HXB2)
Epitope `MFSALSEGATPQDLNTMLNT`
Subtype B

T-Helper CD4+

Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DRB1*1302, DRB1*1503
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic unteated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.
- Responding patient had autologous sequence exactly matching this peptide.

HXB2 Location p24 (41–56)
Author Location p24 (173–187)
Epitope `SALSEGATPQDLNTMC`
Immunogen in vitro stimulation or selection
Species (MHC) human
References Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.

HXB2 Location p24 (48–62)
Author Location p24 (180–194)
Epitope `TPQDLNTMLNTVGGH`
Immunogen HIV-1 infection
Species (MHC) human
References Adams *et al.* 1997

- One of four immunogenic Gag peptides used in study of proliferative response to p24.
- Homology to an SIV epitope recognized by macaque T-cells.
- T-cells from 8 of 19 HIV+ individuals responded to this epitope.
- Improved assay system (increase in culture time to 8 days and addition of IL-2 to cultures) gave increased detection of proliferative response.

HXB2 Location p24 (49–63)
Author Location Gag (181–195 HXB2)
Epitope `PQDLNTMLNTVGGHQ`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DRB1*1302, DRB1*1503
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic unteated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.
- Responding patient had autologous sequence exactly matching this peptide.

HXB2 Location p24 (49–64)
Author Location p24 (49–64)
Epitope `PQDLNMMLNIVGGHQA`
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag
Species (MHC) human
Assay type proliferation, CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords vaccine antigen design
References Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.
- 2/8 subjects responded to this epitope.

HXB2 Location p24 (49–71)
Author Location
Epitope `PQDLNMMLNIVGGHQAAMQMLKD`
Epitope name HIV-VAX-1045
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 2/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was LNIVGGHQA.

HXB2 Location p24 (51–66)
Author Location p24 (183–197)
Epitope `DLNTMLNTYGGHQAAC`
Immunogen in vitro stimulation or selection
Species (MHC) human
References Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.

HXB2 Location p24 (51–82)
Author Location Gag (183–214 LAI)
Epitope `DLNTMLNTVGGHQAAMQMLKETINEEAAEWDR`
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide
Species (MHC) human
References Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.

T-Helper CD4+

- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 2/10 reacted to this peptide.
- 9/12 tested mounted a CTL responses to at least one of the six peptides, each of the six peptides elicited a CTL response in at least one individual.
- None of the 12 tested had an IgG response to this peptide.

HXB2 Location p24 (53–66)
Author Location Gag (49–51)
Epitope NTMLNTVGGHQAAM
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was not detectable.

HXB2 Location p24 (59–78)
Author Location Gag (191–210 HXB2)
Epitope VGGHQAAMQMLKETINEEAA?
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DRB1*1302, DRB1*1503
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic unteated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.
- Responding patient had autologous sequence exactly matching this peptide.

HXB2 Location p24 (69–88)
Author Location p24 (201–220 IIIB)
Epitope LKETINEEAAEWDRVHPVHA
Epitope name P21
Immunogen in vitro stimulation or selection
Species (MHC) human (DR)
Donor MHC DQ2, DQ3, DR4, DR7
Keywords immunodominance, Th1, Th2, TCR usage
References Venturini *et al.* 2002

- PBMC from a seronegative donor, the healthy brother of a pair of monozygotic twins discordant for HIV-1 infection, were used to generate HIV-1 Gag-specific CD4+ T-cell clones by *in vitro* immunization with HIV-1 overlapping 20mer peptides spanning p55. Six clones were generated by limiting dilution. All reacted with p24 except one which recognized a p24 peptide and a p6 peptide. All CD4+ T cell clones were HLA class II DR restricted.
- Clone 85 recognized this peptide using TCR Vβ 8 and 18; the two TCR receptors indicates this limiting dilution represents a mixed population. This clone was only activated by peptide, not by processed protein from vaccinia virus Gag-infected B-LCL.

HXB2 Location p24 (69–88)
Author Location Gag (201–220 HXB2)
Epitope LKETINEEAAEWDRVHPVHA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DRB1*1302, DRB1*1503; DRB1*0405, DRB1*0701
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic unteated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.

HXB2 Location p24 (71–86)
Author Location p24 (203–220)
Epitope ETINEEAAEWDRVHPC
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human
References Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.

HXB2 Location p24 (71–88)
Author Location p24 (203–220 HXB2)
Epitope ETINEEAAEWDRVHPVHA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101)
Donor MHC DQ1, DQ5, DR51, DRB1*0101, DRB1*1501
Assay type proliferation, T-cell Elispot, Intracellular cytokine staining
Keywords HAART, ART
References Boritz *et al.* 2003

- HIV infected individuals with advanced disease often have only weak or undetectable HIV specific Th responses, and HAART can sometimes restore Th HIV recognition in such cases. The repertoire of Th responses to p24 in an individual who responded to HAART after having a CD4+ T-cell count of 0 cells/ul was determined. Eleven clonotypes were found

T-Helper CD4+

among 13 clones, recognizing eight distinct epitopes, with a range of MHC affinities and functional avidities. Multiple Gag p24 peptides were recognized using CD4 Elispot assays based on samples from six additional HAART-treated CD4 T-cell-reconstituted subjects.

- The Th clone that recognized this epitope utilized TCR Vβ17.

HXB2 Location p24 (71–92)
Author Location p24 (203–224 HXB2)
Epitope ETINEEAAEWDRVHPVHAGPIA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101)
Donor MHC DQ1, DQ5, DR51, DRB1*0101, DRB1*1501
Assay type proliferation, T-cell Elispot, Intracellular cytokine staining
Keywords HAART, ART
References Boritz *et al.* 2003

- HIV infected individuals with advanced disease often have only weak or undetectable HIV specific Th responses, and HAART can sometimes restore Th HIV recognition in such cases. The repertoire of Th responses to p24 in an individual who responded to HAART after having a CD4+ T-cell count of 0 cells/ul was determined. Eleven clonotypes were found among 13 clones, recognizing eight distinct epitopes, with a range of MHC affinities and functional avidities. Multiple Gag p24 peptides were recognized using CD4 Elispot assays based on samples from six additional HAART-treated CD4 T-cell-reconstituted subjects.

HXB2 Location p24 (73–83)
Author Location Gag (205–215)
Epitope INEEAAEWDRV
Epitope name Gag 11.2
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade *HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu
Species (MHC) macaque
Assay type T-cell Elispot, Intracellular cytokine staining
Keywords subtype comparisons, memory cells
References Amara *et al.* 2005

- Clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02_AG consensus Gag in macaques. The activity was better-conserved for CD8 than CD4 T cells.
- 3/5 CD8 epitopes and 2/8 CD4 epitopes were conserved across multiple HIV-1 clades. All 5 CD8, and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation.
- CD4 T-cell epitope previously reported for human is ETINEEAAEWDRVHPC. HLA restriction: DRB1*03, DRB1*0101.
- The response elicited to the B clade epitope INEEAAEWDRV does not cross-react with the CRF02_AG form INdEAAEWDRV. The epitope is however conserved in CRF01_AE and CRF02_AG consensus sequences. Other clades tend to have L in the last position (INEEAAEWDR[v/l]).

HXB2 Location p24 (73–83)
Author Location Gag (208–218)
Epitope INEEAAEWDRL
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was not detectable.

HXB2 Location p24 (73–97)
Author Location p24 (205–229 PV22)
Epitope INEEAAEWDRVHPVHAGPIAPGQMR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*03)
Donor MHC A29, A30, B35, B8, DRB1*03, DRB1*13
Keywords HAART, ART, Th1, Th2, TCR usage
References Lotti *et al.* 2002

- 10/49 chronically HIV-1 infected patients had low p55-Gag-specific CD4+ T cell responses prior to therapy, and these responses remained unchanged 3 and 6 months after initiation of HAART. There was no difference in level of response in those with or without a detectable p55 response.
- For one individual, patient F45 CDC stage A2, CD4+ p55 responding clones were generated. Her response was consistently strong and heterogeneous in terms of HLA restriction and Vβ usage, and some clones had a Th1 cytokine secretion profile (high IFNgamma production) while some had a Th2 profile (high IL-4 and IL-5 production). 5/10 CD4+ clones could also induce cytotoxicity.
- 4/10 clones from patient F45 had their epitopes mapped using overlapping peptides. Clone 12 recognized this peptide sequence restricted by DRB1*03 using TCR Vβ 22. This clone had a SI of 12.4 to p55, 49.6 to peptide, secreted low levels of IFNgamma, indicative of a Th1 response. Clone 12 had cytotoxic activity, mediated through both a perforin and a Fas-based pathway.

HXB2 Location p24 (76–85)
Author Location p24 (208–217)
Epitope EAAEWDRVHP
Immunogen HIV-1 infection
Species (MHC) human
References Adams *et al.* 1997

- One of four immunogenic Gag peptides used in study of the proliferative response to p24.

T-Helper CD4+

- T-cells from 11 of 24 HIV+ individuals responded to this epitope.
- Improved assay system (increase in culture time to 8 days and addition of IL-2 to cultures) gave increased detection of proliferative response.

HXB2 Location p24 (76–90)
Author Location p24 (208–222 IIIB, B10)
Epitope EAAEWDRVHPVHAGP
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location p24 (79–88)
Author Location p24 (211–220 HXB2)
Epitope EWDRVHPVHA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101)
Donor MHC DQ1, DQ5, DR51, DRB1*0101, DRB1*1501
Assay type proliferation, T-cell Elispot, Intracellular cytokine staining
Keywords HAART, ART
References Boritz *et al.* 2003

- HIV infected individuals with advanced disease often have only weak or undetectable HIV specific Th responses, and HAART can sometimes restore Th HIV recognition in such cases. The repertoire of Th responses to p24 in an individual who responded to HAART after having a CD4+ T-cell count of 0 cells ul was determined. Eleven clonotypes were found among 13 clones, recognizing eight distinct epitopes, with a range of MHC affinities and functional avidities. Multiple Gag p24 peptides were also recognized using CD4 Elispot assays based on samples from six additional HAART-treated CD4 T-cell-reconstituted subjects. Two clones recognized this epitope.

HXB2 Location p24 (79–98)
Author Location Gag (211–230 LAI)
Epitope EWDRVHPVHAGPIAPGQMRE
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other
Species (MHC) transgenic mouse (DR1)
Country France
Assay type proliferation, CD4 T-cell Elispot - IFNγ, Chromium-release assay
Keywords computational epitope prediction, Th1
References Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQNANPDCKTILKALGPA, KTILKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTILKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQNANPDCKTILKALGPA, NKIVRMYSPTSILDIRQGPK.

HXB2 Location p24 (79–98)
Author Location Gag (211–230 HXB2)
Epitope EWDRVHPVHAGPIAPGQMRE
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DRB1*0405, DRB1*0701; DRB1*0301, DRB1*0401; DRB1*0901, DRB1*1202; DRB1*0701, DRB1*1601
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic unteated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.

HXB2 Location p24 (81–95)
Author Location p24 (215–229 SF2)
Epitope DRVHPVHAGPIAPGQ
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *Strain:* B clade SF2 *HIV component:* p24 Gag
Species (MHC) macaque
References Mills *et al.* 1990

- Responses to 3 T-cell and multiple linear B-cell epitopes were found in vaccinated macaques.

HXB2 Location p24 (81–102)
Author Location p24 (213–234 SF2)
Epitope DRVHPVHAGPIAPGQMREPRGS
Immunogen HIV-1 infection
Species (MHC) human
References Rosenberg *et al.* 1997

- While anti-HIV CD4 Th responses are characteristically undetectable in chronic infections, strong p24-specific proliferative responses were inversely correlated with low viral load in 10 chronically infected people.
- The dominant proliferative response in one of two long term survivors was to this peptide.

HXB2 Location p24 (81–102)
Author Location p24 (81–102)
Epitope DRVHPVHAGPIAVPGQMREPRGS

T-Helper CD4+

Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Netherlands
Assay type Cytokine production
References Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. DRVHPVHAGPIAVPGQMREPRGS had fixation of 1 mutation (DRVHPVHAGPI[a/p]VPGQMREPRGS) in 1 of the patients.

HXB2 Location p24 (82–92)
Author Location Gag (217–227)
Epitope `RLHPVHAGPIA`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was not detectable.

HXB2 Location p24 (85–99)
Author Location
Epitope `PVHGPIAPGQMREP`
Epitope name G055
Immunogen HIV-1 infection
Species (MHC) human
Country Canada
Assay type proliferation, Flow cytometric T-cell cytokine assay
Keywords memory cells
References Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN-γ, but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN-γ only-producing cells are short lived.

HXB2 Location p24 (86–94)
Author Location p24 (NY5)
Epitope `VHAGPIAPG`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DQ7)
Keywords HAART, ART, supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection, cross-presentation by different HLA, early treatment, TCR usage
References Norris *et al.* 2001

- Gag-specific CD4+ helper T-cell clones were derived from 1 LTNP (CTS-01) and 3 individuals given therapy during acute infection, 2 before (AC-01 and AC-36) and 1 after (AC-25) STI. Gag peptide recognition induced proliferation, IFN-γ production, and perforin-mediated cytotoxicity in all CD4+ T-cell clones isolated.
- 3/23 p24-derived peptides tested induced proliferative p24-specific Th cell responses in the LTNP CTS-01. The immunodominant response was to the peptide DRVHPVHAGPIAPGQMREPRGS (81-102), and 9/10 CD4+ T-cell clones reacted with it. One was characterized in detail and used a Bβ4 TCR.
- The minimum peptide recognized by the clones from CTS-01 was VHAGPIAPG and it was restricted by HLA-DQ7.

HXB2 Location p24 (86–94)
Author Location p24 (219–227 NY-5)
Epitope `VHAGPIAPG`
Epitope name VG9
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DQ7)
Donor MHC DQ6, DQ7, DR11, DR15, DRw51, DRw52
Country United States
Assay type proliferation, CD4 T-cell Elispot - IFNγ
Keywords acute/early infection, early treatment, variant cross-recognition or cross-neutralization
References Norris *et al.* 2004

- 5 CD4-T cell epitopes in Gag-p24 were studied, and a minimum epitope length of 6-16 amino acids was found to be required for CD4+ T-cell proliferation. Cross-clade recognition was studied and found to be impaired in 17/32 variants tested.
- Patient CTS01, who was infected with HIV-1 in 1998, was an LTNP, and recognized this epitope.
- This epitope VHAGPIAPG was the most variable of the 5 epitopes studied. Only the C variant Ihagpiapg did not diminish the response. All other variations had impaired responses: vhagpVapg, found in clades A, B, C, and D; vQagpVapg,clades B, C, D; AQagpFPpg, IhagpVapg, AhagpVapg, and vQagpiP, all found in clade A; AQagpiapg, clade B; and vPagpiapg, clade C.
- Minimum length peptides for the epitopes studies were not particularly optimal, and peptides longer than the minimum, up to 22 amino acids, were often as potent, in marked contrast to CD8+ T-cell responses.

HXB2 Location p24 (87–101)
Author Location p24 (219–233 BRU)
Epitope `HAGPIAPGQMREPRG`

T-Helper CD4+

Immunogen in vitro stimulation or selection
Species (MHC) mouse (H-2^b)
References Vaslin *et al.* 1994

- Peptide G2: could prime for *in vitro* immunoproliferative responses and for subsequent IgG responses.

HXB2 Location p24 (89–108)
Author Location Gag (221–240 HXB2)
Epitope `GPIAPGQMREPRGSDIAGTT`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DRB1*0301, DRB1*0401
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic unteated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.

HXB2 Location p24 (93–107)
Author Location
Epitope `PGQMREPRGSDIAGT`
Epitope name G057
Immunogen HIV-1 infection
Species (MHC) human
Country Canada
Assay type proliferation, Flow cytometric T-cell cytokine assay
Keywords memory cells
References Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN-γ, but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN-γ only-producing cells are short lived.

HXB2 Location p24 (94–104)
Author Location Gag (229–239)
Epitope `GQMREPRGSDI`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was not detectable.

HXB2 Location p24 (96–103)
Author Location p24 (228–235 LAI)
Epitope `MREPRGSD`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

HXB2 Location p24 (96–110)
Author Location p24 (228–242 IIIB, B10)
Epitope `MREPRGSKIAGTTST`
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location p24 (98–107)
Author Location p24 (231–240 NY-5)
Epitope `EPRGSDIAGT`
Epitope name ET10
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DQ7)
Donor MHC DQ3, DQ5, DR11, DR14, Drw52
Country United States
Assay type proliferation, CD4 T-cell Elispot - IFNγ, Chromium-release assay
Keywords acute/early infection, early treatment, variant cross-recognition or cross-neutralization
References Norris *et al.* 2004

- 5 CD4-T cell epitopes in Gag-p24 were studied, and a minimum epitope length of 6-16 amino acids was found to be required for CD4+ T-cell proliferation. Cross-clade recognition was found to be impaired in 17/32 variants tested.
- Patient AC-01, who was infected with HIV-1 in 1997, recognized this epitope and epitope EPRGSDIAGT during acute infection, and 19 months post-initiation of ART therapy started during primary infection.
- This was the most variable of the 5 epitopes studied. REPRGSDIAGT natural variants were tested and did not usually diminish the response by much (rDprgsdiagt, clades B and C; and rDprgsdiagA and rGprgsdiagt, both clade C), although the CRF01_AE variant reprgAdiagt abrogated the response.
- Minimum length peptides for the epitopes studies were not particularly optimal, and peptides longer than the minimum, up to 22 amino acids, were often as potent, in marked contrast to CD8+ T cell responses. This peptide was the exception, as REPRGSDIAGTT, which is elongated by 2 amino acids compared to the minimum epitope, elicited a stronger proliferative immune response as well as IFN-γ secretion and cytolyis.

T-Helper CD4+

HXB2 Location p24 (99–118)
Author Location p24 (231–250 IIIB)
Epitope PRGSDIAGTTSTLQEQIGWM
Epitope name P24
Immunogen in vitro stimulation or selection
Species (MHC) human (DR4)
Donor MHC DQ2, DQ3, DR4, DR7
Keywords immunodominance, Th1, Th2, TCR usage
References Venturini *et al.* 2002

- PBMC from a seronegative donor, the healthy brother of a pair of monozygotic twins discordant for HIV-1 infection, were used to generate HIV-1 Gag-specific CD4+ T-cell clones by *in vitro* immunization with HIV-1 overlapping 20mer peptides spanning p55. Six clones were generated by limiting dilution. All reacted with p24 except one which recognized a p24 peptide and a p6 peptide. All CD4+ T cell clones were HLA class II DR restricted.
- Clone 6 recognized three peptides including this one with a Th1 response using TCR Vβ 6 (6s5A1N1). Sequencing TCR Vβ regions of colonies from clone 6 suggested this was a clonal population. Assays using different peptide concentrations suggest that this peptide does not carry the main epitope of this clone.

HXB2 Location p24 (99–118)
Author Location Gag (231–250 HXB2)
Epitope PRGSDIAGTTSTLQEQIGWM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DRB1*1302, DRB1*1503; DRB1*0405, DRB1*0701; DRB1*0301, DRB1*0401
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic unteated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.
- 1/3 responding patients had autologous sequence exactly matching this peptide.

HXB2 Location p24 (101–115)
Author Location p24 (235–249 SF2)
Epitope GSDIAGTTSTLQEQI
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *Strain:* B clade SF2 *HIV component:* p24 Gag
Species (MHC) macaque
References Mills *et al.* 1990

- Responses to 3 T-cell and multiple linear B-cell epitopes were found in vaccinated macaques – epitope response defined by T-cell clone.

HXB2 Location p24 (101–115)
Author Location Gag (233–247 HXB-2)
Epitope GSDIAGTTSTQEQI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DQB1*0301, DQB1*0601, DRB1*1303, DRB1*1502, DRB3*0101, DRB5*0102
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

HXB2 Location p24 (101–116)
Author Location p24
Epitope GSDIAGTTSTLQEQIC
Immunogen in vitro stimulation or selection
Species (MHC) human
References Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.

HXB2 Location p24 (106–116)
Author Location Gag (241–251)
Epitope GTTSTLQEQIA
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was not detectable.

HXB2 Location p24 (109–123)
Author Location
Epitope STLQEQIGWMTNNPP
Epitope name G061
Immunogen HIV-1 infection
Species (MHC) human
Country Canada
Assay type proliferation, Flow cytometric T-cell cytokine assay
Keywords memory cells
References Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.

T-Helper CD4+

- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN-γ, but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN-γ only-producing cells are short lived.

HXB2 Location p24 (109–128)
Author Location Gag (241–260 LAI)
Epitope STLQEQIGWMTNNPPIPVGE
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other
Species (MHC) transgenic mouse (DR1)
Country France
Assay type proliferation, CD4 T-cell Elispot - IFNγ, Chromium-release assay
Keywords computational epitope prediction, Th1
References Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQNANPDCKTILKALGPA, KTILKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTILKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQNANPDCKTILKALGPA, NKIVRMYSPTSILDIRQGPK.

HXB2 Location p24 (109–128)
Author Location p24 (241–260 IIIB)
Epitope STLQEQIGWMTNNPPIPVGE
Epitope name P25
Immunogen in vitro stimulation or selection
Species (MHC) human
Donor MHC DQ2, DQ3, DR4, DR7
Keywords immunodominance, Th1, Th2, TCR usage
References Venturini *et al.* 2002

- PBMC from a seronegative donor, the healthy brother of a pair of monozygotic twins discordant for HIV-1 infection, were used to generate HIV-1 Gag-specific CD4+ T-cell clones by *in vitro* immunization with HIV-1 overlapping 20mer peptides spanning p55. Six clones were generated by limiting dilution. All reacted with p24 except one which recognized a p24 peptide and a p6 peptide. All CD4+ T cell clones were HLA class II DR restricted.
- Clone 50 recognized this peptide with a Th0 response (Th0 means that cytokines characteristic of both Th1 and Th2 responses were stimulated), using TCR Vβ 17, and was a homogeneous T-cell population. This clone was only activated by peptide, not by processed protein from vaccinia virus Gag-infected B-LCL.

HXB2 Location p24 (110–128)
Author Location p24
Epitope TLQEQIGWMTSNPPIPVGD
Immunogen HIV-1 infection, vaccine
Vector/Type: modified vaccinia Ankara (MVA) *Strain:* A clade, multiple epitope immunogen *HIV component:* p17/p24 Gag
Species (MHC) human
Country United Kingdom
Assay type proliferation, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords HAART, ART, vaccine-induced epitopes, therapeutic vaccine
References Ondondo *et al.* 2006

- A vaccinia-gag vaccine stimulated broad functional T helper responses in 16 chronically infected HAART patients. Gag-specific CD4+ T cell responses targeted known and new epitopes, several of which were also recognized by HIV-uninfected subjects.
- TLQEQIGWMTSNPPIPVGD contains three possible HLA-DR4 binding sequences: LQEQIGWMT, IGWMTSNPP and MTSNPPIPV. Peptides that included these sequences and were at least 10 aa in length stimulated responses.

HXB2 Location p24 (111–132)
Author Location p24 (243–264 SF2)
Epitope LQEQIGWMTNNPPIPVGEIYKR
Immunogen HIV-1 infection
Species (MHC) human
References Rosenberg *et al.* 1997

- Low viral load correlated with strong HIV-1-specific proliferative response.
- A proliferative response to this epitope was detected in two long term survivors.

HXB2 Location p24 (113–127)
Author Location Gag (248–262)
Epitope EQIAWMTSNPPVPVG
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was not detectable.

HXB2 Location p24 (117–127)
Author Location Gag (251–261)
Epitope WMTSNPPVPVG

Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was not detectable.

HXB2 Location p24 (119–133)
Author Location p24 (251–265)
Epitope `TNNPPIPBGEIYKRW`
Immunogen HIV-1 infection
Species (MHC) human (DRB1*1301)
Keywords binding affinity, HAART, ART
References Blankson & Siliciano 2001; Malhotra *et al.* 2001

- The DRB1*13-DQB1*06 haplotype is associated with maintained viral suppression after HAART – 7/7 early-treated DRB1*13-DQB1*06 positive people, but only 3/14 (21%) of those who did not have DRB1*13-DQB1*06, maintained viral suppression for 18 months.
- PBMC from individuals with the haplotype DRB1*13-DQB1*06 displayed increased IFN-γ secretion and stronger proliferative responses against p24 80 weeks post treatment.
- DRB1*13-DQB1*06 was also found to be enriched among long-term non-progressors (LTNPs) (it was in 9/18 versus, versus 21% of the general population)
- This epitope was mapped with truncated peptides using the Elispot assay.
- Two distinct DRB1*13 epitopes were defined in the peptide region spanning 251 to 270, and this 20-mer bound with very high affinity to DRB1*1302 – DRB1*1301 and DRB1*1302 would be expected to have very similar binding properties.

HXB2 Location p24 (119–133)
Author Location p24 (119–133)
Epitope `TNNPPIPBGEIYKRW`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Netherlands
Assay type Cytokine production
References Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted T-helper epitopes were analyzed. TNNPPIPBGEIYKRW had fixation of R14K mutation (TNNPPIPBGEIYKkW) in 1 of the patients.

HXB2 Location p24 (119–138)
Author Location Gag (251–270 HXB2)
Epitope `TNNPPIPVGEIYKRWIILGL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DRB1*0503, DRB1*1302
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic unteated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.
- Responding patient had autologous sequence exactly matching this peptide.

HXB2 Location p24 (121–136)
Author Location p24 (253–267)
Epitope `NPPIPVGEIYKRWIIC`
Immunogen in vitro stimulation or selection
Species (MHC) human
References Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.

HXB2 Location p24 (121–140)
Author Location Gag (253–272 SF2)
Epitope `NPPIPVGEIYKRWILGLNK`
Immunogen vaccine
Vector/Type: Listeria monocytogenes *Strain:* B clade SF2 *HIV component:* p24 Gag
Species (MHC) mouse (H-2^d)
Keywords immunodominance, Th1
References Mata & Paterson 1999

- *Listeria monocytogenes* is an intracellular bacterium that lives in the cytoplasm and generates a cell-mediated immune response.
- *L. monocytogenes* vaccine expressing HIV-1 p24 protein (Lm-Gag) was used to stimulate gag specific CD4+ T cell proliferative responses in BALB/c(H-2d) and C57BL/6(H-2b) mice.
- 2/3 reactive p24 peptides (out of 22 overlapping peptides that span p24) were recognized by both murine strains; this epitope is immunodominant in BALB/c mice and did not stimulate a C57BL/6 response.
- The proliferative response is due to CD4+ IFN-γ-producing cells, a Th1 response.

HXB2 Location p24 (121–140)
Author Location p24 (253–272 HXB2)
Epitope `NPPIPVGEIYKRWIILGLNK`
Subtype B

T-Helper CD4+

Immunogen vaccine
Vector/Type: Listeria monocytogenes *Strain:* B clade HXB2 *HIV component:* Gag
Species (MHC) mouse (H-2^d)
Keywords immunodominance
References Mata & Paterson 1999

- BALB/c and C57BL/6 mice were immunized with *Listeria monocytogenes* (Lm-Gag) expressing HIV-1 HXB2 Gag.
- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm; secreted *L. monocytogenes* antigens are processed and presented by both class I and class II pathways.
- The class II Th response was probed using 20mer peptides that overlapped by 10; the peptide MPPIPVGEIYKRWIILGLNK gave the immunodominant response for the H-2^d haplotype, but was not recognized in H-2^b mice.

HXB2 Location p24 (121–140)
Author Location Gag (197–205)
Epitope `NPPIPVGEIYKRWIILGLNK`
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade HXB2 *HIV component:* Gag
Species (MHC) mouse (H-2^d)
Country United States
Assay type proliferation, T-cell Elispot
Keywords vaccine antigen design
References Kwak *et al.* 2004

- A recombinant vaccinia virus with HIV-1 Gag replacing the cytoplasmic domain of the B5R protein was shown to induce better primary CD4 response than recombinant vaccinia virus expressing Gag from the TK-locus; CD8 responses were less specific. When immunized BALB/c mice were challenged with a recombinant Listeria that expresses HIV-Gag, lower colony counts of Listeria were found in the liver and spleen of mice immunized with virus expressing B5R-Gag fusion protein.

HXB2 Location p24 (121–140)
Author Location p24 (121–140)
Epitope `NPPIPVGEIYKRWIILGLNK`
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) mouse (H-2^d)
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- NPPIPVGEIYKRWIILGLNK is a previously known epitope that is a part of TCI fragment NPPIPVGEIYRWIIL-GLNKIVRMYSPTSI in this vaccine construct.

HXB2 Location p24 (121–140)
Author Location
Epitope `NPPIPVGRIYKRWILGLNK`
Subtype C
Immunogen vaccine
Vector/Type: DNA, DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* C clade Du422, C clade Du151 *HIV component:* Gag, gp160 deletions, Nef, RT, Tat
Species (MHC) mouse
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, Th1
References Shephard *et al.* 2008

- DNA (SAAVI DNA-C) and MVA (SAAVI MVA-C) vaccines were tested in BALB/c mice. Combining the vaccines in a DNA prime and MVA boost regimen increased the cumulative peptide response compared to the DNA vaccine alone by 10-fold.
- Th1 cytokine IFN-γ and TNF-α levels from HIV-specific CD8 and CD4 T cells increased 20- and 8- fold respectively, with a SAAVI MVA-C boost.
- Effector and effector memory RT- and Env-specific memory CD8 T cell subsets were boosted after MVA immunizations.
- CD4 peptide NPPIPVGRIYKRWILGLNK was used for detection of IFN-γ-secreting cells.

HXB2 Location p24 (121–152)
Author Location Gag (183–214 LAI)
Epitope `NPPIPVGEIYKRWIILGLNKIVRMYSPTSILD`
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide
Species (MHC) human
References Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 9/10 reacted to this peptide.
- 9/12 tested mounted a CTL responses to at least one of the six peptides, each of the six peptides elicited a CTL response in at least one individual – this peptide was particularly immunogenic, eliciting a CTL response in four vaccinees.
- All of the 12 tested had an IgG response to this peptide.

T-Helper CD4+

HXB2 Location p24 (125–139)
Author Location Gag (257–271 SF2)
Epitope PVGEIYKRWIILGLN
Epitope name Peptide 65
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* Gag, Tat *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse (H-2^d)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords vaccine-induced epitopes
References Cellini *et al.* 2008

- In order to increase the known number of epitopes in Gag protein so that they can be assayed for reactivity in vaccine studies, BALB/c mice were inoculated with Gag or Gag+Tat. OLPs were used to elicit T-cell immune responses from mouse splenocytes and tested for by cytotoxicity or ELISpot assays. 5 novel predicted optimal CTL epitopes, 2 novel predicted CD4 epitopes and 2 immune response eliciting peptides were found.
- Peptide PVGEIYKRWIILGLN contains a previously defined Gag CD4 epitope and IYKRWIILGL CD8 epitope.

HXB2 Location p24 (125–139)
Author Location Gag (257–271 HXB-2)
Epitope PVGEIYKRWIILGLN
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DQB1*0301, DQB1*0601, DRB1*1303, DRB1*1502, DRB3*0101, DRB5*0102
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 2/22 patients responded to this peptide.

HXB2 Location p24 (125–139)
Author Location
Epitope PVGEIYKRWIILGLN
Epitope name G065
Immunogen HIV-1 infection
Species (MHC) human
Country Canada
Assay type proliferation, Flow cytometric T-cell cytokine assay
Keywords memory cells
References Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN-γ, but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN-γ only-producing cells are short lived.

HXB2 Location p24 (126–148)
Author Location
Epitope VGEIYKRWIILGLNKIVRMYSPV
Epitope name HIV-VAX-1044
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 7/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was WIILGLNKI.

HXB2 Location p24 (127–141)
Author Location Gag (294–308)
Epitope GEIYKRWIILGLNKI
Epitope name Gag 294
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Keywords subtype comparisons
References Wilson *et al.* 2001

- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicted proliferative responses from multiple HIV-infected donors.
- This epitope binds ten HLA-DR alleles: DRB1*0101, DRB1*1501, DRB1*0405, DRB1*1101, DRB1*1302, DRB1*0701, DRB1*0802, DRB1*0901, DRB5*0101 and DRB4*0101 with an IC_{50} threshold below 1,000 nM.
- This epitope sequence is conserved in 95% of clade B isolates.
- 6/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

HXB2 Location p24 (127–141)
Author Location p24 (294–308)
Epitope GEIYKRWIILGLNKI
Epitope name Gag2
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Country United Kingdom
Assay type Cytokine production, proliferation
Keywords supertype, rate of progression
References Boaz *et al.* 2003

- Proliferative and cytokine (IFNgamma and Il-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNPs (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive.
- Gag-specific CD4+ T cells in LTNPs showed increased numbers of IFN gamma and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFNgamma, levels were correlated with proliferation.

HXB2 Location p24 (127–141)
Author Location p24 (127–141)
Epitope `GEIYRWIILGLNKI`
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human (DR supermotif)
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- GEIYRWIILGLNKI is a previously known epitope that is a part of TCI fragment NPPIPVGEIYRWIILGLNKIVRMYSPTSI in this vaccine construct.

HXB2 Location p24 (128–137)
Author Location p24 (260–269)
Epitope `EIYKRWIILG`
Immunogen HIV-1 infection
Species (MHC) human (DRB1*1301, DRB1*1302)
Keywords binding affinity, HAART, ART, Th1
References Blankson & Siliciano 2001; Malhotra *et al.* 2001

- The DRB1*13-DQB1*06 haplotype is associated with maintained viral suppression after HAART – 7/7 early-treated DRB1*13-DQB1*06 positive people, but only 3/14 (21%) of those who did not have DRB1*13-DQB1*06, maintained viral suppression for 18 months.
- PBMC from individuals with the haplotype DRB1*13-DQB1*06 displayed increased IFN-γ secretion and stronger proliferative responses against p24 80 weeks post treatment.
- DRB1*13-DQB1*06 was also found to be enriched among long-term non-progressors (it was in 9/18 versus, versus 21% of the general population)
- The truncated peptide that gave the optimal proliferative response for a Th1 phenotype clone was this nine-mer.
- This region, shared by 2 overlapping peptides, was the reactive region for clones from two DRB1*13 patients, one carried DRB1*1301 and one DRB1*1302.
- Two distinct epitopes were defined in the peptide region spanning 251 to 270, and this 20-mer bound with very high affinity to DRB1*1302 – DRB1*1301 and DRB1*1302 would be expected to have very similar binding properties.

HXB2 Location p24 (128–137)
Author Location p24 (128–137)
Epitope `EIYRWIILG`
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human (DRB1*1301, DRB1*1302)
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- EIYRWIILG is a previously known epitope that is a part of TCI fragment NPPIPVGEIYRWIILGLNKIVRMYSPTSI in this vaccine construct.

HXB2 Location p24 (129–143)
Author Location Gag (261–275 HXB-2)
Epitope `IYKRWIILGLNKIVR`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DQB1*0301, DQB1*0601, DRB1*1303, DRB1*1502, DRB3*0101, DRB5*0102
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 2/22 patients responded to this peptide.

T-Helper CD4+

HXB2 Location p24 (129–148)
Author Location p24 (261–280 IIIB)
Epitope IYKRWIILGLNKIVRMYSPT
Epitope name P27
Immunogen in vitro stimulation or selection
Species (MHC) human
Donor MHC DQ2, DQ3, DR4, DR7
Keywords immunodominance, Th1, Th2, TCR usage
References Venturini *et al.* 2002

- PBMC from a seronegative donor, the healthy brother of a pair of monozygotic twins discordant for HIV-1 infection, were used to generate HIV-1 Gag-specific CD4+ T-cell clones by *in vitro* immunization with HIV-1 overlapping 20mer peptides spanning p55. Six clones were generated by limiting dilution. All reacted with p24 except one which recognized a p24 peptide and a p6 peptide. All CD4+ T cell clones were HLA class II DR restricted.
- Clone 74 recognized two peptides including this one with a Th1 response using TCR Vβ 13 (13s1); it required 200 ng/ml (100 nM) and 1 μg/ml (0.5 μM) for stimulation by peptides 480-500 and 261-280, respectively. Sequencing TCR Vβ regions of colonies from clone 74 suggested this was a clonal population.

HXB2 Location p24 (129–148)
Author Location Gag (261–280 HXB2)
Epitope IYKRWIILGLNKIVRMYSPT
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DRB1*0503, DRB1*1302
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic unteated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.
- Responding patient had autologous sequence exactly matching this peptide.

HXB2 Location p24 (129–148)
Author Location p24 (129–148)
Epitope IYKRWIILGLNKIVRMYSPT
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- IYRWIILGLNKIVRMYSPT is a previously known epitope that is a part of TCI fragment NPPIPVGEIYRWIILGLNKIVRMYSPTSI in this vaccine construct.

HXB2 Location p24 (131–145)
Author Location Gag (298–312)
Epitope KRWIILGLNKIVRMY
Epitope name Gag 298
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Keywords subtype comparisons
References Wilson *et al.* 2001

- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
- This epitope binds thirteen HLA-DR alleles: DRB4*0101, DRB5*0101, DRB1*0901, DRB1*0802, DRB1*0701, DRB1*1302, DRB1*1201, DRB1*1101, DRB1*0405, DRB1*0401, DRB*0301, DRB1*1501 and DRB1*0101, with an IC_{50} threshold below 1,000 nM.
- This epitope sequence is conserved in 94% of clade B isolate.
- 8/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

HXB2 Location p24 (131–145)
Author Location p24 (298–312)
Epitope KRWIILGLNKIVRMY
Epitope name Gag3
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Country United Kingdom
Assay type proliferation, Intracellular cytokine staining
Keywords supertype, rate of progression
References Boaz *et al.* 2003

- Proliferative and cytokine (IFNgamma and Il-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNPs (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive.
- Gag-specific CD4+ T cells in LTNPs showed increased numbers of IFN gamma and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFNgamma, levels were correlated with proliferation.

HXB2 Location p24 (131–145)
Author Location p24 (131–145)
Epitope KRWIILGLNKIVRMY
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human (DR supermotif)
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- KRWIILGLNKIVRMY is a previously known epitope that is a part of TCI fragment NPPIPVGEIYRWIILGLNKIVRMYSPTSI in this vaccine construct.

HXB2 Location p24 (131–145)
Author Location Gag (263–277 LAI)
Epitope KRWIILGLNKIVRMY
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other
Species (MHC) transgenic mouse (DR1)
Country France
Assay type proliferation, CD4 T-cell Elispot - IFNγ, Chromium-release assay
Keywords computational epitope prediction, Th1
References Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQNANPDCKTILKALGPA, KTILKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTILKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQNANPDCKTILKALGPA, NKIVRMYSPTSILDIRQGPK.

HXB2 Location p24 (131–145)
Author Location p24 (265–279 SF2)
Epitope KRWIILGLNKIVRMY
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *Strain:* B clade SF2 *HIV component:* p24 Gag
Species (MHC) macaque
References Mills *et al.* 1990

- Responses to 3 T-cell and multiple linear B-cell epitopes were found in vaccinated macaques – epitope response defined by T-cell clone.

HXB2 Location p24 (131–150)
Author Location Gag (264–283)
Epitope KRWIILGLNKIVRMYSPTSI
Epitope name p24.14
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101)
Assay type Tetramer binding
Keywords assay standardization/improvement
References Scriba *et al.* 2005a

- Conditions required for optimal HLA class II tetramer staining of DR1- and DR4-restricted CD4+ T cells were studied. Staining was rapid and efficient and did not require internalization. Ultrasensitive detection of rare CD4+ T cells was performed by combining tetramer staining with magnetic bead enrichment, and level of detection was much higher than by standard flow-cytometric techniques.

HXB2 Location p24 (131–150)
Author Location Gag (264–283)
Epitope KRWIILGLNKIVRMYSPTSI
Epitope name p24.14
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101)
Assay type Tetramer binding, CD4 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, supervised treatment interruptions (STI)
References Scriba *et al.* 2005b

- HIV-specific T helper cell numbers were studied in patients with early-stage HIV infection, who were given a short course of ART, while on ART, during and after ART cessation.
- Magnetic bead enrichment technique was used to enhance sensitivity of HLA class II tetramer staining. CD4+ T cells were consistently detected at frequencies below the detection limit of direct flow cytometric analysis.
- No significant destruction of CD4+ T cell clones was found when HIV viremia rebounded.

HXB2 Location p24 (131–150)
Author Location p24 (131–150 clade B consensus)
Epitope KRWIILGLNKIVRMYSPTSI
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (DRB, DRB1*0101, DRB1*0301, DRB1*0401, DRB1*0405, DRB1*0701, DRB1*1101, DRB1*1302)
Country Brazil
Assay type CD4 T-cell Elispot - IFNγ, HLA binding

T-Helper CD4+

Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 brazilian HIV-1 chronically infected individuals.
- While the reacting peptide is KRWIILGLNKIVRMYSPTSI, shorter WIILGLNKIVRMYSPTSI peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

HXB2 Location p24 (131–152)
Author Location p24 (263–284 SF2)
Epitope `KRWIILGLNKIVRMYSPTSILD`
Immunogen HIV-1 infection
Species (MHC) human
References Rosenberg *et al.* 1997

- Low viral load correlated with strong HIV-1-specific proliferative response.
- A proliferative response to this epitope was detected in two long term survivors.

HXB2 Location p24 (133–143)
Author Location Gag (265–275)
Epitope `WIILGLNKIVR`
Epitope name Gag 14.2
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade *HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu
Species (MHC) macaque
Assay type T-cell Elispot, Intracellular cytokine staining
Keywords subtype comparisons, variant cross-recognition or cross-neutralization, memory cells
References Amara *et al.* 2005

- Clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02_AG consensus Gag in macaques. The activity was better-conserved for CD8 than CD4 T cells.
- 3/5 CD8 epitopes and 2/8 CD4 epitopes were conserved across multiple HIV-1 clades. All 5 CD8, and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation.
- The similar reported human epitope in this case is KRWIILGLNKIVRMY, which is presented by 13 HLA-DR alleles.
- The response elicited to the B clade epitope WIILGLNKIVR cross-reacts with the CRF02_AG form WIvLGLNKIVR. WIILGLNKIVR is mostly conserved across other clades.

HXB2 Location p24 (133–144)
Author Location p24 (133–144)
Epitope `WIILGLNKIVRM`
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human (DRB1*0101, DRB1*0401, DRB1*0405, DRB1*1101, DRB1*1302, DRB1*1501, DRB5*0101)
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- KRWIILGLNKIVRMY is a previously known epitope that is a part of TCI fragment NPPIPVGEIYRWIILGLNKIVRMYSPTSI in this vaccine construct.

HXB2 Location p24 (133–144)
Author Location p24 (133–144 B Consensus)
Epitope `WIILGLNKIVRM`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101, DRB1*1101, DRB1*1302, DRB1*1501, DRB5*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This is the core of the peptide and was very often recognized, with responses by 25% of the study group. The core epitope, WIILGLNKIVRM, could bind 5/8 HLA-DR molecules tested.

HXB2 Location p24 (133–147)
Author Location Gag (265–279 HXB-2)
Epitope `WIILGLNKIVRMYSP`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human

T-Helper CD4+

Donor MHC DQB1*0602, DQB1*0604, DRB1*1302, DRB1*1501, DRB3*0301, DRB5*0101; DQB1*0301, DQB1*0601, DRB1*1303, DRB1*1502, DRB3*0101, DRB5*0102
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 2/22 patients responded to this peptide.

HXB2 Location p24 (133–147)
Author Location
Epitope WIILGLNKIVRMYSP
Epitope name G067
Immunogen HIV-1 infection
Species (MHC) human
Country Canada
Assay type proliferation, Flow cytometric T-cell cytokine assay
Keywords memory cells
References Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN-γ, but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN-γ only-producing cells are short lived.

HXB2 Location p24 (133–150)
Author Location p24 (133–150 B Consensus)
Epitope WIILGLNKIVRMYSPTSI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101, DRB1*0401, DRB1*0405, DRB1*0701, DRB1*1101, DRB1*1302, DRB1*1501, DRB5*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 25% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.
- The peptides that were recognized by the most people were able to bind broadly to multiple HLA-DR molecules. This peptide showed very high cross-reactive binding capacity, and bound to 8/8 common HLA-DR molecules.

HXB2 Location p24 (133–150)
Author Location p24 (133–150)
Epitope WIILGLNKIVRMYSPTSI
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human (DRB1*0701, DRB1*1101, DRB1*1302, DRB1*1501, DRB5*0101)
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- WIILGLNKIVRMYSPTSI is a previously known epitope that is a part of TCI fragment NPPIPVGEIYRWIIL-GLNKIVRMYSPTSI in this vaccine construct.

HXB2 Location p24 (135–145)
Author Location p24 (135–145 B Consensus)
Epitope ILGLNKIVRMY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0401, DRB1*1302, DRB1*1501)
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

T-Helper CD4+

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This is the core of the peptide and was very often recognized, with responses by 25% of the study group. The core epitope, ILGLNKIVRMY, could bind 3/8 HLA-DR molecules tested.

HXB2 Location p24 (135–145)
Author Location p24 (135–145)
Epitope `ILGLNKIVRMY`
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human (DRB1*0401, DRB1*1302, DRB1*1501)
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- ILGLNKIVRMY is a previously known epitope that is a part of TCI fragment NPPIPVGEIYRWIILGLNKIVRMYSPTSI in this vaccine construct.

HXB2 Location p24 (135–154)
Author Location p24 (267–286)
Epitope `ILGLNKIVRMYSPTSILDIR`
Immunogen HIV-1 infection
Species (MHC) human
References Adams *et al.* 1997

- One of four immunogenic Gag peptides used in study of the proliferative response to p24.
- 8 of 24 HIV+ individuals responded to this epitope.
- Improved assay system (increase in culture time to 8 days and addition of IL-2 to cultures) gave increased detection of proliferative response.

HXB2 Location p24 (135–157)
Author Location
Epitope `ILGLNKIVRMYSPVSILDIRQGP`
Epitope name HIV-VAX-1043
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 3/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was VRMYSPVSI.

HXB2 Location p24 (137–151)
Author Location Gag (269–285 HXB-2)
Epitope `GLNKIVRMYSPTSIL`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DQB1*0301, DQB1*0601, DRB1*1303, DRB1*1502, DRB3*0101, DRB5*0102
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

HXB2 Location p24 (138–152)
Author Location p24 (138–152)
Epitope `LNKIVRMYSPVSILD`
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag
Species (MHC) human
Assay type proliferation, CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords vaccine antigen design
References Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.
- 2/8 subjects responded to this epitope.

HXB2 Location p24 (139–148)
Author Location p24 (271–280 HZ321)
Epitope `NKIVRMYSPT`
Subtype AG

T-Helper CD4+

Immunogen vaccine
Vector/Type: gp120 depleted virus HZ321 (REMUNE(TM)) *Strain:* AG recombinant HZ321 *HIV component:* virus *Adjuvant:* Incomplete Freund's Adjuvant (IFA), CpG immunostimulatory sequence (ISS)
Species (MHC) macaque
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords vaccine-induced epitopes, adjuvant comparison, vaccine antigen design
References Silvera *et al.* 2004

- Macaques were immunized with gp120-depleted HIV-1 together with incomplete Freund's adjuvant and CpG-ODN. All four immunized animals had high anti-p24 antibody titers, while three animals showed HIV-1-specific CD4+ and CD8+ T-cell responses. This is one of two CD4+ T-cell epitopes in Gag that was mapped.

HXB2 Location p24 (139–157)
Author Location p24 (271–290 IIIB)
Epitope `NKIVRMYSPTSILDIRQGP`
Epitope name P28
Immunogen in vitro stimulation or selection
Species (MHC) human (DR4)
Donor MHC DQ2, DQ3, DR4, DR7
Keywords immunodominance, Th1, Th2, TCR usage
References Venturini *et al.* 2002

- PBMC from a seronegative donor, the healthy brother of a pair of monozygotic twins discordant for HIV-1 infection, were used to generate HIV-1 Gag-specific CD4+ T-cell clones by *in vitro* immunization with HIV-1 overlapping 20mer peptides spanning p55. Six clones were generated by limiting dilution. All reacted with p24 except one which recognized a p24 peptide and a p6 peptide. All CD4+ T cell clones were HLA class II DR restricted.
- Clone 6 recognized three peptides including this one with a Th1 response using TCR Vβ 6 (6s5A1N1). Sequencing TCR Vβ regions of colonies from clone 6 suggested this was a clonal population. Assays using different peptide concentrations suggest that this peptide, 271-290, contains the main epitope of this clone. Upon activation, clone 6 was observed to induce a cytopathic effect in the adherent layer of fibroblasts expressing HLA DR4W14 and -W15. Clone 6 was activated in response to vaccinia virus Gag-infected B-LCL, so it could recognize naturally processed epitopes.
- Clone 37 recognized this peptide sequence with a Th2 response using TCR Vβ 3, and was a homogeneous T-cell population. This clone was only activated by peptide, not by processed protein from vaccinia virus Gag-infected B-LCL.
- Clone 97 recognized this peptide sequence with a using TCR Vβ 9 and 14; the two TCR receptors used indicates this limiting dilution represents a mixed population. This clone was only activated by peptide, not by processed protein from vaccinia virus Gag-infected B-LCL.

HXB2 Location p24 (139–158)
Author Location Gag (271–290 LAI)
Epitope `NKIVRMYSPTSILDIRQGPK`
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other
Species (MHC) transgenic mouse (DR1)
Country France
Assay type proliferation, CD4 T-cell Elispot - IFNγ, Chromium-release assay
Keywords computational epitope prediction, Th1
References Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQNANPDCKTILKALGPA, KTILKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTILKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQNANPDCKTILKALGPA, NKIVRMYSPTSILDIRQGPK.

HXB2 Location p24 (139–158)
Author Location Gag (271–290 HXB2)
Epitope `NKIVRMYSPTSILDIRQGPK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DRB1*0701, DRB1*1601
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic unteated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.

HXB2 Location p24 (140–148)
Author Location p24 (272–280 HXB2)
Epitope `KIVRMYSPT`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101)
Donor MHC DQ1, DQ5, DR51, DRB1*0101, DRB1*1501
Assay type proliferation, T-cell Elispot, Intracellular cytokine staining
Keywords HAART, ART
References Boritz *et al.* 2003

- HIV infected individuals with advanced disease often have only weak or undetectable HIV specific Th responses, and HAART can sometimes restore Th HIV recognition in such cases. The repertoire of Th responses to p24 in an individual who responded to HAART after having a CD4+ T-cell count

T-Helper CD4+

of 0 cells/ul was determined. Eleven clonotypes were found among 13 clones, recognizing eight distinct epitopes, with a range of MHC affinities and functional avidities. Multiple Gag p24 peptides were recognized using CD4 Elispot assays based on samples from six additional HAART-treated CD4 T-cell-reconstituted subjects.
- The Th clone that recognized this epitope utilized TCR Vβ 5.2.

HXB2 Location p24 (140–149)
Author Location Gag (272–281)
Epitope KIVRMYSPTS
Immunogen in vitro stimulation or selection
Species (MHC) human (DR4)
Assay type proliferation
Keywords variant cross-recognition or cross-neutralization
References Venturini *et al.* 2006
- Cross-reactivity of a human HIV-1 gag-specific CD4+ T cell clone obtained from an HIV-1 seronegative donor was studied using combinatorial peptide library analysis. Peptides from other pathogens were able to activate T cell clone.
- HIV gag peptides with several mutations in KIVRMYSPTS, corresponding to the existing HIV strains were able to strongly activate the T cell clone.
- 2 bacterial peptides from Burkolderia cepacia (KLARLYTPAR) and from Ralstonia picketttii (TLARLYTPVR) activated the T cell clone with the same potency as the HIV peptides.

HXB2 Location p24 (141–156)
Author Location p24 (273–287)
Epitope IVRMYSPTSILDIRQC
Immunogen in vitro stimulation or selection
Species (MHC) human
References Bedford *et al.* 1997
- Epitope elicits a primary proliferative response in PBMC from uninfected donors.
- Matches 3/3 anchor residues for HLA DR: **I**VRMY**S**PTS

HXB2 Location p24 (141–158)
Author Location p24 (141–158 B Consensus)
Epitope IVRMYSPTSILDIRQGPK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004
- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 17% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p24 (141–158)
Author Location p24 (141–158)
Epitope IVRMYSPTSILDIRQGPK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Netherlands
Assay type Cytokine production
References Geels *et al.* 2006
- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. IVRMYSPTSILDIRQGPK had fixation of 1 mutation (IVRMYSP[t/v]SILDIRQGPK) in 1 of the patients.

HXB2 Location p24 (146–160)
Author Location p24 (278–292 IIIB, B10)
Epitope SPTSILDIRQGPKEP
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a
- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location p24 (149–168)
Author Location p24 (281–300 IIIB)
Epitope SILDIRQGPKEPFRDYVDRF
Epitope name P29
Immunogen in vitro stimulation or selection
Species (MHC) human (DR4)
Donor MHC DQ2, DQ3, DR4, DR7
Keywords immunodominance, Th1, Th2, TCR usage
References Venturini *et al.* 2002
- PBMC from a seronegative donor, the healthy brother of a pair of monozygotic twins discordant for HIV-1 infection, were used to generate HIV-1 Gag-specific CD4+ T-cell clones by *in vitro* immunization with HIV-1 overlapping 20mer peptides spanning p55. Six clones were generated by limiting dilution. All reacted with p24 except one which recognized a p24 peptide and a p6 peptide. All CD4+ T cell clones were HLA class II DR restricted.

T-Helper CD4+

- Clone 6 recognized three peptides including this one with a Th1 response using TCR Vβ 6 (6s5A1N1). Sequencing TCR Vβ regions of colonies from clone 6 suggested this was a clonal population. Assays using different peptide concentrations suggest that this peptide does not carry the main epitope of this clone.

HXB2 Location p24 (150–169)
Author Location p24 (282–301)
Epitope `ILDIRQGPKEPFRDYVDRFY`
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

HXB2 Location p24 (151–166)
Author Location p24 (283–297)
Epitope `LDIRQGPKEPFRDYVC`
Immunogen in vitro stimulation or selection
Species (MHC) human
References Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.

HXB2 Location p24 (153–167)
Author Location
Epitope `IRQGPKEPFRDYVDR`
Epitope name G072
Immunogen HIV-1 infection
Species (MHC) human
Country Canada
Assay type proliferation, Flow cytometric T-cell cytokine assay
Keywords memory cells
References Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN-γ, but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN-γ only-producing cells are short lived.

HXB2 Location p24 (155–177)
Author Location p24 (287–309)
Epitope `QGPKEPFRDYVDRFYKTLRAEQA`
Immunogen vaccine
Vector/Type: peptide
Species (MHC) mouse
References Nakamura *et al.* 1997

- Mice immunized with this peptide generated proliferative responses, CTLs and antibodies.
- This immunogenic domain is from a highly conserved region of p24.

HXB2 Location p24 (156–170)
Author Location p24 (288–302 IIIB, B10)
Epitope `GPKEPFRDYVDRFYK`
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location p24 (156–173)
Author Location p24 (156–173 B Consensus)
Epitope `GPKEPFRDYVDRFYKTLR`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p24 (156–174)
Author Location p24 (287–306)
Epitope `QPKEPFRDYVDRFYKTLRA`
Immunogen HIV-1 infection
Species (MHC) human
References Adams *et al.* 1997

- One of four immunogenic Gag peptides used in study of the proliferative response to p24.
- T-cells from 5 of 21 HIV+ individuals responded to this epitope.
- Improved assay system (increase in culture time to 8 days and addition of IL-2 to cultures) gave increased detection of proliferative response.

HXB2 Location p24 (157–165)
Author Location p24 (289–297 HXB2)
Epitope `PKEPFRDYV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DQ5)

T-Helper CD4+

Donor MHC DQ1, DQ5, DR51, DRB1*0101, DRB1*1501
Assay type proliferation, T-cell Elispot, Intracellular cytokine staining
Keywords HAART, ART
References Boritz *et al.* 2003

- HIV infected individuals with advanced disease often have only weak or undetectable HIV specific Th responses, and HAART can sometimes restore Th HIV recognition in such cases. The repertoire of Th responses to p24 in an individual who responded to HAART after having a CD4+ T-cell count of 0 cells ul was determined. Eleven clonotypes were found among 13 clones, recognizing eight distinct epitopes, with a range of MHC affinities and functional avidities. Multiple Gag p24 peptides were recognized using CD4 Elispot assays based on samples from six additional HAART-treated CD4 T-cell-reconstituted subjects.

HXB2 Location p24 (159–178)
Author Location Gag (291–310 LAI)
Epitope `EPFRDYVDRFYKTLRAEQAS`
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other
Species (MHC) transgenic mouse (DR1)
Country France
Assay type proliferation, CD4 T-cell Elispot - IFNγ, Chromium-release assay
Keywords computational epitope prediction, Th1
References Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQNANPDCKTILKALGPA, KTILKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTILKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQNANPDCKTILKALGPA, NKIVRMYSPTSILDIRQGPK.

HXB2 Location p24 (159–178)
Author Location Gag (291–310 HXB2)
Epitope `EPFRDYVDRFYKTLRAEQAS`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DRB1*1302, DRB1*1503; DRB1*0405, DRB1*0701; DRB1*0701, DRB1*1601
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic unteated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.

HXB2 Location p24 (159–178)
Author Location Gag (291–310 HXB2)
Epitope `EPFRDYVDRFYKTLRAEQAS`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DRB1*1302, DRB1*1503; DRB1*0405, DRB1*0701; DRB1*0701, DRB1*1601; DRB1*0301, DRB1*0401
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic unteated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.

HXB2 Location p24 (161–171)
Author Location Gag (296–306)
Epitope `FRDYVDRFFKT`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was not detectable.

HXB2 Location p24 (161–180)
Author Location Gag (294–313)
Epitope `FRDYVDRFYKTLRAEQASQD`
Epitope name p24.17
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101)
Assay type Tetramer binding
Keywords assay standardization/improvement
References Scriba *et al.* 2005a

- Conditions required for optimal HLA class II tetramer staining of DR1- and DR4-restricted CD4+ T cells were studied. Staining was rapid and efficient and did not require internalization. Ultrasensitive detection of rare CD4+ T cells was performed by combining tetramer staining with magnetic bead

T-Helper CD4+

enrichment, and level of detection was much higher than by standard flow-cytometric techniques.

HXB2 Location p24 (161–180)
Author Location Gag (294–313)
Epitope FRDYVDRFYKTLRAEQASQD
Epitope name p24.17
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101)
Assay type Tetramer binding, CD4 T-cell Elispot - IFNγ
Keywords assay standardization/improvement, supervised treatment interruptions (STI)
References Scriba *et al.* 2005b

- HIV-specific T helper cell numbers were studied in patients with early-stage HIV infection, who were given a short course of ART, while on ART, during and after ART cessation.
- Magnetic bead enrichment technique was used to enhance sensitivity of HLA class II tetramer staining. CD4+ T cells were consistently detected at frequencies below the detection limit of direct flow cytometric analysis.
- No significant destruction of CD4+ T cell clones was found when HIV viremia rebounded.

HXB2 Location p24 (161–180)
Author Location Gag (293–312 SF2)
Epitope FRDYVDRFYKTLRAEQASQD
Immunogen vaccine
Vector/Type: Listeria monocytogenes *Strain:* B clade SF2 *HIV component:* p24 Gag
Species (MHC) mouse (H-2^b, H-2^d)
Keywords Th1
References Mata & Paterson 1999

- *Listeria monocytogenes* is an intracellular bacterium that lives in the cytoplasm and generates a cell-mediated immune response.
- *L. monocytogenes* vaccine expressing HIV-1 p24 protein (Lm-Gag) was used to stimulate gag specific CD4+ T cell proliferative responses in BALB/c(H-2d) and C57BL/6(H-2b) mice.
- 2/3 reactive p24 peptides (out of 22 overlapping peptides that span p24) were recognized by both murine strains; this peptide stimulated a response in both BALB/c and C57BL/6 mice.
- The proliferative response is due to CD4+ IFN-γ-producing cells, a Th1 response.

HXB2 Location p24 (161–180)
Author Location p24 (293–312 HXB2)
Epitope FRDYVDRFYKTLRAEQASQD
Subtype B
Immunogen vaccine
Vector/Type: Listeria monocytogenes *Strain:* B clade HXB2 *HIV component:* Gag
Species (MHC) mouse (H-2^b, H-2^d)
References Mata & Paterson 1999

- BALB/c and C57BL/6 mice were immunized with *Listeria monocytogenes* (Lm-Gag) expressing HIV-1 HXB2 Gag.
- *L. monocytogenes* is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm; secreted *L. monocytogenes* antigens are processed and presented by both class I and class II pathways.
- The class II Th response was probed using 20mer peptides that overlapped by 10; the peptides VHQAISPRTLNAWVKVVEEK and FRDYVDRFYKTLRAEQASQD were recognized in H-2^b and H-2^d mice.

HXB2 Location p24 (161–180)
Author Location
Epitope FRDYVDRFFKTLRAEQATQE
Subtype C
Immunogen vaccine
Vector/Type: DNA, DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* C clade Du422, C clade Du151 *HIV component:* Gag, gp160 deletions, Nef, RT, Tat
Species (MHC) mouse
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, Th1
References Shephard *et al.* 2008

- DNA (SAAVI DNA-C) and MVA (SAAVI MVA-C) vaccines were tested in BALB/c mice. Combining the vaccines in a DNA prime and MVA boost regimen increased the cumulative peptide response compared to the DNA vaccine alone 10-fold.
- Th1 cytokine IFN-γ and TNF-α levels from HIV-specific CD8 and CD4 T cells increased 20- and 8- fold respectively, with a SAAVI MVA-C boost.
- Effector and effector memory RT- and Env-specific memory CD8 T cell subsets were boosted after MVA immunizations.
- CD4 peptide FRDYVDRFFKTLRAEQATQE was used for detection of IFN-γ-secreting cells. A response to this peptide was aabsent when either vaccine was tested alone, but was induced wuth the combination of SAAVI DNA-C and MVA-C.

HXB2 Location p24 (163–175)
Author Location Gag (295–307)
Epitope DYVDRFYKTLRAE
Immunogen HIV-1 infection
Species (MHC) human (DR0101)
Assay type Cytokine production, proliferation, Tetramer binding, CD4 T-cell Elispot - IFNγ
Keywords HAART, ART, supervised treatment interruptions (STI)
References Iyasere *et al.* 2003

- Fifteen patients recieving HAART with strong CD4+ proliferative responses to HIV antigens while on therapy were examined, to see the effects of viremia on these responses during treatment interruptions. Increased viremia occurred in 12/15 patients during at least one treatment interruption. Anti-HIV proliferative responses were inhibited during viremia, but IFNgamma production to Gag, Pol, and Nef peptide pools were maintained.

T-Helper CD4+

- IL-2 production diminished during viremia, and exogenous IL-2 revived *in vitro* proliferation of HIV-specific T-cells to Gag or Pol DR0101 epitopes in a tetramer, as well as Gag-specific total CD4 T-cell responses.

HXB2 Location p24 (163–177)
Author Location p24 (295–309)
Epitope DYVDRFYKTLRAEQA
Immunogen HIV-1 infection
Species (MHC) human (DRB1*1302)
Keywords HAART, ART
References Blankson & Siliciano 2001; Malhotra *et al.* 2001

- The DRB1*13-DQB1*06 haplotype is associated with maintained viral suppression after HAART – 7/7 early-treated DRB1*13-DQB1*06 positive people, but only 3/14 (21%) of those who did not have DRB1*13-DQB1*06, maintained viral suppression for 18 months.
- PBMC from individuals with the haplotype DRB1*13-DQB1*06 displayed increased IFN-γ secretion and stronger proliferative responses against p24 80 weeks post treatment.
- DRB1*13-DQB1*06 was also found to be enriched among long-term non-progressors (it was in 9/18 versus, versus 21% of the general population)
- This epitope was mapped with truncated peptides using the Elispot assay, and is highly conserved.

HXB2 Location p24 (163–177)
Author Location p24 (295–309)
Epitope DYVDRFYKTLRAEQA
Immunogen HIV-1 infection
Species (MHC) human (DRB1*1302)
Keywords HAART, ART
References Blankson & Siliciano 2001; Malhotra *et al.* 2001

- The DRB1*13-DQB1*06 haplotype is associated with maintained viral suppression after HAART – 7/7 early-treated DRB1*13-DQB1*06 positive people, but only 3/14 (21%) of those who did not have DRB1*13-DQB1*06, maintained viral suppression for 18 months.
- PBMC from individuals with the haplotype DRB1*13-DQB1*06 displayed increased IFN-γ secretion and stronger proliferative responses against p24 80 weeks post treatment.
- DRB1*13-DQB1*06 was also found to be enriched among long-term non-progressors (it was in 9/18 versus, versus 21% of the general population)
- This epitope was mapped with truncated peptides using the Elispot assay, and is highly conserved.

HXB2 Location p24 (164–181)
Author Location p24 (164–181 B Consensus)
Epitope YVDRFYKTLRAEQASQEV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101, DRB1*0401, DRB1*0405, DRB1*0701, DRB1*1101, DRB1*1302, DRB1*1501, DRB5*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The peptides that were recognized by the most people were able to bind broadly to multiple HLA-DR molecules. This peptide showed very high cross-reactive binding capacity, and bound to 8/8 tested common HLA-DR molecules.
- This peptide was the most often recognized, with a responses by 58% of the study group.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p24 (164–181)
Author Location p24 (164–181)
Epitope YVDRFYKTLRAEQASQEV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Netherlands
Assay type Cytokine production
References Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. YVDRFYKTLRAEQASQEV had fixation of 1 mutation (YVDRFYKTLRAEQA[s/t]QEV) in 1 of the patients.

HXB2 Location p24 (165–179)
Author Location Gag (297–311 SF2)
Epitope VDRFYKTLRAEQASQ
Epitope name Peptide 75
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* Gag, Tat *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse (H-2^d)
Assay type CD8 T-cell Elispot - IFNγ, Chromium-release assay

T-Helper CD4+

Keywords vaccine-induced epitopes
References Cellini *et al.* 2008

- In order to increase the known number of epitopes in Gag protein so that they can be assayed for reactivity in vaccine studies, BALB/c mice were inoculated with Gag or Gag+Tat. OLPs were used to elicit T-cell immune responses from mouse splenocytes, tested for by cytotoxicity or ELISpot assays. 5 novel predicted optimal CTL epitopes, 2 novel predicted CD4 epitopes and 2 immune response eliciting peptides were found.
- Peptide VDRFYKTLRAEQASQ contains a Gag CD4 epitope.

HXB2 Location p24 (165–179)
Author Location Gag (297–311 HXB-2)
Epitope VDRFYKTLRAEQASQ
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DQB1*0602, DQB1*0604, DRB1*1302, DRB1*1501, DRB3*0301, DRB5*0101; DQB1*0301, DQB1*0601, DRB1*1303, DRB1*1502, DRB3*0101, DRB5*0102; DQB1*0301, DRB1*0401, DRB1*1101, DRB3*0202, DRB4*0103; DQB1*0202, DQB1*0602, DRB1*0701, DRB1*1501, DRB4*0103, DRB5*0101
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 4/22 patients responded to this peptide.

HXB2 Location p24 (165–179)
Author Location Gag (297–311)
Epitope VDRFYKTLRAEQASQ
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade SF162 *HIV component:* Gag, gp120, gp140ΔV2 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Th support of CTL response, Chromium-release assay
Keywords vaccine-induced epitopes, Th1, Th2
References Gavioli *et al.* 2008

- It was demonstrated that co-immunization with Tat broadens in vivo epitope-specific CD8 and CD4 responses to heterologous proteins and thus can be considered as an adjuvant. Mice immunized with Gag and Tat responded to 11 T cell Gag epitopes, 5 more than those detected in mice vaccinated with Gag alone. Mice immunized with Env and Tat, responded to 17 T cell Env epitopes, 12 more than those detected in mice vaccinated with Env alone.
- Co-immunization with Tat specifically drove Th1 responses and did not affect Th2 responses.
- Both Th1 and Th2 responses against Tat were not significantly affected by co-immunization with Env.
- This peptide epitope was recognized by both mice co-immunized with Gag and Tat, and by mice immunized with Gag alone.

HXB2 Location p24 (166–178)
Author Location p24
Epitope DRFFKTLRAEQAT
Immunogen HIV-1 infection, vaccine
Vector/Type: modified vaccinia Ankara (MVA) *Strain:* A clade, multiple epitope immunogen *HIV component:* p17/p24 Gag
Species (MHC) human
Country United Kingdom
Assay type proliferation, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords HAART, ART, vaccine-induced epitopes, therapeutic vaccine
References Ondondo *et al.* 2006

- A vaccinia-gag vaccine stimulated broad functional T helper responses in 16 chronically infected HAART patients. Gag-specific CD4+ T cell responses targeted known and new epitopes, several of which were also recognized by HIV-uninfected subjects.
- Both DRFFKTLRAEQAT and FFKTLRAEQATQE stimulated stronger response than 15-mer originally tested peptide DRFFKTLRAEQATQE. Peptides lacking FKTLRAEQA (FKTLRAEQATQEVKNW and RDYVDRFFKTLRAEQA) did not stimulate a response, suggesting that the FKTLRAEQA, which fits the predicted peptide-binding motif for HLA-DRB1*1301 and *1302, represented the core binding region of two distinct epitopes in this region.

HXB2 Location p24 (166–180)
Author Location p24 (166–180)
Epitope DRFFKTLRAEQATQE
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag
Species (MHC) human
Assay type proliferation, CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords vaccine antigen design
References Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.
- 3/8 subjects responded to this epitope.

T-Helper CD4+

HXB2 Location p24 (167–178)
Author Location p24 (167–178 B Consensus)
Epitope RFYKTLRAEQAS
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101, DRB1*0401, DRB1*0405, DRB1*0701, DRB1*1101, DRB1*1501, DRB5*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This is the core of the peptide and was the most often recognized, with responses by 58% of the study group. The core epitope, RFYKTLRAEQAS, could bind 7/8 HLA-DR molecules tested.

HXB2 Location p24 (168–179)
Author Location p24 (168–179 B Consensus)
Epitope FYKTLRAEQASQ
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101, DRB1*0401, DRB1*1101, DRB5*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This is the core of the peptide and was the most often recognized, with responses by 58% of the study group. The core epitope, FYKTLRAEQASQ, could bind 4/8 HLA-DR molecules tested.

HXB2 Location p24 (168–180)
Author Location p24 (168–180 B Consensus)
Epitope FYKTLRAEQASQE
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101, DRB1*0401, DRB1*0405, DRB1*1101, DRB1*1501, DRB5*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This is the core of the peptide and was the most often recognized, with responses by 58% of the study group. The core epitope, FYKTLRAEQASQE, could bind 6/8 HLA-DR molecules tested.

HXB2 Location p24 (168–180)
Author Location p24
Epitope FFKTLRAEQATQE
Immunogen HIV-1 infection, vaccine
Vector/Type: modified vaccinia Ankara (MVA) *Strain:* A clade, multiple epitope immunogen *HIV component:* p17/p24 Gag
Species (MHC) human
Country United Kingdom
Assay type proliferation, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords HAART, ART, vaccine-induced epitopes, therapeutic vaccine
References Ondondo *et al.* 2006

- A vaccinia-gag vaccine stimulated broad functional T helper responses in 16 chronically infected HAART patients. Gag-specific CD4+ T cell responses targeted known and new epitopes, several of which were also recognized by HIV-uninfected subjects.
- Both DRFFKTLRAEQAT and FFKTLRAEQATQE stimulated stronger response than 15-mer originally tested peptide DRFFKTLRAEQATQE. Peptides lacking FKTLRAEQA (FKTLRAEQATQEVKNW and RDYVDRFFKTLRAEQA) did not stimulate a response, suggesting that the FKTLRAEQA, which fits the predicted peptide-binding motif for HLA-DRB1*1301 and *1302, represented the core binding region of two distinct epitopes in this region.

HXB2 Location p24 (169–177)
Author Location p24 (169–177 B Consensus)
Epitope YKTLRAEQA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101)

T-Helper CD4+

Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This is the core of the peptide and was most often recognized, with responses by 58% of the study group. This core epitope could bind only 1/8 of HLA-DR molecules tested.

HXB2 Location p24 (169–178)
Author Location p24 (301–310 HZ321)
Epitope YKTLRAEQAS
Subtype AG
Immunogen vaccine
Vector/Type: gp120 depleted virus HZ321 (REMUNE(TM)) *Strain:* AG recombinant HZ321 *HIV component:* virus *Adjuvant:* Incomplete Freund's Adjuvant (IFA), CpG immunostimulatory sequence (ISS)
Species (MHC) macaque
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords vaccine-induced epitopes, adjuvant comparison, vaccine antigen design
References Silvera *et al.* 2004

- Macaques were immunized with gp120-depleted HIV-1 together with incomplete Freund's adjuvant and CpG-ODN. All four immunized animals had high anti-p24 antibody titers, while three animals showed HIV-1-specific CD4+ and CD8+ T-cell responses.

HXB2 Location p24 (169–179)
Author Location Gag (301–311)
Epitope YKTLRAEQASQ
Epitope name Gag 15.5
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade *HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu
Species (MHC) macaque
Assay type T-cell Elispot, Intracellular cytokine staining
Keywords subtype comparisons, variant cross-recognition or cross-neutralization, memory cells
References Amara *et al.* 2005

- Clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02_AG consensus Gag in macaques. The activity was better-conserved for CD8 than CD4 T cells.
- 3/5 CD8 epitopes and 2/8 CD4 epitopes were conserved across multiple HIV-1 clades. All 5 CD8, and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation.
- The similar reported human epitopes in this case is DYVDRFYKTLRAEQA. HLA restriction: DRB1*1302.
- The response elicited to the B clade epitope YKTLRAEQASQ cross-reacts with the CRF02_AG form fKTLRAEQAtQ. Other clades mostly have same substitutions in these positions ([y/f]KTLRAEQA[s/t]Q).

HXB2 Location p24 (169–183)
Author Location
Epitope YKTLRAEQASQEVKN
Epitope name G076
Immunogen HIV-1 infection
Species (MHC) human
Country Canada
Assay type proliferation, Flow cytometric T-cell cytokine assay
Keywords memory cells
References Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN-γ, but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN-γ only-producing cells are short lived.

HXB2 Location p24 (169–188)
Author Location Gag (301–320 LAI)
Epitope YKTLRAEQASQEVKNWMTET
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other
Species (MHC) transgenic mouse (DR1)
Country France
Assay type proliferation, CD4 T-cell Elispot - IFNγ, Chromium-release assay
Keywords computational epitope prediction, Th1
References Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQNANPDCKTILKALGPA, KTILKALGPAATLEEMMTAC) were novel.

T-Helper CD4+

- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTILKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQNANPDCKTILKALGPA, NKIVRMYSPTSILDIRQGPK.

HXB2 Location p24 (173–187)
Author Location Gag (301–315 HXB-2)
Epitope RAEQASQEVKNWMTE
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC DQB1*0301, DQB1*0601, DRB1*1303, DRB1*1502, DRB3*0101, DRB5*0102
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

HXB2 Location p24 (175–199)
Author Location p17 (307–331 PV22)
Epitope EQASQEVKNWMTETLLVQNANPDCK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*03)
Donor MHC A29, A30, B35, B8, DRB1*03, DRB1*13
Keywords HAART, ART, Th1, Th2, TCR usage
References Lotti *et al.* 2002

- 10/49 chronically HIV-1 infected patients had low p55-Gag-specific CD4+ T cell responses prior to therapy, and these responses remained unchanged 3 and 6 months after initiation of HAART. There was no difference in level of response in those with or without a detectable p55 response.
- For one individual, patient F45 CDC stage A2, CD4+ p55 responding clones were generated. Her response was consistently strong and heterogeneous in terms of HLA restriction and Vβ usage, and some clones had a Th1 cytokine secretion profile (high IFNgamma production) while some had a Th2 profile (high IL-4 and IL-5 production). 5/10 CD4+ clones could also induce cytotoxicity.
- 4/10 clones from patient F45 had their epitopes mapped using overlapping peptides. Clone 26 recognized this peptide sequence restricted by DRB1*03. This clone had a SI of 4.1 to p55, 5.3 to peptide, secreted high levels of IFN-γ, indicative of a Th1 response, but also IL-4 and IL-5. Clone 26 had no cytotoxic activity.

HXB2 Location p24 (181–198)
Author Location p24 (313–327)
Epitope VKNWMTETLLVQNANC
Immunogen in vitro stimulation or selection
Species (MHC) human
References Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.
- Matches 3/3 anchor residues for HLA DR: **V**KNWM**T**ET**L**

HXB2 Location p24 (185–202)
Author Location p24 (185–202 B Consensus)
Epitope MTETLLVQNANPDCKTIL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p24 (189–203)
Author Location Gag (324–338)
Epitope LLVQNANPDCKTILR
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was not detectable.

HXB2 Location p24 (189–208)
Author Location Gag (321–340 LAI)
Epitope LLVQNANPDCKTILKALGPA
Subtype B

T-Helper CD4+

Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other
Species (MHC) human, transgenic mouse (DR1)
Country France
Assay type proliferation, CD4 T-cell Elispot - IFNγ, Chromium-release assay
Keywords computational epitope prediction, Th1
References Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQNANPDCKTILKALGPA, KTILKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTILKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQNANPDCKTILKALGPA, NKIVRMYSPTSILDIRQGPK.

HXB2 Location p24 (199–217)
Author Location Gag (331–350 LAI)
Epitope `KTILKALGPAATLEEMMTA`
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other
Species (MHC) human, transgenic mouse (DR1)
Country France
Assay type proliferation, CD4 T-cell Elispot - IFNγ, Chromium-release assay
Keywords computational epitope prediction, Th1
References Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQNANPDCKTILKALGPA, KTILKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTILKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQNANPDCKTILKALGPA, NKIVRMYSPTSILDIRQGPK.

HXB2 Location p24 (201–215)
Author Location Gag (333–347 HXB-2)
Epitope `ILKALGPAATLEEMM`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

HXB2 Location p24 (205–219)
Author Location Gag (337–351 HXB-2)
Epitope `LGPAATLEEMMTACQ`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
References Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

HXB2 Location p24
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A01, A32, B*1410, B15; A*3101, A68, B*4403, B51
Country Spain
Assay type proliferation, CD4 T-cell Elispot - IFNγ
Keywords HAART, ART, supervised treatment interruptions (STI)
References Arnedo-Valero *et al.* 2004

- T cell immune responses following STI were monitored in two chronically HIV-1 infected partners (A and B) who had contracted HIV-1 during 1992. STI induced strong transitory CD4+ and CD8+ T cell responses in both patients. The viruses remained very closely related over 10 years, despite the two individuals having different HLA types; the authors suggest the maintained similarity does not support a strong role for HLA driven HIV diversity as has been claimed in Moore et al. (Science 2002).
- During the second treatment stop, patient A developed a strong proliferative response to p24, and multiple strong CD8+ T cell repsonses to Env, Pol, Gag and Nef. This patient was able to control viral load for two years follow up without therapy. Patient B developed a very weak CD4+ T cell response against p24 during breaks in therapy, and had CD8+ responses to two epitopes. Patient A: A01, A32, B*1410, B15; Patient B: A*3101, A68, B*4403, B51.

HXB2 Location p24
Author Location p24
Epitope
Immunogen vaccine
HIV component: p24 Gag *Adjuvant:* Keyhole Limpit Haemocyanin (KLH)
Species (MHC) human
Country United States
Assay type proliferation, Th support of CTL response, Delayed-type hypersensitivity (DTH)
Keywords HAART, ART, immune dysfunction
References Lange *et al.* 2004

- ART treated HIV-1 infected patients with strong lymphoproliferative responses to HIV p24 did not have enhanced immune responses relative to those that had low level proliferative responses. Immune function was measured by DTH to diphteria/tetanus-toxoid and Keyhole limpet hemocyanin, maturation and frequency of CD8+ T cells, frequency of CD4 and CD8+ T cells, and cytotoxic molecules on HIV specific T cells.
- A higher level of persistant viral replication in circulating CD4+ cells was associated with patients who showed high lymphoproliferative responses to HIV p24.

HXB2 Location p24
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type proliferation, Intracellular cytokine staining
Keywords HAART, ART, immune dysfunction
References Palmer *et al.* 2004

- The cytokine and maturation profiles as well as the proliferative capacity of HIV-1 Gag-specific CD4+ T cells was analyzed in 4 groups of HIV-1 infected patients: HAART treated, HAART suppressed, treatment naive and untreated, slowly progressing. Measurements of Gag-specific CD4+ T cell maturation, proliferation and plasma viremia indicate that virologic control is impaired due to HIV-1 affects on the maturation profiles of CD4+ T cells.

HXB2 Location p24
Author Location p24 (HXB2)
Epitope
Subtype B
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human
Country Canada, Kenya
Assay type proliferation, Intracellular cytokine staining
Keywords HIV exposed persistently seronegative (HEPS)
References Alimonti *et al.* 2005

- CD4+ T cell responses were studied in high-risk HIV-seronegative (Kenya) women, HIV-positive women (Kenya) and low-risk HIV-seronegative women (Canada), using 15mer peptides (overlapping by 11 amino acids) spanning p24 HXB2 sequence.
- Compared to HIV-positive women, high-risk HIV-seronegative women had significantly lower level of CD4+ specific immune activation and apoptosis. Lower proportion of HIV-seronegative women showed responses by the short-term CD4+ specific inracellular cytokine staining assay, while the proportions showing responses by the long-term CD8+-depleted T cell proliferation assay were similar. HIV-seronegative responders had 4.5-fold stronger response than the HIV+ group.

HXB2 Location p24
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country Australia
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords rate of progression
References Dyer *et al.* 2008

- Mechanisms that differentiate long term non-progressors from delayed progressors were studied.
- While host and viral genetic factors contribute to delayed progression, the single factor that functionally defined non-progression was Gag-specific CD4+ T cell proliferation. Decline in this protective p24 response in slow progressors preceded or coincided with disease progression.

III-B-4 Gag p2p7p1p6 Helper/CD4+ T-cell epitopes

HXB2 Location p2p7p1p6 (8–25)
Author Location (clade B consensus)
Epitope TNSATIMMQRGNFRNQRK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*02, A*03, B*1402, B*5101, Cw*15, DRB1*01AH, DRB1*1302
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords escape
References Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- QKQEtIDKELYPLASLk variant was present at first time point and coincided with a positive CD4+ response. QKQEttDKELYPLASLk variant was present 4 weeks later and response was lost.

HXB2 Location p2p7p1p6 (16–30)
Author Location (clade B consensus)
Epitope QRGNFRNQRKTVKCF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*02, A*03, B*1402, B*5101, Cw*15, DRB1*01AH, DRB1*1302

T-Helper CD4+

Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords escape
References Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- QkGNFRNQgKTVKCF variant was present at first time point and coincided with a positive CD4+ response. QkGNFkNQgKTVKCF variant was present 4 weeks later and also coincided with a positive response.

HXB2 Location p2p7p1p6 (18–37)
Author Location p24 (384–400 HXB2)
Epitope `GNFRNQRKIVKCFNCGKEGH`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*1501 or DR51)
Donor MHC DQ1, DQ5, DR51, DRB1*0101, DRB1*1501
Assay type proliferation, T-cell Elispot, Intracellular cytokine staining
Keywords HAART, ART, Th1
References Boritz *et al.* 2003

- HIV infected individuals with advanced disease often have only weak or undetectable HIV-specific Th responses, and HAART can sometimes restore Th HIV recognition in such cases. The repertoire of Th responses to p24 in an individual who responded to HAART after having a CD4+ T-cell count of 0 cells/ul was determined. Eleven clonotypes were found among 13 clones, recognizing 8 distinct epitopes, with a range of MHC affinities and functional avidities. Multiple Gag p24 peptides were recognized using CD4 EliSpot assays based on samples from 6 additional HAART-treated CD4 T-cell-reconstituted subjects.
- The two Th clones that recognized this epitope utilized TCR Vβ2 and Bβ8.1.

HXB2 Location p2p7p1p6 (22–32)
Author Location Gag (385–395)
Epitope `NQRKIVKCFNC`
Epitope name Gag 20.2
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade *HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu
Species (MHC) macaque
Assay type T-cell Elispot, Intracellular cytokine staining
Keywords subtype comparisons, memory cells
References Amara *et al.* 2005

- Clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02_AG consensus Gag in macaques. The activity was better-conserved for CD8 than CD4 T cells.
- 3/5 CD8 epitopes and 2/8 CD4 epitopes were conserved across multiple HIV-1 clades. All 5 CD8, and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation.
- The similar reported human epitope in this case is GNFRNQRKIVKCFNCGKEGH. HLA restriction: DR15/51.
- The response elicited to the B clade epitope NQRKIVKCFNC does not cross-react with the CRF02_AG form gQRIlKCFNC. The epitope is highly variable across other clades.

HXB2 Location p2p7p1p6 (27–37)
Author Location Gag (390–400)
Epitope `VKCFNCGKGEH`
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was not detectable.

HXB2 Location p2p7p1p6 (30–44)
Author Location p15 (393–407 IIIB, B10)
Epitope `FNCGKEGHTARNCRA`
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location p2p7p1p6 (37–52)
Author Location p15 (37–52 B Consensus)
Epitope `HIAKNCRAPRKKGCWK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 14% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.

T-Helper CD4+

- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p2p7p1p6 (43–60)
Author Location (clade B consensus)
Epitope RAPRKKGCWKCGKEGHQM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0201, A*290201, B*1501, B*4403, Cw*0304, Cw*1601, DRB1*0401, DRB1*0701; A*0101, A*0201, B*4001, C*0304, DRB1*0801, DRB1*1301
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords escape
References Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- In one patient, HIArNCkAPRKKGCWK variant was present at first time point and there was no CD4+ response. HIArNCkAPRrKGCWK variant was present 4 weeks later and coincided with a positive response. In another patient, B consensus variant HIAKNCRAPRKKGCWK was present at first time point and coincided with a positive response. HIAKNCRAsRKKGCWK variant present four weeks later coincided with a significantly diminished response.

HXB2 Location p2p7p1p6 (43–60)
Author Location (clade B consensus)
Epitope RAPRKKGCWKCGKEGHQM
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0201, A*290201, B*1501, B*4403, Cw*0304, Cw*1601, DRB1*0401, DRB1*0701
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords escape
References Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- In one patient, kAPRKKGCWKCGKEGHQM variant was present at first time point and there was no CD4+ response. kAPRrKGCWKCGKEGHQM variant was present 4 weeks later and coincided with a positive response. In another patient, B consensus variant RAPRKKGCWKCGKEGHQM was present at first time point and coincided with no response. RAsRKKGCWKCGKEGHQM variant present four weeks later also coincided with no response.

HXB2 Location p2p7p1p6 (55–69)
Author Location p15 (418–432 IIIB, B10)
Epitope KEGHQMKDCTERQAN
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location p2p7p1p6 (60–74)
Author Location p15 (423–437 IIIB, B10)
Epitope MKDCTERQANFLGKI
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location p2p7p1p6 (62–72)
Author Location Gag (426–436)
Epitope DCTERQANFLG
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was not detectable.

HXB2 Location p2p7p1p6 (66–81)
Author Location p15 (66–81 B consensus)
Epitope RQANFLGKIWPSHKGR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DR01*0401, DRB1*0101, DRB1*0405, DRB1*1101, DRB1*1302, DRB1*1501, DRB5*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 28% of the study group.

T-Helper CD4+

- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The peptides that were recognized by the most people were able to bind broadly to multiple HLA-DR molecules.This peptide showed high cross-reactive binding capacity and bound to 7/8 tested HLA-DR molecules.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p2p7p1p6 (72–89)
Author Location p15 (72–89 B Consensus)
Epitope GKIWPSHKGRPGNFLQSR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 17% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p2p7p1p6 (76–83)
Author Location p24 (439–446 LAI)
Epitope PSYKGRPG
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.
- Schrier lists this peptide as p24(439-446), but because of the numbering used for Gag epitopes, we placed it in p2p7p1p6.

HXB2 Location p2p7p1p6 (83–97)
Author Location p15 (446–460 BRU)
Epitope GNFLQSRPEPTAPPA
Immunogen in vitro stimulation or selection
Species (MHC) mouse (H-2^{b})
References Vaslin *et al.* 1994

- Peptide G4: could prime for *in vitro* immunoproliferative responses and for subsequent IgG responses.

HXB2 Location p2p7p1p6 (89–96)
Author Location p24 (466–473 LAI)
Epitope REETTTPS
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.
- Schrier lists this peptide as p24(466-473), but it is in p2p7p1p6.

HXB2 Location p2p7p1p6 (93–112)
Author Location p15 (93–112 B Consensus)
Epitope TAPPEESFRFGEETTTPSQK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 14% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p2p7p1p6 (98–112)
Author Location p15 (473–487 IIIB, B10)
Epitope ESFRSGVETTTPPQK
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- Peptides were identified that commonly evoke T-cell responses – 50% of 90 HIV+ people had a T-cell response to this peptide.

HXB2 Location p2p7p1p6 (103–120)

Author Location (clade B consensus)
Epitope GEETTTPSQKQEPIDKEL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*2402, A*680301, B*3502, B*3905, Cw*0401, Cw*0702, DRB1*0407, DRB1*1104
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords escape
References Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- GEEiTTPSQKQEtIDKEL variant was present at first time point and coincided with a positive CD4+ response. GEEiTTPSQKQEttDKEL variant was present 4 weeks later and response was lost.

HXB2 Location p2p7p1p6 (104–113)
Author Location Gag (466–476)
Epitope FEETTPAPPKQ
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was detectable.

HXB2 Location p2p7p1p6 (106–116)
Author Location Gag (469–479)
Epitope TTTPPQKQEPI
Epitope name Gag 24.3
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade *HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu
Species (MHC) macaque
Assay type T-cell Elispot, Intracellular cytokine staining
Keywords subtype comparisons, memory cells
References Amara *et al.* 2005

- Clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02_AG consensus Gag in macaques. The activity was better-conserved for CD8 than CD4 T cells.
- 3/5 CD8 epitopes and 2/8 CD4 epitopes were conserved across multiple HIV-1 clades. All 5 CD8, and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation. TTTPPQKQEPI was not reported for human infections.
- The response elicited to the B clade epitope TTTPPQKQEPI does not cross-react with the CRF02_AG form ipssP-KQEPr. The epitope is highly variable across other clades.

HXB2 Location p2p7p1p6 (111–127)
Author Location p15 (111–127 B Consensus)
Epitope QKQEPIDKELYPLASLR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 17% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location p2p7p1p6 (111–127)
Author Location (clade B consensus)
Epitope QKQEPIDKELYPLASLR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*2402, A*680301, B*3502, B*3905, Cw*0401, Cw*0702, DRB1*0407, DRB1*1104
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords escape
References Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.

- QKQEtIDKELYPLASLk variant was present at first time point and coincided with a positive CD4+ response. QKQEttDKELYPLASLk variant was present 4 weeks later and response was lost.

HXB2 Location p2p7p1p6 (117–131)
Author Location p6 (32–46 clade B consensus)
Epitope DKELYPLASLRSLFG
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (DRB1*0101, DRB1*0401, DRB1*0405, DRB1*0701, DRB1*1101, DRB1*1501, DRB5*0101)
Country Brazil
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 brazilian HIV-1 chronically infected individuals.
- While the reacting peptide is DKELYPLASLRSLFG, shorter LYPLASLRS was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

HXB2 Location p2p7p1p6 (117–137)
Author Location Gag p6 (480–500 IIIB)
Epitope DKELYPLTSLRSLFGNDPSSQ
Immunogen in vitro stimulation or selection
Species (MHC) human
Donor MHC DQ2, DQ3, DR4, DR7
Keywords immunodominance, Th1, Th2, TCR usage
References Venturini *et al.* 2002

- PBMC from a seronegative donor, the healthy brother of a pair of monozygotic twins discordant for HIV-1 infection, were used to generate HIV-1 Gag-specific CD4+ T-cell clones by *in vitro* immunization with HIV-1 overlapping 20mer peptides spanning p55. Six clones were generated by limiting dilution. All reacted with p24 except one which recognized a p24 peptide and a p6 peptide. All CD4+ T cell clones were HLA class II DR restricted.
- Clone 74 recognized two peptides, including this one, with a Th1 response using TCR Vβ 13 (13s1); it required 200 ng/ml (100 nM) and 1 µg/ml (0.5 µM) for stimulation by peptides 480-500 and 261-280, respectively. Sequencing TCR Vβ regions of colonies from clone 74 suggested this was a clonal population. Clone 74 was activated in response to vaccinia virus Gag-infected B-LCL, so it could recognize naturally processed epitopes.

HXB2 Location p2p7p1p6 (118–128)
Author Location Gag (479–489)
Epitope KDREPLTSLKS
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country India
Assay type CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords subtype comparisons
References Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN-γ response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN-γ CD4+ response). IL-2 response was not detectable.

HXB2 Location p2p7p1p6 (118–137)
Author Location p15 (118–137 B Consensus)
Epitope KELYPLASLRSLFGNDPSSQ
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 17% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

III-B-5 Gag Helper/CD4+ T-cell epitopes

HXB2 Location Gag
Author Location p55
Epitope
Immunogen HIV-1 infection
Species (MHC) human (DRB1*03, DRB1*13)
Donor MHC A29, A30, B35, B8, DRB1*03, DRB1*13
Keywords HAART, ART, Th1, Th2, TCR usage
References Lotti *et al.* 2002

- 10/49 chronically HIV-1 infected patients had low p55-Gag-specific CD4+ T cell responses prior to therapy, and these responses remained unchanged 3 and 6 months after initiation of HAART. There was no difference in level of response in those with or without a detectable p55 response.
- For one individual, patient F45 CDC stage A2, CD4+ p55 responding clones were generated. Her response was consistently strong and heterogeneous in terms of HLA restriction and Vβ usage. Two clones were DRB1*13 restricted and used TCR Vβ 17+19 or 5.1. Three clones were DRB1*03 restricted and used TCR Vβ 22. Some clones had a Th1 cytokine secretion profile (high IFNgamma production) while some had a Th2 profile (high IL-4 and IL-5 production).

HXB2 Location Gag
Author Location p24
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Gag
Species (MHC) mouse (H-2^d)
References Qiu *et al.* 2000

- Mice were injected with plasmid DNA at 0, 2 and 4 weeks and lymphocyte proliferation was measured after 6 weeks with recombinant p24 protein.
- Secreted HIV-1 Gag expression vectors generated a stronger response than standard Gag or cytoplasmic Gag expression vectors.
- IFN-γ levels were increased compared to an undetectable IL-4 response.
- CTL levels were also increased in secreted Gag expression vaccination studies.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen vaccine
Vector/Type: DNA, DNA with protein boost *Strain:* B clade LAI *HIV component:* Gag, Nef, Tat *Adjuvant:* IL-18
Species (MHC) mouse (H-2^d)
Keywords Th1, Th2
References Billaut-Mulot *et al.* 2001

- DNA vaccinated BALB/c mice primed and boosted with a multiepitopic vaccine with IL18 showed lymphoproliferative responses 7 weeks post immunization.
- Strong but non-lasting HIV-specific CTL responses were detected by a Cr-release assay and DNA prime + DNA boost was more effective than DNA prime + protein boost.
- Immunization with either the multiepitopic DNA or with the mixed DNA vaccine resulted in Th1 cytokines production (IL-2 and IFN-γ) in spleen cell cultures stimulated by Tat and Gag, while Th2 cytokines IL-4 and IL-10 production was not detectable.
- Co-administration of IL18 increased T-cell responses but decreased anti-HIV antibody levels.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen vaccine
Vector/Type: coxsackievirus *HIV component:* p24 Gag
Species (MHC) mouse (H-2^d)
References Halim *et al.* 2000

- An avirulent rec coxsackievirus (CB4-P) construct was generated that can express p24 Gag sequences – CB4-P is attenuated even in immunodeficient mice and T help responses can be elicited from peptides embedded in a surface loop of the VP1 capsid.
- This paper describes the vaccine strategy and generation of constructs, and employs amino-terminal fusion of Gag sequences to the viral polyprotein with subsequent cleavage to elicit CTL responses via MHC class I presentation in BALB/c mice.

HXB2 Location Gag
Author Location gp120 (V3) and p24 (IIIB, MN, BH10)
Epitope
Subtype A, B
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *Strain:* A clade UG5.94UG018, B clade IIIB *HIV component:* Gag, gp120
Species (MHC) mouse (H-2^d)
Keywords subtype comparisons
References Buonaguro *et al.* 2002

- Different HIV strains were used for different regions: gp120 A clade UG5.94UG018; Gag HIV-1 IIIB
- BALB/c mice were given intraperitoneal immunization in the absence of adjuvants with virus-like particles (VLPs) expressing recombinant subtype A gp120 and Pr55gag.
- High dose-independent humoral responses were elicited against both gp120 and p24 peptides, and CTL responses were observed against target cells carrying vaccinia expressed gp120 and Gag.

HXB2 Location Gag
Author Location Gag (HXB2)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: Listeria monocytogenes *Strain:* B clade HXB2 *HIV component:* Gag
Species (MHC) mouse (H-2^b, H-2^d)
Keywords Th1
References Mata *et al.* 2001

- BALB/c and C57BL/6 mice were immunized with *Listeria monocytogenes* (Lm-Gag) expressing HIV-1 HXB2 Gag and mice were challenged with vaccinia expressing Gag.
- *L. monocytogenes* is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm; secreted *L. monocytogenes* antigens are processed and presented by both class I and class II pathways.
- CD4+ Th1 T-cells mediated the Gag specific immunological protection in mice immunized with Lm-Gag and challenged with vaccinia-Gag.
- Gag-specific CTL may enhance viral clearance via IFN-γ secretion, but are not essential for immunity.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen vaccine
Vector/Type: Listeria monocytogenes *HIV component:* Gag
Species (MHC) mouse (H-2^b, H-2^d)
Keywords review, Th1
References Mata & Paterson 2000

- BALB/c and C57BL/6 mice were immunized with *Listeria monocytogenes* (Lm-Gag) expressing HIV-1 HXB2 Gag and mice were challenged with vaccinia expressing Gag.
- *L. monocytogenes* is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm; secreted *L. monocytogenes* antigens are processed and presented by both class I and class II pathways.
- This article is a review of *L. monocytogenes* biology and its potential as a vaccine vector for HIV, comparing to other vector systems, and discussing CD4+ Th1 T-cell-mediated Gag specific immunological protection in mice and the Gag CTL response.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: virus-like particle (VLP) *HIV component:* p17 Gag, p24 Gag
Species (MHC) human
References Kelleher *et al.* 1998b

- Immunization of HIV+ people with a p24-VLP virus-like particle did not significantly impact CD4+ lymphocyte count, viral load, or p24 antibody titre.
- Immunization with p24-VLP showed a modest, short-lived increased proliferative response to p24.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: gp120 depleted virus HZ321 (REMUNE(TM)), protein *Strain:* AG recombinant HZ321 *HIV component:* gp120 depleted virus, p24 Gag
Species (MHC) human
References Maino *et al.* 2000

- 18 HIV-1-seropositive patients with a low frequency or no detectable CD4+ T cell response to HIV-1 antigen received an HIV-1 immunogen consisting of 10 units of native p24 and 100 ug of HZ321, a gp120 depleted antigen.
- Using flow-cytometric methods, HIV-1 specific CD4+ T cells were shown to increase in response to immunization – in many patients significant enhancement was observed after a single immunization.
- The frequency of CD4+ T cells expressing cytokines in response to antigen by FACS was correlated with a lymphoproliferation assay.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, supervised treatment interruptions (STI)
References Ruiz *et al.* 2000

- Structured treatment interruption in chronically infected patients allowed recovery of p24 Th proliferative responses after HAART therapy discontinuation in 2/12 patients.
- The Th response to p24 was identified during peak viremia in one patient, while in the second it was noted when viremia was controlled after restarting antiviral therapy.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Lori *et al.* 1999

- Ten patients with acute, pre-seroconversion HIV-1 infections were treated with didanosine, indinavir and hydroxyurea – this treatment is associated with normalization of immune parameters.
- A vigorous HIV-specific Th response (stimulation index greater than 8) was observed in 7/8 patients treated before complete WB seroconversion, but in only 1/5 controls treated after seroconversion.
- Vigorous Th responses were detected as early as 34 days after treatment begin.
- Patients treated prior to seroconversion had no loss of naive CD4 T lymphocytes, recovery of up to 35% of the naive CD8 cells in several weeks, and a reduced latent viral reservoir.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, supervised treatment interruptions (STI), Th1
References Haslett *et al.* 2000

- 11/22 adult patients on HAART showed strong CD4+ T-cell IFN-γ producing Th1 responses to HIV p24.
- The magnitude of the Th1 response correlated with previous interruptions in HAART, suggesting the interruptions primed or boosted the response.
- In contrast, the magnitude of the CD8+ CTL response did not correlate with interruptions in therapy, although a greater breadth in response was associated with interruptions in HAART.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: virus-like particle (VLP) *HIV component:* p17 Gag, p24 Gag
Species (MHC) human
References Klein *et al.* 1997

T-Helper CD4+

- Immunization of HIV+ people with a HIV-1 p17/p24 Ty virus-like particle (p24-VLP) resulted in a marginal, short-lived increased proliferative response to p24 and p17 and a transient elevation in viral load.
- Two of four subjects that received 500 or 1000 ug of p24-VLP had an increase in gag-specific CTL.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen vaccine
Vector/Type: gp120 depleted virus HZ321 (REMUNE(TM)) *Strain:* AG recombinant HZ321 *HIV component:* gp120 depleted virus
Species (MHC) human
Keywords subtype comparisons
References Moss *et al.* 1998

- Immunization with gp120 depleted HZ321 virus (REMUNE^{TM}) triggered an increase in lymphocyte proliferative response to native p24, a clade B virus and clade E viral antigens – Z321 is clade A in env and clade G in gag. Moss *et al.* [1998]

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Rosenberg *et al.* 1999

- This paper reviews the role of T-cells in viral control and HIV disease outcome.
- Strong anti-p24 lymphoproliferative responses were found in seven persons who were treated with potent anti-viral therapy during acute HIV-1 infection syndrome.
- This suggests that Th cells are part of the normal response to HIV-1 infection, but their numbers are rapidly diminished by either being infected during the peak viremia or by activation-induced cell death – if peak viremia can be controlled, a robust anti-p24 Th response can be maintained.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Rosenberg & Walker 1998

- Strong Th responses have been found in rare individuals who effectively maintain low viral loads.
- If aggressive anti-retroviral therapy is given prior to sero-conversion, strong helper responses can be maintained.

HXB2 Location Gag
Author Location p17
Epitope
Immunogen vaccine
Vector/Type: protein *HIV component:* p17 Gag
Species (MHC) mouse
References Birk *et al.* 1998a

- Different p17 genes derived from the same quasispecies and expressed and purified in E. coli primed different Th 1 and Th 2 subsets in mice, depending on their H-2 type.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Schiller *et al.* 2000

- Study of parameters that might influence the performance or reproducibility of clinical Th proliferative assays.
- HIV-1 replication *in vitro* is unlikely to influence the assay.
- Gag proteins including p17 and possibly p7 as well as p24 perform better than p24 alone.
- Frozen samples can be used in T-proliferative assays, but with lower radiolabled thymidine incorporation.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Pitcher *et al.* 1999

- In contrast to earlier studies suggesting that HIV-1 specific Th responses were eliminated in the early stages of infection in most HIV+ individuals, this paper shows using flow cytometric detection of antigen-induced cytokines that Th-1 CD4+ memory gag-specific Th cells are detectable in most HIV+ subjects.
- Effective anti-viral therapy reduces the frequency of these cells, presumably due to reduced antigenic stimulus.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Plana *et al.* 1998

- Patients from later stages of infection given HAART do not show restoration of HIV-1 specific Th proliferative responses.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Kelleher *et al.* 1998a

- Env and gag Th epitopes were pooled and used to test Th proliferative responses after IL2 therapy – while IL2 therapy causes an increase in CD4+ lymphocyte count, it does not increase HIV-1 specific proliferative responses.

HXB2 Location Gag
Author Location Gag (LAI)

T-Helper CD4+

Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost *Strain:* B clade LAI *HIV component:* Env, Gag
Species (MHC) macaque
Keywords Th1, Th2
References Kent *et al.* 1998

- Priming with an HIV-DNA vaccine and boosting with a vaccinia construct induced greater levels of HIV T-cell immunity than either vaccine alone.
- The proliferative response to Env and Gag after the DNA vaccination had a mean SI of 1.5-4, but after boosting with rHIV-fowlpox virus, there was a 6-17 fold increase in the mean SI for HIV Gag and Env – The Th response happened despite a fall in Ab titers, suggesting that the Th response was primarily Th1, not Th2. The CTL response was also enhanced.

HXB2 Location Gag
Author Location
Epitope
Immunogen vaccine
Vector/Type: DNA, protein, virus-like particle (VLP), ISCOM
Species (MHC) macaque
Keywords Th1, Th2
References Heeney *et al.* 1999

- Ten different vaccine strategies were evaluated for their ability to protect from infection in a rhesus macaque model using a non-pathogenic SHIV challenge.
- Protection correlated with the magnitude of NAb responses, beta-chemokines, and a balanced Th response.
- DNA, protein+adjuvant, VLP and ISCOM vaccines were tested.
- HIV-1/ISCOMS gave the highest NAb titers, Th1 and Th2 responses, was the only vaccine formulation tested with a detectable CTL response, and gave enhanced beta-chemokine production.

HXB2 Location Gag
Author Location Gag/Pol (MN)
Epitope
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade MN *HIV component:* Env, Gag, Pol *Adjuvant:* CD80, CD86
Species (MHC) chimpanzee
References Kim *et al.* 1998

- Co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine used to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses.

HXB2 Location Gag
Author Location Gag/Pol (LAI, MN)
Epitope
Immunogen vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Protease
Species (MHC) human
References Salmon-Ceron *et al.* 1999

- A live attenuated canarypox vector expressing MN gp120 and LAI gp41/gag/protease could induce CTL and a lymphoproliferative response in healthy uninfected volunteers.

HXB2 Location Gag
Author Location p55 (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Zhang *et al.* 2001b

- T-helper cell proliferative responses to HIV p24, p55 and gp120 were tested in 27 patients with HIV infection – vigorous responses directed at Gag were detected in ten patients, but an Env specific response was detected in only one patient.
- Untreated patients showed a negative correlation between plasma viral load and HIV p24-specific T-cell responses, and the responses could be detected after extended HAART therapy with viremia below the detection limit.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, supervised treatment interruptions (STI), kinetics, Th1
References Carcelain *et al.* 2001

- Repeated structured HAART therapy interruptions (STI) in 3 chronically HIV infected patients induced rapid but transient (< 3 weeks) HIV-1 specific CD4+ Th1 responses concurrently with viral rebound, as measured by proliferation assays and by IFN-γ production by CD8-depleted PBMC.
- Kinetics suggest that viral replication leads to rapid destruction of the HIV-specific Th1 cell response.
- HIV-specific CD8+ T-cell responses were delayed relative to the Th1 responses and were not sustained.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Blankson *et al.* 2001

- 5/10 chronically HIV infected patients with low CD4+ counts who received HAART therapy and experienced immune reconstitution displayed p24, p17 and p66 T-helper CD4 proliferative responses, in contrast to 0/8 chronically HIV infected patients with high CD4+ counts at the initiation of antiretroviral treatment.
- This surprising result could be due to the low CD4 nadir patients being more likely to have thymic regeneration or a peripheral expansion of T cells.

T-Helper CD4+

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Angel *et al.* 2001

- Prolonged viral suppression resulting from potent anti-retroviral therapy allowed a T helper response to Gag p24 and PHA to develop in many HIV+ patients.
- At baseline, 2/41 (4.9%) subjects had a proliferative response to Gag p24, and 7/41 (17.1%) had a response to PHA, but by week 72 of therapy, 53% had a detectable response to p24 and 94% to PHA.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Blazevic *et al.* 2000

- Prolonged viral suppression resulting from potent anti-retroviral therapy did not allow an HIV T helper response to p24 or gp160, but Th proliferative responses to influenza, alloantigen, and PHA did develop in many HIV+ patients, and asymptomatic patients had stronger and more frequent Th response recovery than AIDS patients.

HXB2 Location Gag
Author Location Gag (SF2)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, acute/early infection
References Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the CTL response was determined using Elispot by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Individuals who were given HAART during acute or early in infection had significantly stronger proliferative responses than individuals who were chronically infected.

HXB2 Location Gag
Author Location p24 (IIIB)
Epitope
Immunogen in vitro stimulation or selection
Species (MHC) human
Keywords dendritic cells
References Engelmayer *et al.* 2001

- Recombinant canarypox virus vector containing HIV-1 sequences, upon infection of mature dendritic cells, can trigger specific lysis *in vitro* by T-cells from HIV-1 infected individuals at levels comparable to the response seen to HIV carried in vaccinia vectors.
- Recombinant canarypox virus vector containing HIV-1 sequences can also stimulate HIV-specific IFN-γ CD4+ helper T cell responses to Gag from bulk or purified CD4+ T cells.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- In 3/4 responders tested p24 gave the strongest T helper response.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen vaccine
Vector/Type: gp120 depleted whole killed virus *Strain:* AG recombinant HZ321 *HIV component:* virus *Adjuvant:* Complete Freund's Adjuvant (CFA), CpG immunostimulatory sequence (ISS)
Species (MHC) rat
References Moss *et al.* 2001

- Different HIV strains were used for different regions: subtype A env, subtype G gag
- Lewis rats simultaneously immunized with HIV-1 antigen and with immunostimulatory sequences CpG had increased Th proliferative responses, but when CpG was given as a prime prior to the injection of HIV-1 antigen it was not as effective.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen vaccine
Vector/Type: gp120 depleted whole killed virus *Strain:* AG recombinant HZ321 *HIV component:* virus *Adjuvant:* Complete Freund's Adjuvant (CFA), CpG immunostimulatory sequence (ISS)
Species (MHC) rat
References Moss *et al.* 2000

- Different HIV strains were used for different regions: subtype A env, subtype G gag

T-Helper CD4+

- Lewis rats co-immunized with HIV-1 antigen in Freund's and with immunostimulatory sequences CpG stimulated increased IFN-γ expressing CD4+ and CD8+ T cells and anti-p24 antibodies relative to antigen in Freund's without CpG.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression, Th1
References Kalams *et al.* 1999a

- The strength of p24 specific Gag proliferative responses (SIs) were inversely correlated with viral load in 21 ARV naive patients. The responses were Th1, IFN-γ producing. Proliferative responses against gp160 were rarely observed (only 4 cases).
- Gag specific CTL levels were correlated with Gag proliferative responses but were not correlated with viral load. 8 subjects lacked p24 specific Gag proliferative responses, and 4/8 had no CTLp to any HIV-1 antigen tested.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, review, rate of progression
References Kalams & Walker 1998

- This paper reviews the role of specific T cell help in many viral infections, and covers the interplay between Th, CTL and survival, and discusses briefly advantages of HAART during acute HIV infection to prevent the early decimation of the Th response in HIV infections.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression, Th1, Th2
References Wilson *et al.* 2000b

- Dysfunction of HIV-1 specific proliferative responses, but not responses to other antigens, is evident in HIV-1 progressive disease.
- Vigorous HIV-1 specific responses to p24, Nef and gp120 with SI between 8-99 were seen in 6/7 long term non-progressors (LTNP), the seventh had a borderline responses. IL-2 production was seen in all cases, and IL-4 production was also evident many responses.
- None of the progressors (0/5) had HIV-1 specific proliferative responses, or IL-2 or IL-4 induction.
- Non-HIV antigens (cytomegalovirus, PPD, Staphylococcus enterotoxin B, tetanus toxoid) gave similar responses in HIV-1 + LTNP, progressors, and HIV-1 controls.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression, Th1
References Alatrakchi *et al.* 2002

- LTNP co-infected with HCV and HIV showed higher frequencies of Th1 response to both HIV-1 p24 and HCV antigens.
- HIV-1 CD4 Th1 responses in untreated LTNP were inversely correlated with viral load.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Lange *et al.* 2002

- Cross-sectional study compares CD4 T-cell count and age matched untreated HIV-1 + patients (N = 14) with patients undergoing HAART therapy (N = 14).
- The fractions of naive and memory T-cells were comparable for both groups, as were proliferative responses to non-HIV antigens. Lymphocyte proliferation responses to HIV-1 p24 were of greater magnitude in the group treated with HAART (5/10 had SI >10, versus 1/12 in the untreated group), suggesting that ongoing viral replication impairs the anti-Gag response, and the response can be improved and restored through HAART.
- DTH responses to recall antigens were tested, and responses to C. albicans and Trichophyton were comparable in both treated and untreated patients, although patients on therapy had higher responses to mumps.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, subtype comparisons, escape, acute/early infection
References Fidler *et al.* 2002

- 37/45 patients with primary HIV infection underwent a short course of antiretroviral therapy (SCART). 29/37 patients received triple ART therapy and eight patients received four ART drugs. Initiation of SCART was effective in controlling HIV replication by ten weeks in all patients and preserving CD4+ T cell responses for up to 64 weeks after therapy.
- No induction of drug escape mutations was observed, although two individuals had escape mutations in their infecting virus at baseline.
- 34 UK infected patients were clade B infected. 11/45 subjects had non-UK acquired HIV infection, 2 were clade A, 1 was A/E, 1 was C, 1 was "untypable", the rest were B.
- Recombinant HIV-1 derived gp120, p24, p66 and overlapping peptide pools spanning Tat and Nef were employed to measure CD4 T-cell frequencies in ELISPOT assays. The strongest preservation of T helper responses 12 weeks off SCART was seen for p24-specific CD4+ T-cell responses.
- 6/8 of the untreated individuals were tested for CD4+ T-cell responses. 1 had no detectable response. 1 had detectable responses to all HIV-1 proteins tested at baseline, but this narrowed to p24 and gp120, then became undetectable by 52

T-Helper CD4+

weeks. 3 had detectable and persistent responses, but only to p24.

- Post-therapy, the average spot forming cells for all proteins tested in 17/37 with 24 weeks of follow up had not declined, although the plasma viral RNA was increasing. SFU using p24 were measurable following SCART and preserved at levels comparable to baseline.

HXB2 Location Gag
Author Location
Epitope
Subtype B
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *Strain:* B clade IIIB *HIV component:* p17 Gag, p24 Gag *Adjuvant:* aluminum hydroxide
Species (MHC) human
Keywords rate of progression
References Klein *et al.* 1997; Lindenburg *et al.* 2002

- HIV-1 p17/p24:Ty virus-like particles therapeutic vaccination of 56 HIV-1 infected patients had no effect on disease progression, AIDS and CD4+ T-cell decline in a longitudinal study, despite some evidence suggesting it can enhance Th anti-Gag proliferative responses in HIV+ individuals Klein *et al.* [1997]

HXB2 Location Gag
Author Location p24 (NY5)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection, cross-presentation by different HLA, early treatment
References Norris *et al.* 2001

- Gag-specific CD4+ helper T-cell clones were derived from 1 LTNP (CTS-01) and 3 individuals given therapy during acute infection, 2 before (AC-01 and AC-36) and 1 after (AC-25) STI.
- The immunodominant response in LTNP CTS-01 was to peptide 9, and 9/10 clones derived from this patient reacted with it. Three, two, and one clones were obtained from the 3 patients given therapy. These 6 clones all reacted with different p24 peptides, and all had peptide induced proliferative responses, IFN-γ production, and cytotoxic responses. The implications of cytotoxic responses in CD4+ T-helper cells are discussed.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Palmer *et al.* 2002

- CD4+ T cell proliferative responses from 33 HIV-1 infected patients with HAART suppression were compared to 19 patients with active viral replication (HAART failures and HAART naive). Patients with HAART suppression showed stronger p24- and p66-specific proliferative responses compared to patient groups with active HIV-1 replication, suggesting active viral replication *in vivo* specifically reduces proliferation responses.
- No differences in the frequency of HIV-specific CD4+ T-cells that were positive for cytokine secretion in a flow cytometry assay were found in the HAART suppressed group versus the group with active viral replication.

HXB2 Location Gag
Author Location p24 (SF2)
Epitope
Subtype B, G
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression, Th1, Th2
References Imami *et al.* 2002b

- 70 patients with chronic disease progression, 10 clinical non-progressors, and 3 immunologically discordant progressors (individuals who controlled viremia but had progressive CD4+ T-cell decline) were analyzed for their T-helper cell responses to p24 and cytokine profile.
- SF2 p24 20mer peptides overlapping by 10 were used to assess the response in the different groups. At least 1/10 and up to 7/10 nonprogressors had a proliferative response with every one of the 22 p24 overlapping peptides. All peptides produced an IL-2 (Th1) response in at least one of the 10 non-progressors. IL-4 (Th2) responses were strong, but somewhat less comprehensive as 6/22 peptides elicited no IL-4 production, and fewer IL-4 responses were see per peptide. In contrast, only 1/10 progressors had a clear proliferative and IL-2 response to 2/22 peptides, and neither one made an IL-4 response.
- The results taken together suggest that a balanced Th1/Th2 response to HIV is important for viral control in long-term non-progression.
- One immunologically discordant progressor became symptomatic while on the study. He showed a rapid decline in proliferative activity at that point, and a shift from a Th1 to a Th2 IL-4 producing response.

HXB2 Location Gag
Author Location (BRU)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade BRU *HIV component:* virus *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse
References Haas *et al.* 1991

- Of 5 mouse inbred lines tested: DBA/2 (H-2d, Ad, Ed), B10.A(4R) (H-2h4, Ak) and B10.A(5R) (H-2i5) showed particularly good CD4+ T cell proliferative responses to HIV proteins (gp160, gp120, p17, p24, Nef and RT), after vaccination with inactivated virus.

- B10.BR (H-2k, Ak, Ek) and C57BL/6 (H-2b and Ab) had weaker responses.

HXB2 Location Gag
Author Location Gag (III-B)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* Gag
Species (MHC) mouse
Donor MHC H-2^d
Keywords vaccine-specific epitope characteristics, Th1
References Bojak *et al.* 2002a

- Codon-optimized gag gene DNA vaccines were compared to wild type by vaccination of BALB/c mice. Codon optimized DNA gave a Th1 polarized Th response, a strong antibody response that persisted from more than 20 weeks, and CTL responses, while wild-type DNA induced weak and inconsistent immune respones.

HXB2 Location Gag
Author Location Gag (MN)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type Cytokine production, proliferation, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords HAART, ART, acute/early infection
References Malhotra *et al.* 2003

- 92 acute- or early-HIV infected subjects were tested for Env- and Gag-specific Th responses. There was an overall low probability of detecting HIV-1-specific Th responses, Env responses were rare and (5%) and only detected very early in infection, probably reflecting a low frequency of response and impaired lymophoproliferative capacity, not viral escape. Gag-specific Th responses were observed more frequently (16%), were found throughout the acute and early infection phases, and predominated after ARV therapy.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: gp120 depleted virus HZ321 (REMUNE(TM)), protein *Strain:* AG recombinant HZ321 *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human
Assay type Cytokine production, proliferation, T-cell Elispot
Keywords HAART, ART, supervised treatment interruptions (STI), immunotherapy
References Moss *et al.* 2003

- Structured treatment interruptions (STIs) were compared in individuals that had been given prior therapeutic vaccines, and those that had not. Therapeutic immunization increased gag p24 stimulated proliferative responses and MIP-1β responses prior to STIs, although total CD4 counts viral RNA levels were unchanged. Proliferative responses and chemokine induction in the vaccinated group correlated with the control of viremia during subsequent STIs.

HXB2 Location Gag
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Assay type proliferation, T-cell Elispot, Intracellular cytokine staining
Keywords supertype
References Papasavvas *et al.* 2003

- Children with full or partial viral supression along with stable CD4+ T cell counts had significantly increased levels of anti-HIV CD4+ T cell proliferative responses, and decreased CD38+ T-cells.
- Preservation of high levels of CD4+ T-cells was associated with a high percentage of CD4+ naive T-cells relative to memory T-cells.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: gp120 depleted virus HZ321 (REMUNE(TM)) *Strain:* AG recombinant HZ321 *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human
Assay type proliferation, T-cell Elispot, Delayed-type hypersensitivity (DTH)
Keywords HAART, ART, immunotherapy
References Robbins *et al.* 2003

- Augmented Th cell responses to Gag p24 were seen in five out of five chronically infected individuals who had virological control with HAART, after therapeutic immunization with REMUNE (gp120 depleted inactived virus). The magnitude of responses ranged from a 5- to 200-fold increase, with fluctuation in magnitude over time.
- There was no change in the magnitude and breadth of CTL responses, CD4 counts or percentages, or DTH responses.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A1, A2, B44, B8, DR15, DR4; LTNP S24: A11, A2, B55, B57, DR13, DR4; LTNP C135: A1, A33, B50, B57, DR13, DR7
Assay type Cytokine production, proliferation, CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords rate of progression, immunodominance

References Wang *et al.* 2002a

- A 51 year old male, infected presumably in 1988, diagnosed seropositive in 1993, has remained asymptomatic and is a long term non-progressor. He had very low proviral copy number in his PBMCs with high levels of G-A hypermutation, resulting in multiple stop codons, and viral replication was not evident. He was heterozygous for the CCR5 delta 32 allele, and has undergone a variety of treatments through the years. T cell responses in this patient and in two additional LTNPs were described, and this patient had particularly intense CD4+ Th responses.
- PBMC from this patient resisted infection from CCR5, CXCR4 and dual-tropic HIV-1 strains. Purified CD4+ T cells became infected, however, without detectable cytopathic effect. CD8+ T cells were shown to protect PBMCs from infection, and this protection was not mediated by IFNgamma. Undefined CD8 T-cell secreted factors were stimulated by Gag, Pol and Nef genes introduced into target cells with vaccinia and processed through a class I pathway were responsible for the protective effect. This factor resembled CAF, the CD8+ cell antiviral factor described in Mackewicz and Levy (ARHR 8:1039, 1992)
- The CD4+ and CD8+ T-cell populations were both strongly skewed toward the CD45RO+ phenotype, many of which were terminally differentiated, CD28-, and expressed the activation markers CD38+ and HLA-DR+. Cell turnover, however, wasn't much elevated as measured by apoptosis or Ki-67+ and Bcl-2 dim expression.
- Vigorous p24-specific Th proliferative responses were observed, and 50% of CD4+ T-cells proliferated in response to p24 Gag, an extraordinary percentage. Responses were also detected against other regions in Gag, gp120 and Nef. It remains unclear how such vigorous Th responses are maintained with undetectable ongoing viral replication.
- Strong CD4+ T-cell IFNgamma Elispot responses were mapped to many peptides in Gag for this patient. T-cells from two other LTNPs were tested here, and they did not react with as many Gag peptides as the main study subject of the paper. NIH reference Gag peptide set was used, but the sequences of the reactive peptides and the precise strain was not indicated in the paper, so we could not record them in the database.
- CD8+ T cell Elispot responses to Gag, Env, Nef, and Pol were detected as well, although CTL were not prominent, consistent with undetectable viremia.
- This subject had strong NAb responses when tested using the X4 primary isolate 228 200.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC)
Assay type proliferation
Keywords HAART, ART
References Sullivan *et al.* 2003

- Lymphoproliferative responses to HIV antigens p24, gp120 and Nef were enhanced in eight patients who were switched from protease inhibitors to non-nucleoside reverse transcriptase inhibitors.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Assay type Cytokine production, proliferation
Keywords HAART, ART
References Hardy *et al.* 2003

- Upon initiating HAART, CD4+ T cell proliferative responses in 36 patients were restored to specific antigens, mitogens, and IL-2. Restored recall responses were largely to persistent antigens, and not to HIV-1 or new antigens, and recall responses were associated with IL-2, not IL-4 production.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 and HCV co-infection
Species (MHC) human
Assay type CD4 T-cell Elispot - IFNγ
Keywords HAART, ART, Th1
References Alatrakchi *et al.* 2004

- Treatment with IFNalpha and ribavirin induced a threefold decrease of type 1 T-helper cell frequencies specific for HIV (p24) and CMV in HIV/HCV co-infected patients undergoing HAART therapy, suggesting this therapy might negatively impact viral-specific immune responses.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country Spain
Assay type proliferation
Keywords HAART, ART, supervised treatment interruptions (STI)
References Plana *et al.* 2004

- Study evaluated the dynamics of CD4+ and CD8+ T-cell responses during 4 cycles of STI in 45 patients, who had early-stage, chronic HIV-1 infection. Lymphoproliferative responses (LPRs) increased between the beginning of the first STI cycle through the 4th STI, but then decreased. Viral load at the end of the 4th STI was inversely correlated with p24 LPRs, but the LPRs were transient and after 12 weeks no longer were correlated with low viral low.
- STIs can boost CTL and LPR responses, but the lack of durable T-helper responses leads to lack of long term viral control.

HXB2 Location Gag
Author Location
Epitope
Subtype CRF02_AG
Immunogen HIV-1 or HIV-2 infection
Species (MHC) human
Country Senegal
Assay type CD4 T-cell Elispot - IFNγ
Keywords rate of progression, variant cross-recognition or cross-neutralization

T-Helper CD4+

References Zheng *et al.* 2004
- Gag, Env, Tat, and Nef-specific T-cell responses were evaluated in 68 HIV-1 and 55 HIV-2 infected drug naive, generally asymptomatic, infected Senegalese patients.
- HIV-1 peptides were derived from HIV-1 CRF-02 (HIV-1 A/G, AJ251056)and HIV-2 peptides spanning HIV-2 ROD (M15390).
- Gag specific responses dominated in both groups, but overall magnitude and frequencies did not correlate with viral load or CD4 counts. CD4+ Helper T-cell responses were found in only 8% of HIV-1 + people, but in 48% of HIV-2 + people, suggesting helper T cell responses may contribute to improved control of viremia in HIV-2 infected patients. Lower viral load was associated magnitude of T-cell responses in HIV-1 infection only when the T-cell responses were measured for cross-reactivity with HIV-2.

HXB2 Location Gag
Author Location p24
Epitope
Subtype A, AG, B
Immunogen HIV-1 infection
Species (MHC) human
Country Cote D'Ivoire
Assay type Cytokine production, CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ
Keywords HIV exposed persistently seronegative (HEPS)
References Jennes *et al.* 2004
- Env(gp120)- and Gag(p24)-specific T helper responses were compared between HIV-exposed seronegative (ESN) and seropositive female sex workers in Africa (Abidjan, Cote d'Ivoire).
- HIV-specific CD4+ T cells were detected in both study groups; low level EliSpot responses were found in 8/40 ESN sex workers. The presence of HIV specific CD4+ T-cells was detected by flow cytometry in 3/8 (38%) in the ESN group, was associated with the frequency and not with the duration of HIV exposure. The ESN reponses were detected in women with more clients on the previous working day and more exposures per month.
- B subtype peptides were used to probe these responses because of availability, however the predominant clades circulating in the area are A and CRF02.

HXB2 Location Gag
Author Location Gag
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country Netherlands
Assay type proliferation, Intracellular cytokine staining
References Jansen *et al.* 2006
- Functional CD4+ T cells were compared in long-term asymptomatic individuals (LTA) and progressors to AIDS. Gag-specific CD4+ T cells producing IL-2 or IFN-γ were lost in progressors late in infection.

HXB2 Location Gag
Author Location
Epitope
Immunogen vaccine
Vector/Type: DNA with CMV promotor *Strain:* B clade HXB2, B clade NL43, A clade 92RW020, C clade 97ZA012 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords therapeutic vaccine
References Catanzaro *et al.* 2006
- 14 volunteers uninfected with HIV completed a set of injections with a 6-plasmid DNA vaccine encoding EnvA, EnvB, EnvC, and subtype B Gag, Pol, and Nef. CD4 and CD8 T cell responses to Env and Gag were most frequently detected.
- For Gag, 12/14 subjects showed a positive CD4+ T cell response by ICS.

HXB2 Location Gag
Author Location
Epitope
Immunogen vaccine
Vector/Type: adenovirus type 5 (Ad5) *HIV component:* Env, Gag *Adjuvant:* Cholera toxin (CT)
Species (MHC) macaque
Assay type proliferation, CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords vaccine antigen design
References Mercier *et al.* 2007
- 3 rhesus macaques were given oral immunizations with an enteric-coated mixture of adenoviral vectors expressing HIV-1 gag and a string of conserved env peptides representing broadly cross-reactive CD4+ and CD8+ epitopes. The macaques were boosted intranasally with a mixture of 6 HIV-1 envelope peptides plus cholera toxin adjuvant.
- The immunizations increased cellular immune responses, including antigen-specific IFNgamma-producing CD4+ and CD8+ effector memory T cells in the intestine. After only the oral immunization, there were no EliSpot responses to env peptides or to gag. After the intranasal boost, EliSpot responses against env peptides and against inactivated HIV were markedly increased, but gag responses were not.

HXB2 Location Gag
Author Location Gag (HXB2)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost *Strain:* B clade HXB2 *HIV component:* Gag
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, Chromium-release assay
Keywords vaccine-induced epitopes, Th1

References Arruda *et al.* 2006

- p55 Gag cellular trafficking of two chimeras (DNA plasmid with either lysosomal-associated membrane protein LAMP/gag or human dendritic cell CD-LAMP/gag) was studied in mice. Both produces potent T and B cell immune responses, but DC-LAMP produces stronger Th1 response. The chimeras produces also significant responses to cryptic epitopes that were not recognized after immunization with native gag DNA.

HXB2 Location Gag
Author Location p24
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type proliferation, Intracellular cytokine staining
References Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

HXB2 Location Gag
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country Kenya
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords responses in children, rate of progression
References Chakraborty *et al.* 2005

- A study of long-term surviving children in Kenya revealed CD8 T-cell responses in all progression groups. The most striking atttribute of long term surviving children was strong CD4 T-cell responses, which may be significant in delaying disease progression.
- Preservation of Gag-specific CD4+ Th responses have been described for adult non-progressors, and this study described similar responses for slow and non-progressing children.

HXB2 Location Gag
Author Location
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade
Species (MHC) macaque
Assay type Intracellular cytokine staining
Keywords subtype comparisons, vaccine antigen design
References Smith *et al.* 2005

- Macaques were immunized with a clade B HIV vaccine and tested for responses to pools of clade B and A/G Env and Gag peptides. While CD4 responses were more frequent than CD8 responses, higher cross-clade responses were found for CD8 responses. The authors suggest that the better cross-clade reactivity of the CD8 responses reflects the size difference between CD8 and CD4 epitopes; the smaller CD8 epitopes provide a smaller target for mutation.
- All 5 pools of B Env and Gag peptides stimulated CD4 responses, while only 2 pools of A/G peptides stimulated responses, suggesting that 1 or 2 out of 5 CD4 epitopes were cross-reactive.

HXB2 Location Gag
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Assay type Intracellular cytokine staining
Keywords acute/early infection
References Zaunders *et al.* 2005

- In 6/7 patients with very early HIV infection, CD4+ T cells producing IFN-g in response to Gag peptides were readily detected, and most CD4+ T cells were CCR5+CD38+++. In PHI subjects with later presentation, antigen specific CD4+ T cells could not be readily detected, coinciding with a lower level of CCR5+CD38+++ CD4+ T cells.

III-B-6 Protease Helper/CD4 + T-cell epitopes

HXB2 Location Protease (7–21)
Author Location Protease (7–21 clade B consensus)
Epitope `QRPLVTIKIGGQLKE`
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (DRB1*0101, DRB1*1101, DRB1*1501, DRB5*0101)
Country Brazil
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 brazilian HIV-1 chronically infected individuals.
- While the reacting peptide is QRPLVTIKIGGQLKE, shorter LVTIKIGGQ peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

HXB2 Location Protease (49–72)
Author Location
Epitope `GIGGFIKVRQYDQILIEICGKKAI`
Epitope name HIV-VAX-1048
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States

T-Helper CD4+

Assay type CD4 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 3/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was VRQYDQILI.

HXB2 Location Protease (74–96)
Author Location
Epitope `TVLVGPTPVNIIGRNLLTQIGCT`
Epitope name HIV-VAX-1046
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 3/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was PVNIIGRNL.

HXB2 Location Protease (80–94)
Author Location Protease (80–94 clade B consensus)
Epitope `TPVNIIGRNLLTQIG`
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (DRB1*0101, DRB1*1101, DRB1*1302, DRB1*1501)
Country Brazil
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 brazilian HIV-1 chronically infected individuals.
- While the reacting peptide is TPVNIIGRNLLTQIG, shorter VNIIGRNLLTQ peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

III-B-7 RT Helper/CD4+ T-cell epitopes

HXB2 Location RT (19–37)
Author Location
Epitope `PKVKQWOLTEVKIKALTAI`
Subtype C
Immunogen vaccine
Vector/Type: DNA, DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* C clade Du422, C clade Du151 *HIV component:* Gag, gp160 deletions, Nef, RT, Tat
Species (MHC) mouse
Country South Africa
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords vaccine-induced epitopes, Th1
References Shephard *et al.* 2008

- DNA (SAAVI DNA-C) and MVA (SAAVI MVA-C) vaccines were tested in BALB/c mice. Combining the vaccines in a DNA prime and MVA boost regimen increased the cumulative peptide response compared to the DNA vaccine alone 10-fold.
- Th1 cytokine IFN-γ and TNF-α levels from HIV-specific CD8 and CD4 T cells increased 20- and 8- fold respectively, with a SAAVI MVA-C boost.
- Effector and effector memory RT- and Env-specific memory CD8 T cell subsets were boosted after MVA immunizations.
- CD4 peptide PKVKQWOLTEVKIKALTAI was used for detection of IFN-γ-secreting cells.

HXB2 Location RT (36–52)
Author Location RT (36–52 BRU)
Epitope `EICTEMEKEGKISKIGP`
Immunogen HIV-1 infection
Species (MHC) human
References De Groot *et al.* 1991

- 9 out of 17 humans can make strong IL2 responses to this epitope.

HXB2 Location RT (36–52)
Author Location RT (36–52)
Epitope `EICTEMEKEGKISKIGP`
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.

T-Helper CD4+

- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- EICTEMEKEGKISKIGP is a previously known epitope that is a part of this vaccine construct.

HXB2 Location RT (38–52)
Author Location RT (38–52 BRU)
Epitope CTEMEKEGKISKIGP
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU
HIV component: RT
Species (MHC) mouse (H-2^k)
References De Groot *et al.* 1991
- T-cells from RT immunized mice have enhanced proliferative response with peptide.

HXB2 Location RT (39–53)
Author Location RT (194–208)
Epitope TEMEKEGKISKIGPE
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995a
- Protein priming induced T-cells that recognize peptide, 4 clones from a single donor recognized this peptide.

HXB2 Location RT (48–62)
Author Location RT (48–62 BRU)
Epitope SKIGPENPYNTPVFA
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU
HIV component: RT
Species (MHC) mouse (H-2^k)
References De Groot *et al.* 1991
- T-cells from RT immunized mice have enhanced proliferative response with peptide.

HXB2 Location RT (62–77)
Author Location RT (62–77 BRU)
Epitope AIKKKDSTKWRKLVDF
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU
HIV component: RT
Species (MHC) mouse (H-2^k)
References De Groot *et al.* 1991
- T-cells from RT immunized mice have enhanced proliferative response with peptide.

HXB2 Location RT (88–102)
Author Location RT (88–102 BRU)
Epitope WEVQLGIPHPAGLKK
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU
HIV component: RT
Species (MHC) mouse (H-2^{t4})
References De Groot *et al.* 1991
- T-cells from RT immunized mice have enhanced proliferative response with peptide.

HXB2 Location RT (124–138)
Author Location Pol (303–317)
Epitope FRKYTAFTIPSINNE
Epitope name Pol 303
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Keywords subtype comparisons
References Wilson *et al.* 2001
- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
- This epitope binds seven HLA-DR alleles: DRB1*0901, DRB1*0802, DRB1*0701, DRB1*0405, DRB1*0401, DRB1*1501 and DRB1*0101, with an IC_{50} threshold below 1,000 nM.
- This epitope sequence is conserved in 68% of clade B isolates.
- 8/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

HXB2 Location RT (124–138)
Author Location RT (303–317)
Epitope FRKYTAFTIPSINNE
Epitope name Pol1
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Country United Kingdom
Assay type proliferation, Intracellular cytokine staining
Keywords supertype, rate of progression
References Boaz *et al.* 2003
- Proliferative and cytokine (IFNgamma and Il-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNPs (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive.
- Gag-specific CD4+ T cells in LTNPs showed increased numbers of IFN gamma and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFNgamma, levels were correlated with proliferation.

HXB2 Location RT (124–138)
Author Location Pol (303–317)
Epitope FRKYTAFTIPSINNE
Epitope name Pol 303
Immunogen vaccine
Vector/Type: DNA with CMV promotor, peptide *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (DR, I-A^b)

T-Helper CD4+

Donor MHC H-2b
Keywords vaccine-specific epitope characteristics, immunodominance
References Livingston *et al.* 2002

- 4 Th HIV epitopes presented by HLA-DR molecules were identified that also could be presented by murine class II molecule I-Ab, enabling testing of vaccine strategies in H-2b mice.
- Responses to pooled peptides, polyepitope peptides in a linear construct or in a branched MAP construct, and a DNA polyepitope construct with a CMV promoter were compared. A linear arrangement in polyepitope construct created a junctional epitope that could be disrupted with the addition of GPGPG spacers. The linear polyepitope construct with the GPGPG spacer worked well in terms of eliciting responses to all 4 peptides, using either DNA or protein for the vaccination.

HXB2 Location RT (133–147)
Author Location RT (133–147 BRU)
Epitope `PSINNETPGIRYQYN`
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU *HIV component:* RT
Species (MHC) mouse (H-2^{i5}, H-2^{k})
References De Groot *et al.* 1991

- T-cells from RT immunized mice have enhanced proliferative response with peptide.

HXB2 Location RT (144–158)
Author Location RT (144–158 BRU)
Epitope `YQYNVLPQGWKGSPA`
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU *HIV component:* RT
Species (MHC) mouse (H-2^{t4})
References De Groot *et al.* 1991

- T-cells from RT immunized mice have enhanced proliferative response with peptide.

HXB2 Location RT (156–170)
Author Location Pol (335–349)
Epitope `SPAIFQSSMTKILEP`
Epitope name Pol 596
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Keywords subtype comparisons
References Wilson *et al.* 2001

- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
- This epitope binds nine HLA-DR alleles: DRB1*0101, DRB1*1501, DRB1*0405, DRB1*1101, DRB1*1302, DRB1*0701, DRB1*0901, DRB5*0101 and DRB3*0101, with an IC_{50} threshold below 1,000 nM.
- This epitope sequence is conserved in 79% of clade B isolates.
- 7/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

HXB2 Location RT (156–170)
Author Location RT (335–349)
Epitope `SPAIFQSSMTKILEP`
Epitope name Pol2
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Country United Kingdom
Assay type proliferation, Intracellular cytokine staining
Keywords supertype, rate of progression
References Boaz *et al.* 2003

- Proliferative and cytokine (IFNgamma and Il-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNPs (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive.
- Gag-specific CD4+ T cells in LTNPs showed increased numbers of IFN gamma and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFNgamma, levels were correlated with proliferation.
- Pol2 was 1 of 3 peptides that had a negative correlation between absolute number of responding cells and viral load.

HXB2 Location RT (156–170)
Author Location RT (156–170)
Epitope `SPAIFQCSSMTKILEP`
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human (DR supermotif)
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- SPAIFQCSSMTKILEP is a previously known epitope that is a part of TCI fragment WKGSPAIFQCSSMTKILEPFRKQNPDIVIYQYMDDL in this vaccine construct.

HXB2 Location RT (156–170)
Author Location Pol (335–449)
Epitope `SPAIFQSSMTKILEP`
Epitope name Pol 335

Immunogen vaccine
Vector/Type: DNA with CMV promotor, peptide *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (DR, I-A^b)
Donor MHC H-2b
Keywords vaccine-specific epitope characteristics, immunodominance
References Livingston *et al.* 2002

- 4 Th HIV epitopes presented by HLA-DR molecules were identified that also could be presented by murine class II molecule I-Ab, enabling testing of vaccine strategies in H-2b mice.
- Responses to pooled peptides, polyepitope peptides in a linear construct or in a branched MAP construct, and a DNA polyepitope construct with a CMV promoter were compared. A linear arrangement in polyepitope construct created a junctional epitope that could be disrupted with the addition of GPGPG spacers. The linear polyepitope construct with the GPGPG spacer worked well in terms of eliciting responses to all 4 peptides, using either DNA or protein for the vaccination.

HXB2 Location RT (171–189)
Author Location Pol (171–189 HXB2)
Epitope `FRKQNPDIVIYQYMDDLYV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DR0101)
Assay type Cytokine production, proliferation, Tetramer binding, CD4 T-cell Elispot - IFNγ
Keywords HAART, ART, supervised treatment interruptions (STI)
References Iyasere *et al.* 2003

- Fifteen patients recieving HAART with strong CD4+ proliferative responses to HIV antigens while on therapy were examined, to see the effects of viremia on these responses during treatment interruptions. Increased viremia occurred in 12/15 patients during at least one treatment interruption. Anti-HIV proliferative responses were inhibited during viremia, but IFNgamma production to Gag, Pol, and Nef peptide pools were maintained.
- IL-2 production diminished during viremia, and exogenous IL-2 revived *in vitro* proliferation of HIV-specific T-cells to Gag or Pol DR0101 epitopes in a tetramer, as well as Gag-specific total CD4 T-cell responses.

HXB2 Location RT (171–190)
Author Location RT (171–190 HXB2)
Epitope `FRKQNPDIVIYQYMDDLYVG`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DR1, DR2 or DR3, DR4, DR7)
Keywords Th1
References van der Burg *et al.* 1999

- T-cells specific for this epitope from the three donors were stimulated when presented with target cells pulsed with whole RT, indicating that the peptide is naturally processed for multiple HLA-DR molecules.
- Epitope binds to HLA-DR1, -DR2, -DR3, -DR4, and DR7, and can elicit Th1 cells that recognize peptide, protein, and HIV pulsed stimulator cells in the context of DR1, 2 or 3, 4 and 7 – these HLA types cover more than half of the general population.

HXB2 Location RT (171–190)
Author Location RT (171–190 HXB2)
Epitope `FRKQNPDIVIYQYMDDLYVG`
Subtype B
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human (DR1, DR2, DR3, DR4, DR7)
Keywords binding affinity, cross-presentation by different HLA, Th1
References van der Burg *et al.* 1999

- The goal of this study was to identify Th epitopes that could be cross-presented by multiple class II HLA molecules. 5 RT peptides were identified that could bind to more than one HLA class II protein, and but only 2/5 could stimulate strong proliferation responses in PBMC derived from multiple healthy donors.
- This highly conserved epitope binds with high affinity to HLA-DR1, -DR2, -DR3, -DR4, and -DR7 but not HLA-DR5, and stimulated proliferation in 3/3 PBMC individuals with the appropriate HLA alleles.
- This epitope was able to be naturally processed in protein pulsed stimulator cells, and responding clones had a Th1 cytokine profile.
- This epitope is highly conserved and spans the highly conserved YMDD motif, and showing only minor variability in clades A, B, and D.

HXB2 Location RT (174–196)
Author Location
Epitope `QNPDIVIYQYMDDLYVGSDLEIG`
Epitope name HIV-VAX-1055
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 4/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was YQYMDDLYV.

HXB2 Location RT (175–197)
Author Location
Epitope `NPEIVIYQYMDDLYVGSDLEIGQ`
Epitope name HIV-VAX-1051
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ

T-Helper CD4+

Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 2/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was YQYMDDLYV.

HXB2 Location RT (195–209)
Author Location RT (IIIB)
Epitope IGQHRTKIEELRQHL
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Protein priming induced T-cells that recognize peptide.

HXB2 Location RT (196–215)
Author Location RT (351–370)
Epitope GQHRTKIEELRQHLLRWGLT
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995a

- Protein priming induced T-cells that recognize peptide, 4 clones from a single donor recognized this peptide.

HXB2 Location RT (249–263)
Author Location (243–263)
Epitope KDSWTVNDIQKLVGK
Epitope name pep23
Immunogen vaccine
Vector/Type: bacteriophage coat protein, dihydrolipoyl acetyltransferase E2 protein, of Bacillus stearothermophilus *HIV component:* RT
Species (MHC) transgenic mouse (DR)
Assay type Chromium-release assay
Keywords vaccine antigen design
References De Berardinis *et al.* 2003

- An RT T-helper (KDSWTVNDIQKLVGK) that can be promiscuously presented by multiple HLA-DR molecules, and an RT CTL epitope (ILKEPVHGV) presented by HLA-A2, were displayed using two different antigen presentation systems, bacteriophage virions or E2 protein scaffolds. Both systems enabled display of the epitopes in a mouse model system to the immune system. CTL responses were detected in immunized mice, and were processed correctly for both class I and class II presentation.

HXB2 Location RT (249–263)
Author Location RT (249–263)
Epitope KDSWTVNDIQKLVGK
Epitope name RT2
Immunogen vaccine, in vitro stimulation or selection
Vector/Type: HIV-1 peptide in filamentous bacteriophage major coat protein *HIV component:* RT
Species (MHC) human (DR5)
Keywords epitope processing
References De Berardinis *et al.* 2000

- Phage display of the CTL epitope, ILKEPVHGV coupled with T helper epitope KDSWTVNDIQKLVGK, elicited specific CTL responses in PBMC from HIV negative individuals and *in vivo* in immunization of HLA-A2 transgenic mice.
- Bacteriophage presentation of peptides is generally used for stimulation of antibodies, and this novel discovery of CTL epitope processing and presentation suggests new possibilities for these vectors.
- HIV-1 peptides were displayed in filamentous bacteriophage fd virion major coat protein pVIII.

HXB2 Location RT (249–263)
Author Location RT (249–263)
Epitope KDSWTVNDIQKLVGK
Epitope name pep23
Immunogen vaccine, in vitro stimulation or selection
Vector/Type: peptide presented on icosahedral protein scaffold *HIV component:* RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human, transgenic mouse (DR5)
Assay type Cytokine production, T-cell Elispot, Th support of CTL response
References Domingo *et al.* 2003

- A virus-like protein scaffold, called E2DISP, derived from pyruvate dehydrogenase multienzyme from Bacillus stearothermophilus has been engineered to display 60 copies of one or more epitopes on a single molecule. An E2DISP scaffold which displayed pep23, a 15-residue B and T helper epitope from the reverse transcriptase of HIV-1 elicited a T-helper response *in vitro*.
- The E2DISP scaffold displaying pep23 to stimulate a Th responses, and peptide RT2, which is a CTL epitope from HIV-1 reverse transcriptase, was able to elicit a CD8+ T cell response *in vitro* and in a vaccinated HLA-A2 transgenic mouse. Thus the E2DISP scaffold allows cell-entry and access to the class I and class II processing pathways.
- The Th response in vaccinated mice was also able to support Pep23 specific IgG response.

HXB2 Location RT (249–263)
Author Location RT (248–262)
Epitope KDSWTVNDIQKLVGK
Immunogen in vitro stimulation or selection
Species (MHC) human (DR5(11.01))
Donor MHC DR5, DR6
Assay type proliferation
Keywords binding affinity, epitope processing, vaccine-specific epitope characteristics, escape
References Moschella *et al.* 2003

- Two helper T-cell clones specific for this epitope presented in the context of HLA-DR5-11.01 have been characterized. They have different T cell receptor usage. Residue 11 (kdswtvndiqKlvgk)is a natural variant, and K11A, K11G, K11I, and K11L variants were synthesized and studied in two presentation contexts, one as simple peptides, the other embedded in a recombinant protein, GST.

T-Helper CD4+

- The two Th clones and the two presentation contexts gave different outcomes with the peptides. K11I was not stimulatory, and was an antagonist in GST, an agonist as a peptide. K11L retained reactivity when presented in the fusion antigen, and had no activity as a peptide. K11G stimulated in both contexts, but the concentrations required for half maximal reactivity were different. K11A could not bind to the MHC in the processed form and could only stimulate when given as a peptide.
- In conclusion, substitutions in epitopes have different effects on Th stimulation depending on the mode of processing, and this should be considered when interpreting Th escape studies and vaccine development.

HXB2 Location RT (249–263)
Author Location RT (248–262)
Epitope KDSWTVNDIQKLVGK
Immunogen in vitro stimulation or selection
Species (MHC) human (DR5(11.01))
Donor MHC DR5, DR6
Assay type proliferation
Keywords binding affinity, epitope processing, vaccine-specific epitope characteristics, escape, TCR usage
References Bonomi *et al.* 2000

- Two helper T-cell clones specific for this epitope presented in the context of HLA-DR5-11.01 were characterized. One of them used TCR Vβ15, the other used Vβ2. The substitutions D2A, W4A, D8A, I9A, and K15A were generated and only D8A, I9A failed to react with one clone, while W4A, D8A, I9A were all critical for a reaction with the other clone, showing the TCRs focused on different but overlapping residues.
- Moving the epitope to different contexts in recombinant proteins for presentation by APCs, as well as adding polyanalanine and polyserine strings to either side of the epitope, influenced reactivity, suggesting processing context can influence the structure of the presentation complex.

HXB2 Location RT (249–263)
Author Location RT (248–262 HXB2)
Epitope KDSSTVNDIQKLVGK
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DRS)
References Fenoglio *et al.* 1999

- RT pep23 epitope exhibited antagonistic activity against proliferation of gp120-specific T-cells when flanked by unrelated amino acid sequence.
- The glutathione S-transferase (GST)-peptide system can be used to display peptides; antigenicity was maintained when this peptide was expressed at the C-term end, but antagonism resulted when this peptide was expressed at the N-term end.

HXB2 Location RT (249–263)
Author Location RT (IIIB)
Epitope KDSWTWNDIQKLVGK
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming did not induce T-cells that recognize whole protein.

HXB2 Location RT (249–263)
Author Location RT (248–262)
Epitope KDSWTVNDIQKLVGK
Immunogen in vitro stimulation or selection
Species (MHC) human
References De Berardinis *et al.* 1999

- PBMC from donors GD (HLA DR 11; DRB52) and LD (HLA DR 11, 13; DRB52) recognized this epitope (pep23)
- A subset of T-cell lines generated from these donors were capable of recognizing pep23 expressed on the surface of filamentous phage fd, fused to the major coat protein gVIIIp.
- This peptide was selected to study phage presentation of peptide sequences because it was known to serve as a T-cell helper determinant which could induce proliferation from a naive repertoire Manca *et al.* [1995a]

HXB2 Location RT (251–261)
Author Location RT (250–260)
Epitope SSTVNDIQKLV
Immunogen in vitro stimulation or selection
Species (MHC) human (DR5(11.01))
References Manca *et al.* 1996

- This peptide was the minimal stimulatory sequence.
- One Th line was stimulated by p66, one by a Glutathione-S-transferase (GST)-peptide fusion protein.
- Constructs linking GST to the KDSSTVNDIQKLVGK peptide at the N-term end of GST stimulated Th cells, but not constructs linking at the C-term end.
- The C and N termini of GST are not intrinsically permissive or non-permissive, presentation is epitope specific (see FAILKCNNK for contrast)

HXB2 Location RT (258–272)
Author Location RT (IIIB)
Epitope QKLWGKLNWASQIYP
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming did not induce T-cells that recognize whole protein.

HXB2 Location RT (271–290)
Author Location RT (271–290 HXB2)
Epitope YPGIKVRQLCKLLRGTKALT
Subtype B
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human (DR1, DR2, DR3, DR5, DR7)
Keywords binding affinity, cross-presentation by different HLA
References van der Burg *et al.* 1999

T-Helper CD4+

- The goal of this study was to identify Th epitopes that could be cross-presented by multiple class II HLA molecules. 5 RT peptides were identified that could bind to more than one HLA class II protein, but only 2/5 could stimulate strong proliferation responses in PBMC derived from multiple healthy donors.
- This epitope binds with high affinity to HLA-DR1, -DR2, -DR3, -DR5, and -DR7 but not HLA-DR4, and stimulated proliferation in 3/4 individuals with the appropriate HLA alleles.
- This epitope was not able to be naturally processed in protein-pulsed stimulator cells.

HXB2 Location RT (271–290)
Author Location RT (271–290 HXB2)
Epitope YPGIKVRQLCKLLRGTKALT
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References van der Burg *et al.* 1999
- Epitope can bind to at least 5 different HLA-DR molecules, and peptide on target cells can elicit Th responses from PBMC cultures from healthy donors, however it does not seem to be processed properly from whole RT or virus.

HXB2 Location RT (276–290)
Author Location RT (IIIB)
Epitope WRQLCKLLRGTKALT
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b
- Protein priming induced T-cells that recognize peptide.

HXB2 Location RT (285–299)
Author Location RT (IIIB)
Epitope GTKALTEVIPLTEEA
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b
- Protein priming induced T-cells that recognize peptide.

HXB2 Location RT (294–308)
Author Location RT (IIIB)
Epitope PLTEEAELELAENRE
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b
- Protein priming induced T-cells that recognize peptide.

HXB2 Location RT (303–317)
Author Location RT (IIIB)
Epitope LAENREILKEPVHGV
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b
- Protein priming induced T-cells that recognize peptide.

HXB2 Location RT (338–352)
Author Location RT (338–352 HXB2)
Epitope TYQIYQEPFKNLKTG
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DP4)
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, epitope processing, computational epitope prediction, dendritic cells
References Cohen *et al.* 2006
- Motif-based quantitative matrices binding predictions, binding assays and cellular assays were used to identify 4 HLA-DP4 epitopes by scanning the whole HIV-1 genome.
- 21 peptides were predicted to bind HLA-DP4, 17 of them did bind in binding assays, 6 of them were good binders. Of the 6 good binders, 4 peptides primed peptide-specific CD4+ T cell lines restricted to HLA-DP4 molecules.
- TYQIYQEPFKNLKTG primed CD4+ T cells that recognized epitopes of the native proteins processed by immature dendritic cells.
- TYQIYQEPhKNLKTG variant had a lower binding capacity to HLA-DP4 molecules, resulting from the unfavorable accommodation of H in the P6 binding pocket.

HXB2 Location RT (384–398)
Author Location RT (IIIB)
Epitope GKTPKFKLPIQKETW
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b
- Protein priming induced T-cells that recognize peptide.

HXB2 Location RT (414–428)
Author Location Pol (596–610)
Epitope WEFVNTPPLVKLWYQ
Epitope name Pol 596
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Keywords subtype comparisons
References Wilson *et al.* 2001
- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
- This epitope binds eleven HLA-DR alleles: DRB1*0101, DRB1*1501, DRB1*0401, DRB1*0405, DRB1*1101, DRB1*1302, DRB1*0701, DRB1*0802, DRB1*0901, DRB5*0101 and DRB4*0101, with an IC_{50} threshold below 1,000 nM.
- This epitope sequence is conserved in 84% of clade B isolates.
- 6/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

HXB2 Location RT (414–428)
Author Location RT (596–610)
Epitope WEFVNTPPLVKLWYQ
Epitope name Pol3
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Country United Kingdom
Assay type Cytokine production, proliferation
Keywords supertype, rate of progression
References Boaz *et al.* 2003

T-Helper CD4+

- Proliferative and cytokine (IFNgamma and Il-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNPs (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive.
- Gag-specific CD4+ T cells in LTNPs showed increased numbers of IFN gamma and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFNgamma, levels were correlated with proliferation.
- Pol3 was 1 of 2 peptides that had a positive correlation between absolute number and percentage of responding cells and viral load. Pol3 responses were also negatively correlated with CD4 counts. In contrast, the absolute number of 3/11 peptides studied were negatively correlated with viral load.

HXB2 Location RT (426–448)
Author Location
Epitope WYQLEKEPIVGAETFYVDGAANR
Epitope name HIV-VAX-1050
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 4/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was IVGAETFYV.

HXB2 Location RT (429–443)
Author Location RT (IIIB)
Epitope LEKEPIVGAETFYVD
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Protein priming induced T-cells that recognize peptide.

HXB2 Location RT (432–450)
Author Location RT (431–450 HXB2)
Epitope EPIVGAETFYVDGAANRET
Subtype B
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human (DR1, DR2, DR3, DR4)
Keywords binding affinity, cross-presentation by different HLA
References van der Burg *et al.* 1999

- The goal of this study was to identify Th epitopes that could be cross-presented by multiple class II HLA molecules. 5 RT peptides were identified that could bind to more than one HLA class II protein, and but only 2/5 could stimulate strong proliferation responses in PBMC derived from multiple healthy donors.
- This epitope binds with high affinity to HLA-DR1, -DR2, -DR3, and -DR4, but stimulated a strong proliferation response in only 1/4 individuals tested so was not considered broadly cross-presented.

HXB2 Location RT (526–540)
Author Location RT (526–540 BRU)
Epitope IKKEKVYLAWVPAHK
Epitope name W9
Subtype B
Immunogen vaccine
Vector/Type: peptide, protein, inactivated HIV *Strain:* B clade BRU *HIV component:* RT, virus *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 A^d, H-$2D^d$)
References Haas *et al.* 1991

- Of 5 mouse inbred lines tested: DBA/2 (H-2d, Ad, Ed), B10.A(4R) (H-2h4, Ak) and B10.A(5R) (H-2i5) showed particularly good CD4+ T cell proliferative responses to HIV proteins (gp160, gp120, p17, p24, Nef and RT), after vaccination with inactivated virus.
- B10.BR (H-2k, Ak, Ek) and C57BL/6 (H-2b and Ab) had weaker responses.
- The peptide KEKVYLAWVPAHKG was one of two RT peptides with Th cells recognition.

HXB2 Location RT (528–540)
Author Location RT (528–540)
Epitope KEKVYLAWVPAHK
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade BRU *HIV component:* RT *Adjuvant:* P3CSS
Species (MHC) mouse (H-2^b, H-2^d, H-2^k)
Assay type proliferation
References Loleit *et al.* 1996

- BALB/c, C3H/Hej, and C57BL/6 mice were immunized with 22-mer lipopetide tripeptide conjugates P3CSS-[RT-(522-543)] and P3CSS-[RT-(528-549)] of HIV-1 RT, which included the optimal T-helper epitope [RT-(528-540)]. P3CSS conjugated RT epitopes resulted in a specific Th responses, and mice were primed for secondary recognition of native RT. A proximal B cell epitope was also active, containing the motif EQVD.

HXB2 Location RT (528–541)
Author Location RT (528–543 BRU)
Epitope KEKVYLAWVPAHKG
Epitope name A3
Subtype B
Immunogen vaccine

T-Helper CD4+

Vector/Type: peptide, protein, inactivated HIV *Strain:* B clade BRU *HIV component:* RT, virus *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 A^d, H-2D^d)
Donor MHC H-2d, H-2f, H-2k
References Haas *et al.* 1991

- Of 5 mouse inbred lines tested: DBA/2 (H-2d, Ad, Ed), B10.A(4R) (H-2h4, Ak) and B10.A(5R) (H-2i5) showed particularly good CD4+ T cell proliferative responses to HIV proteins (gp160, gp120, p17, p24, Nef and RT), after vaccination with inactivated virus.
- B10.BR (H-2k, Ak, Ek) and C57BL/6 (H-2b and Ab) had weaker responses.
- The peptide KEKVYLAWVPAHKG was one of two RT peptides with Th cells recognition. It could by itself prime different strains of mice for RT-specific Th responses, and the C-term half of the peptide is highly conserved in HIV-1, HIV-2 and SIV strains.

HXB2 Location RT (528–543)
Author Location RT (528–543 BRU)
Epitope `KEKVYLAWVPAHKGIG`
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade BRU
Species (MHC) mouse (H-2^d, H-2^f, H-2^k)
References Haas *et al.* 1991

- T-cells from peptide-primed mice could be restimulated by native RT.

HXB2 Location RT (529–543)
Author Location Pol (711–725)
Epitope `EKVYLAWVPAHKGIG`
Epitope name Pol 711
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Keywords subtype comparisons
References Wilson *et al.* 2001

- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
- This epitope binds ten HLA-DR alleles: DRB1*0101, DRB1*1501, DRB1*0401, DRB1*0405, DRB1*1101, DRB1*0701, DRB1*0802, DRB1*0901, DRB5*0101 and DRB4*0101, with an IC_{50} threshold below 1,000 nM.
- This epitope sequence is conserved in 94% of clade B isolates.
- 6/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

HXB2 Location RT (529–543)
Author Location Protease-RT (711–725)
Epitope `EKVYLAWVPAHKGIG`
Epitope name Pol4
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Assay type proliferation, Intracellular cytokine staining
Keywords rate of progression, superinfection
References Boaz *et al.* 2003

- Proliferative and cytokine (IFNgamma and Il-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNPs (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive.
- Gag-specific CD4+ T cells in LTNPs showed increased numbers of IFN gamma and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFNgamma, levels were correlated with proliferation.

HXB2 Location RT (529–543)
Author Location Pol (711–725)
Epitope `EKVYLAWVPAHKGIG`
Epitope name Pol 711
Immunogen vaccine
Vector/Type: DNA with CMV promotor, peptide *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (DR, I-A^b)
Donor MHC H-2b
Keywords vaccine-specific epitope characteristics, immunodominance
References Livingston *et al.* 2002

- 4 Th HIV epitopes presented by HLA-DR molecules were identified that also could be presented by murine class II molecule I-Ab, enabling testing of vaccine strategies in H-2b mice.
- Responses to pooled peptides, polyepitope peptides in a linear construct or in a branched MAP construct, and a DNA polyepitope construct with a CMV promoter were compared. A linear arrangement in polyepitope construct created a junctional epitope that could be disrupted with the addition of GPGPG spacers. The linear polyepitope construct with the GPGPG spacer worked well in terms of eliciting responses to all 4 peptides, using either DNA or protein for the vaccination.
- Although responses to this peptide indicated it was immunodominant, responses to all 4 peptides were made upon vaccination with linear constructs when GPGPG spacers were used.

HXB2 Location RT (530–544)
Author Location Pol (712–726)
Epitope `KVYLAWVPAHKGIGG`
Epitope name Pol 712
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Keywords subtype comparisons
References Wilson *et al.* 2001

- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
- This epitope binds ten HLA-DR alleles: DRB1*0101, DRB1*1501, DRB1*0401, DRB1*0405, DRB1*1101, DRB1*0701, DRB1*0802, DRB1*0901, DRB5*0101 and DRB4*0101, with an IC_{50} threshold below 1,000 nM.

T-Helper CD4+

- This epitope sequence is conserved in 89% of clade B isolates.
- 6/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

HXB2 Location RT (530–544)
Author Location RT (712–726)
Epitope KVYLAWVPAHKGIGG
Epitope name Pol5
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Country United Kingdom
Assay type proliferation, Intracellular cytokine staining
Keywords supertype, rate of progression
References Boaz *et al.* 2003

- Proliferative and cytokine (IFNgamma and Il-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNPs (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive.
- Gag-specific CD4+ T cells in LTNPs showed increased numbers of IFN gamma and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFNgamma, levels were correlated with proliferation.
- Pol5 was 1 of 2 peptides that had a positive correlation between absolute number and percentage of responding cells and viral load. In contrast, the absolute number of 3/11 peptides studied were negatively correlated with viral load.

III-B-8 RT-Integrase Helper/CD4+ T-cell epitopes

HXB2 Location RT-Integrase (553–3)
Author Location RT (720–730 LAI)
Epitope SAGIRKVLFLD
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

III-B-9 Integrase Helper/CD4+ T-cell epitopes

HXB2 Location Integrase (16–30)
Author Location Pol (758–772)
Epitope HSNWRAMASDFNLPP
Epitope name Pol 758
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Keywords subtype comparisons
References Wilson *et al.* 2001

- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
- This epitope binds eight HLA-DR alleles: DRB4*0101, DRB5*0101, DRB1*0901, DRB1*0701, DRB1*1101, DRB1*0405, DRB1*0401 and DRB1*0101, with an IC_{50} threshold below 1,000 nM.
- This epitope sequence is conserved in 68% of clade B isolates.
- 8/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

HXB2 Location Integrase (16–30)
Author Location Integrase (758–772)
Epitope HSNWRAMASDFNLPP
Epitope name Pol6
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Country United Kingdom
Assay type proliferation, Intracellular cytokine staining
Keywords supertype, rate of progression
References Boaz *et al.* 2003

- Proliferative and cytokine (IFNgamma and Il-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNPs (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive.
- Gag-specific CD4+ T cells in LTNPs showed increased numbers of IFN gamma and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFNgamma, levels were correlated with proliferation.
- Pol6 was 1 of 3 peptides that had a negative correlation between absolute number of responding cells and viral load.

HXB2 Location Integrase (70–84)
Author Location Integrase (70–84 clade B consensus)
Epitope GKIILVAVHVASGYI
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (DRB1*0101, DRB1*0401, DRB1*0405, DRB1*0701, DRB1*1101, DRB1*1302, DRB1*1501, DRB5*0101)
Country Brazil
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References Fonseca *et al.* 2006

T-Helper CD4+

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 brazilian HIV-1 chronically infected individuals.
- While the reacting peptide was GKIILVAVHVASGYI, shorter IILVAVHVASG peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

HXB2 Location Integrase (94–116)
Author Location
Epitope GQETAYFILKLAGRWPVKVIHTD
Epitope name HIV-VAX-1047
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 2/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was ILKLAGRWP.

HXB2 Location Integrase (172–186)
Author Location RT (899–913 LAI)
Epitope LKTAVQMAVFIHNFK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

HXB2 Location Integrase (173–187)
Author Location Pol (915–929)
Epitope KTAVQMAVFFIHNFKR
Epitope name Pol 915
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Keywords subtype comparisons
References Wilson *et al.* 2001

- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
- This epitope binds seven HLA-DR alleles: DRB5*0101, DRB1*1302, DRB1*1101, DRB1*0405, DRB1*0401, DRB1*1501 and DRB1*0101, with an IC_{50} threshold below 1,000 nM.
- This epitope sequence is conserved in 94% of clade B isolates.
- 6/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

HXB2 Location Integrase (173–187)
Author Location Integrase (915–929)
Epitope KTAVQMAVFIHNFKR
Epitope name Pol7
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Country United Kingdom
Assay type proliferation, Intracellular cytokine staining
Keywords supertype, rate of progression, immunoprophylaxis
References Boaz *et al.* 2003

- Proliferative and cytokine (IFNgamma and Il-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNPs (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive.
- Gag-specific CD4+ T cells in LTNPs showed increased numbers of IFN gamma and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFNgamma, levels were correlated with proliferation.

HXB2 Location Integrase (187–204)
Author Location (clade B consensus)
Epitope RKGGIGGYSAGERIVDII
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101, A*0201, B*4001, C*0304, DRB1*0801, DRB1*1301
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords escape
References Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- RKGGIGGYSAGERIVDII variant coincided with a positive response. RKGGIGGYSAGkRIVDII variant 4 weeks later coincided with no response.

HXB2 Location Integrase (195–211)
Author Location (clade B consensus)
Epitope SAGERIVDIIATDIQTK
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101, A*0201, B*4001, C*0304, DRB1*0801, DRB1*1301
Country United States
Assay type CD4 T-cell Elispot - IFNγ

Keywords escape
References Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- SAGERIVDIIATDIQTK variant coincided with a positive response. SAGkRIVDIIATDIQTKI variant 4 weeks later coincided with a diminished response.

HXB2 Location Integrase (196–210)
Author Location RT (923–937 LAI)
Epitope `AGERIVDIIATDIQT`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

HXB2 Location Integrase (214–228)
Author Location Pol (956–970)
Epitope `QKQITKIQNFRVYYR`
Epitope name Pol 956
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Keywords subtype comparisons
References Wilson *et al.* 2001

- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
- This epitope binds twelve HLA-DR alleles: DRB4*0101, DRB5*0101, DRB1*0901, DRB1*0802, DRB1*0701, DRB1*1302, DRB1*1201, DRB1*1101, DRB1*0405, DRB1*0401, DRB1*1501 and DRB1*0101, with an IC_{50} threshold below 1,000 nM.
- This epitope sequence is conserved in 95% of clade B isolates.
- 8/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

HXB2 Location Integrase (214–228)
Author Location Integrase (956–970)
Epitope `QKQITKIQNFRVYYR`
Epitope name Pol8
Immunogen HIV-1 infection
Species (MHC) human (DR supermotif)
Country United Kingdom
Assay type proliferation, Intracellular cytokine staining
Keywords supertype, rate of progression
References Boaz *et al.* 2003

- Proliferative and cytokine (IFNgamma and Il-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNPs (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive.
- Gag-specific CD4+ T cells in LTNPs showed increased numbers of IFN gamma and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFNgamma, levels were correlated with proliferation.
- Pol8 was the only peptide that had higher cytokine responses in LTNPs than SPs (p = 0.0431). No peptide had detectable differences in proliferative responses between the two groups.

HXB2 Location Integrase (215–227)
Author Location RT (942–954 LAI)
Epitope `KQITKIQNFRVYY`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

HXB2 Location Integrase (242–259)
Author Location (clade B consensus)
Epitope `LWKGEGAVVIQDNSDIKV`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101, A*0201, B*4001, C*0304, DRB1*0801, DRB1*1301
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords escape
References Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- LWKGEGAVVIQDNSDIKV variant coincided with a positive response. LWKGEGAVVlQDNSDIKV variant 4 weeks later coincided with a diminished response.

HXB2 Location Integrase (242–264)
Author Location
Epitope `LWKGEGAWIQDNSDIKWPRRK`
Epitope name HIV-VAX-1049
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 1/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was WIQDNSDI.

HXB2 Location Integrase (250–267)
Author Location Integrase (250–267 B Consensus)
Epitope `VIQDNSDIKVVPRRKAKI`
Subtype B

T-Helper CD4+

Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location Integrase (250–267)
Author Location Integrase (250–267)
Epitope VIQDNSDIKVVPRRKAKI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Netherlands
Assay type Cytokine production
References Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. VIQDNSDIKVVPRRKAKI had fixation of 1 mutation (VIQDNSDIK[v/a]VPRRKAKI) in 1 of the patients.

HXB2 Location Integrase (250–267)
Author Location (clade B consensus)
Epitope VIQDNSDIKVVPRRKAKI
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101, A*0201, B*4001, C*0304, DRB1*0801, DRB1*1301
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords escape
References Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- VIQDNSDIKVVPRRKAKI variant coincided with a positive response. VlQDNSDIKVVPRRKAKI variant 4 weeks later also coincided with a positive (but increased) response.

III-B-10 Pol Helper/CD4+ T-cell epitopes

HXB2 Location Pol
Author Location RT (248–256 HXB2)
Epitope
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DR5)
References Manca *et al.* 1995b

- CD4+ T-cell lines from uninfected individuals by stimulation with p66-pulsed APC.
- TcR Vβ Dβ Jβ sequences were obtained from p66-specific T-cell clones.
- There were multiple responses to peptides throughout p66, but because of uncertain locations, they have not been mapped.
- Response to peptide 248-256 was associated with DR5.

HXB2 Location Pol
Author Location RT
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Env, Gag, Pol *Adjuvant:* IFNγ, IL-2, IL-4
Species (MHC) mouse (H-2^d)
Keywords Th1
References Kim *et al.* 2000

- Co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine used to enhance the immune response – co-expression of Th1 cytokine IFN-γ drove Th1 immune responses and enhanced CTL responses.

HXB2 Location Pol
Author Location RT
Epitope
Immunogen vaccine
Vector/Type: Salmonella *HIV component:* RT
Species (MHC) mouse (H-2^d)
References Burnett *et al.* 2000

- A live attenuated bacterial vaccine, Salmonella SL3261-pHART, with an inserted HIV RT gene in the Lpp-OmpA-HIV fusion protein, induced a lymphoproliferative Th response in BALB/c mice.

HXB2 Location Pol
Author Location Gag/Pol
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Gag, Pol, Vif *Adjuvant:* B7, IL-12
Species (MHC) mouse
References Kim *et al.* 1997b

T-Helper CD4+

- A gag/pol DNA vaccine delivered in conjunction with the plasmid encoding the co-stimulatory molecules B7 and IL-12 gives a dramatic increase in both the cytotoxic and proliferative responses in mice.

HXB2 Location Pol
Author Location Gag/Pol
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Gag, gp160, Pol *Adjuvant:* CD86
Species (MHC) mouse
References Kim *et al.* 1997d

- A gag/pol DNA vaccine delivered in conjunction with the plasmid encoding the co-stimulatory molecule CD86 gives an increase in proliferative responses to Pr55 in mice.

HXB2 Location Pol
Author Location Gag/Pol (MN)
Epitope
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade MN *HIV component:* Env, Gag, Pol *Adjuvant:* CD80, CD86
Species (MHC) chimpanzee
References Kim *et al.* 1998

- Co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine used to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses.

HXB2 Location Pol
Author Location Pol
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Blankson *et al.* 2001

- 5/10 chronically HIV infected patients with low CD4+ counts who received HAART therapy and experienced immune reconstitution displayed p24, p17 and p66 T-helper CD4 proliferative responses, in contrast to 0/8 chronically HIV infected patients with high CD4+ counts at the initiation of antiretroviral treatment.
- This surprising result could be due to the low CD4 nadir patients being more likely to have thymic regeneration or a peripheral expansion of T cells.

HXB2 Location Pol
Author Location p66
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.

HXB2 Location Pol
Author Location p66
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Palmer *et al.* 2002

- CD4+ T cell proliferative responses from 33 HIV-1 infected patients with HAART suppression were compared to 19 patients with active viral replication (HAART failures and HAART naive). Patients with HAART suppression showed stronger p24- and p66-specific proliferative responses compared to patient groups with active HIV-1 replication, suggesting active viral replication *in vivo* specifically reduces proliferation responses.
- No differences in the frequency of HIV-specific CD4+ T-cells that were positive for cytokine secretion in a flow cytometry assay were found in the HAART suppressed group versus the group with active viral replication.

HXB2 Location Pol
Author Location (BRU)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade BRU *HIV component:* RT, virus *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse
References Haas *et al.* 1991

- Of 5 mouse inbred lines tested DBA/2 (H-2d, Ad, Ed), B10.A(4R) (H-2h4, Ak) and B10.A(5R) (H-2i5) showed particularly good CD4+ T cell proliferative responses to HIV proteins (gp160, gp120, p17, p24, Nef and RT), after vaccination with inactivated virus.
- B10.BR (H-2k, Ak, Ek) and C57BL/6 (H-2b and Ab) had weaker responses.

III-B-11 Vif Helper/CD4+ T-cell epitopes

HXB2 Location Vif (4–26)
Author Location
Epitope RWQVMIVWQVDRMRIRTWNSLVK
Epitope name HIV-VAX-1052
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ

T-Helper CD4+

Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005
- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 4/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was WQVDRMRIR.

HXB2 Location Vif (65–76)
Author Location Vif (65–80)
Epitope VITTYWGLHTGE
Immunogen HIV-1 infection
Species (MHC) human
References Ranki *et al.* 1997
- T-cell response to this epitope persisted after seroreversion.

HXB2 Location Vif (81–96)
Author Location Vif (81–96)
Epitope LGQGVSIEWRKQRYST
Immunogen HIV-1 infection
Species (MHC) human
References Ranki *et al.* 1997
- T-cell response to this epitope persisted after seroreversion.

HXB2 Location Vif (144–158)
Author Location Vif (144–158 clade B consensus)
Epitope SLQYLALVALVAPKK
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (DRB1*0101, DRB1*0401, DRB1*0405, DRB1*0701, DRB1*1101, DRB1*1501, DRB5*0101)
Country Brazil
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References Fonseca *et al.* 2006
- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 brazilian HIV-1 chronically infected individuals.
- While the reacting peptide was SLQYLALVALVAPKK, shorter LQYLALVALVAPKK peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

HXB2 Location Vif
Author Location Vif
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Nef, Vif, Vpu
Species (MHC) mouse (H-2^d)
Keywords subtype comparisons, Th1
References Ayyavoo *et al.* 2000
- Splenocytes from BALB/c mice immunized with pVVN-P DNA were incubated with Vif, Vpu or Nef antigens for 3 days and assayed for IL-4 and IFN-γ levels.
- Antigen stimulation increased IFN-γ production in pVVN-P immunized mice, indicating a Th1 response.
- IL-4 production was not significantly changed after antigen stimulation compared to control levels.
- Cross-clade CTL activity was also observed: A, B clade, CRF01(AE) clade antigens could serve as targets for the B clade immunization stimulated CTL – an HIV-1 AC recombinant, however, did not stimulate a CTL response, but was expressed at lower levels on the target cell.

III-B-12 Vpr Helper/CD4+ T-cell epitopes

HXB2 Location Vpr (32–46)
Author Location Vpr (32–46 LAI/IIIB)
Epitope RHFPRIWLHGLGQHI
Epitope name Vpr 32-46
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human
Donor MHC DRB1*0101, DRB1*1302, DRB3; DRB1*0301, DRB1*1501, DRB3, DRB5
Country France
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity
References Castelli *et al.* 2008
- CD4+ T-cell response to Tat and Vpr was evaluated in healthy donors. Most donors responded to both Tat and Vpr. In Tat, for 8 HLA-unrelated donors, only one peptide (KALGISYGRKKRRQR) primed all CD4+ responses, while responses to Vpr involved 6 different peptides, depending on the HLA-DR molecules of the donor.
- Vpr 32-46 induced helper T-cell response in two cell lines each from 2 of 9 patients (P191, P200).

HXB2 Location Vpr (35–49)
Author Location Vpr (35–49 LAI/IIIB)
Epitope PRIWLHGLGQHIYET
Epitope name Vpr 35-49
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DRB5)
Country France
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity
References Castelli *et al.* 2008
- CD4+ T-cell response to Tat and Vpr was evaluated in healthy donors. Most donors responded to both Tat and Vpr. In Tat, for 8 HLA-unrelated donors, only one peptide (KALGISYGRKKRRQR) primed all CD4+ responses, while responses to Vpr involved 6 different peptides, depending on the HLA-DR molecules of the donor.
- Based on binding data and experiments with HLA-DR transfected L cells, this peptide was restricted to DRB5.

HXB2 Location Vpr (48–62)
Author Location Vpr (48–64 LAI/IIIB)
Epitope ETYGDTWAGVEAIIR
Epitope name Vpr 48-64
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DRB5)
Country France
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, variant cross-recognition or cross-neutralization
References Castelli *et al.* 2008

- CD4+ T-cell response to Tat and Vpr was evaluated in healthy donors. Most donors responded to both Tat and Vpr. In Tat, for 8 HLA-unrelated donors, only one peptide (KALGISYGRKKRRQR) primed all CD4+ responses, while responses to Vpr involved 6 different peptides, depending on the HLA-DR molecules of the donor.
- Large cross-reactivity was observed for a Vpr 48-64-specific T cell line.
- Based on binding data and experiments with HLA-DR transfected L cells, this peptide was restricted to DRB5.
- Author communication: Sequence ETYGDTWAGVEAIIR clade B variants were ETYGDTWtGVEAIIR, ETYGDTWAGVEAlIR, ETYGDTWtGVEAlIR, ETYGDTWAGVEAItR, dTYGDTWtGVEAlIR, ETYGDTWeGVEAIIR, ETYGDTWvGVEAIIR, gTYGDTWAGVEAlIR.

HXB2 Location Vpr (52–66)
Author Location Vpr (52–66 LAI/IIIB)
Epitope DTWAGVEAIIRILQQ
Epitope name Vpr 52-66
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DR11, DRB5)
Donor MHC DRB1*0101, DRB1*1302, DRB3; DRB1*1101, DRB1*1104, DRB3; DRB1*0301, DRB1*1501, DRB3, DRB5; DRB1*1301, DRB1*1501, DRB3, DRB5; DRB1*1101, DRB1*1301, DRB3; DRB1*1301, DRB1*1501, DRB3, DRB5
Country France
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, cross-presentation by different HLA, variant cross-recognition or cross-neutralization
References Castelli *et al.* 2008

- CD4+ T-cell response to Tat and Vpr was evaluated in healthy donors. Most donors responded to both Tat and Vpr. In Tat, for 8 HLA-unrelated donors, only one peptide (KALGISYGRKKRRQR) primed all CD4+ responses, while responses to Vpr involved 6 different peptides, depending on the HLA-DR molecules of the donor.
- Almost all T-cell lines were stimulated by multiple variants to DTWAGVEAIIRILQQ (Vpr52-66). Sequence DTWAGVEAIIRILQQ has 45.7% frequency in clades B and D. Other variants were all present at <10% frequency and were DTWtGVEAIIRILQQ, DTWAGVEAlIRILQQ (also present in consensus H), DTWAGVEAIIRtLQQ, DTWAGVEAIIRmLQQ, DTWAGVEAItRILQQ, DTWAGVEAIIRvLQQ, DTWAGVEAlIRtLQQ, DTWtGVEAlIRILQQ, DTWtGVEAlIRmLQQ, DTWvGVEAIIRILQQ, DTWeGVEAIIRtLQQ (also present in consensus A, A1, A2), and DTWeGVEAIIRILQQ (also present in consensus F1, F2, G).
- Based on binding data and experiments with HLA-DR transfected L cells, this peptide was restricted to DR11 and DRB5.

HXB2 Location Vpr (58–72)
Author Location Vpr (58–72 clade B consensus)
Epitope EAIIRILQQLLFIHF
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (DRB1*0101, DRB1*0405, DRB1*1501)
Country Brazil
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 brazilian HIV-1 chronically infected individuals.
- While the reacting peptide was EAIIRILQQLLFIHF, shorter IRILQQLLF peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

HXB2 Location Vpr (60–82)
Author Location
Epitope IIRILQQLLFIHFRIGCQHSRIG
Epitope name HIV-VAX-1053
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 2/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was LLFIHFRIG.

HXB2 Location Vpr (64–79)
Author Location Vpr (65–79 LAI/IIIB)
Epitope LQQLLFIHFRIGCRHS
Epitope name Vpr 65-79
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DR11)

Donor MHC DRB1*0404, DRB1*0701, DRB4; DRB1*1101, DRB1*1104, DRB3; DRB1*1301, DRB1*1501, DRB3, DRB5
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, dendritic cells
References Castelli *et al.* 2008

- CD4+ T-cell response to Tat and Vpr was evaluated in healthy donors. Most donors responded to both Tat and Vpr. In Tat, for 8 HLA-unrelated donors, only one peptide (KALGISYGRKKRRQR) primed all CD4+ responses, while responses to Vpr involved 6 different peptides, depending on the HLA-DR molecules of the donor.
- Cross-reactivity was very limited for a Vpr 65-79-specific T-cell line.
- Based on binding data and experiments with HLA-DR transfected L cells, this peptide was restricted to DR11.
- Author communication: Sequence LQQLLFIHFRIGCRHS clade B variants were LQQLLFIHFRIGCqHS, LQQLLFIHFRIGChHS, LQQmLFIHFRIGChHS, LQQLLFIHFRIrCRHS, LQQLLlIHFRIGCRHS, LQQLLFIHFRIGgRHS, LQQLLFtHFRIGCqHS, LQQLmFIHFRIGCRHS, LQQLmFIHFRIGCqHS, LQQLLFtHFRIGCRHS.

HXB2 Location Vpr (65–82)
Author Location Vpr (65–82 clade B consensus)
Epitope `QQLLFIHFRIGCRHSRIG`
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (DRB1*0101, DRB1*0405, DRB1*0701, DRB1*1101, DRB1*1302, DRB1*1501, DRB5*0101)
Country Brazil
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 brazilian HIV-1 chronically infected individuals.
- While the reacting peptide was QQLLFIHFRIGCRHSRIG, shorter LFIHFRIGCRHSR peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

HXB2 Location Vpr (66–80)
Author Location Vpr (66–80 IIIB)
Epitope `QLLFIHFRIGCRHSR`
Immunogen vaccine
Vector/Type: peptide
Species (MHC) mouse (H-2^{d})
References Sarobe *et al.* 1994

- Included as a Th stimulatory component of peptide vaccines that also incorporated B-cell epitopes.

HXB2 Location Vpr (66–80)
Author Location Vpr (66–80 IIIB)
Epitope `QLLFIHFRIGCRHSR`
Immunogen HIV-1 infection
Species (MHC) human
References Sarobe *et al.* 1994

- This peptide was found to stimulate proliferative responses in 37.5% of HIV-1 positive individuals.

HXB2 Location Vpr (70–84)
Author Location Vpr (70–84 LAI/IIIB)
Epitope `IHFRIGCRHSRIGVT`
Epitope name Vpr 70-84
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DR11, DR3, DRB5)
Country France
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity
References Castelli *et al.* 2008

- CD4+ T-cell response to Tat and Vpr was evaluated in healthy donors. Most donors responded to both Tat and Vpr. In Tat, for 8 HLA-unrelated donors, only one peptide (KALGISYGRKKRRQR) primed all CD4+ responses, while responses to Vpr involved 6 different peptides, depending on the HLA-DR molecules of the donor.
- Based on binding data and experiments with HLA-DR transfected L cells, this peptide was restricted to DR11, DR3 and DRB5

III-B-13 Tat Helper/CD4+ T-cell epitopes

HXB2 Location Tat (1–20)
Author Location Tat (1–20 LAI)
Epitope `MEPVDPRLEPWKHPGSQPKT`
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^{d})
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Tat (16–35)
Author Location Tat (16–35 LAI)
Epitope `SQPKTACTTCYCKKCCFHCQ`
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^{d})
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.

- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Tat (17–32)
Author Location Tat (17–32 HXB2)
Epitope QPKTACTNCYCKKCCF
Epitope name D26
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DR5? plus others)
Keywords immunodominance
References Blazevic *et al.* 1993

- 9/14 (64%) of HIV-1 positive patients had proliferative T-cell responses associated with IL-2 production against at least one Tat-derived synthetic peptides of twelve overlapping 15-16 mer peptides spanning Tat. T cell proliferation was associated with IL-2 production.
- 3/12 peptides were recognized.
- This immunodominant, highly conserved and most frequently recognized peptide was recognized by 57% of the HIV-1 infected patients. A beta-sheet secondary structure was predicted at aa residues 21-28, but no amphipathic helix structure, suggested to be most favorable for T-cell epitopes, was indicated.
- This peptide contained epitopes restricted by several HLA DR alleles, although the frequency of DR5 was enriched (3/6) among the patients that recognized the peptide.

HXB2 Location Tat (17–32)
Author Location Tat (17–32)
Epitope QPKTACTNCYCKRCCF
Immunogen HIV-1 infection
Species (MHC) human
References Ranki *et al.* 1997

- T-cell response to this epitope persisted after seroreversion.

HXB2 Location Tat (25–47)
Author Location
Epitope CYCKHCSYHCLVCFQTKGLGISY
Epitope name HIV-VAX-1054
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 3/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was YHCLVCFQT.

HXB2 Location Tat (31–50)
Author Location Tat (31–50 LAI)
Epitope CFHCQVCFTTKALGISYGRK
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^{d})
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Tat (33–48)
Author Location Tat (33–48 HXB2)
Epitope HCQVCFITKALGISYG
Epitope name D28
Immunogen HIV-1 infection
Species (MHC) human (DR5? plus others)
References Blazevic *et al.* 1993

- 9/14 (64%) of HIV-1 positive patients had proliferative T-cell responses associated with IL-2 production against at least one Tat-derived synthetic peptides of twelve overlapping 15-16 mer peptides spanning Tat. T cell proliferation was associated with IL-2 production.
- 3/12 peptides were recognized.
- 4/14 HIV+ people recognized this peptide.
- An alpha-helix structure was predicted at residues 39-44, but charge patterns did not indicate it was an amphipathic helix, suggested to be most favorable for T-cell epitopes.
- This peptide contained epitopes restricted by several HLA DR alleles, although the frequency of DR5 was enriched (2/4) among the patients that recognized the peptide.

HXB2 Location Tat (33–48)
Author Location Tat (33–48)
Epitope HCQVCFMTKGLGISYG
Immunogen HIV-1 infection
Species (MHC) human
References Ranki *et al.* 1997

- T-cell response to this epitope persisted after seroreversion.

HXB2 Location Tat (36–50)
Author Location Tat (36–50 HTLV IIIB)
Epitope VCFITKALGISYGRK?
Subtype B
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA), macrophage activating lipopeptide-2 (MALP-2)
Species (MHC) mouse (H-2^{d})
Assay type Cytokine production, proliferation, T-cell Elispot, Th support of CTL response
Keywords Th1, Th2, mucosal immunity
References Borsutzky *et al.* 2003

- BALB/c mice that were vaccinated intranasally with Tat protein plus mucosal adjuvant macrophage-activating lipopeptide-2 (MALP-2) had increased proliferative, antibody, and IFN-γ producing T-cell responses than did with Tat+IFA delivered by the i.p. route.

T-Helper CD4+

- IFA as adjuvant stimulated a Th2-dominant response pattern, and MALP-2 as adjuvant shifted to a Th1 response. Anti-Tat IgG1 dominated the Ab response with IFA, IgG2b dominated with MALP-2. In animals vaccinated with Tat+MALP-2, IFN-γ and IL-2 were the most prominent cytokines, with some IL-6. In contrast, in mice vaccinated with Tat+IFA, IL-6 was the dominant cytokine. Secreted IL-4, IL-5 and IL-10 were below the detection limit in both cases.
- The strongest proliferation of spenocytes was observed was after re-stimulation with residues 36-50 and 56-70.

HXB2 Location Tat (41–50)
Author Location Tat (40–50 C consensus)
Epitope KGLGISYGRK?
Subtype C
Immunogen vaccine
Vector/Type: DNA *Strain:* C clade consensus *HIV component:* Tat *Adjuvant:* ubiquitin
Species (MHC) mouse
Donor MHC H-2d
Assay type proliferation, CD4 T-cell Elispot - IFNγ
Keywords Th1, vaccine antigen design
References Ramakrishna *et al.* 2004

- BALB/c and C57BL/6 mice were intramuscularly immunized with a codon optimized HIV-1 C-consensus Tat DNA vaccine that was linked to ubiquitin to facilitate rapid processing. Ubiquitin and codon optimization enhanced Th1 T cell responses, with increased proliferative responses, cytotoxic responses, and Th1 responses measured by IFNgamma EliSpot, but not the Th2 responses, measured by IL-4 EliSpot..
- Several immunogenic regions in HIV-1 Tat were identified in BALB/c mice using EliSpot. The strongest immune response was within the core region of Tat; the peptides based on the C subtype consensus positions 30-50 and 40-60 gave the strongest EliSpot responses in BALB/c mice, suggesting a putative helper T-cell epitope spanning the region of overlap, residues 40-50.

HXB2 Location Tat (41–55)
Author Location Tat (41–55 LAI/IIIB)
Epitope KALGISYGRKKRRQR
Epitope name Tat 41-55
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DR11, DR13, DR3, DRB5)
Donor MHC DRB1*0404, DRB1*0701, DRB4; DRB1*0101, DRB1*1302, DRB3; DRB1*1101, DRB1*1104, DRB3; DRB1*0301, DRB1*1501, DRB3, DRB5; DRB1*1301, DRB1*1501, DRB3, DRB5; DRB1*0701, DRB1*0901, DRB4; DRB1*1101, DRB1*1301, DRB3; DRB1*1301, DRB1*1501, DRB3, DRB5
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, cross-presentation by different HLA, variant cross-recognition or cross-neutralization
References Castelli *et al.* 2008

- CD4+ T-cell response to Tat and Vpr was evaluated in healthy donors. Most donors responded to both Tat and Vpr. In Tat, for 8 HLA-unrelated donors, only one peptide (KALGISYGRKKRRQR) primed all CD4+ responses, while responses to Vpr involved 6 different peptides, depending on the HLA-DR molecules of the donor.
- KALGISYGRKKRRQR from LAI/IIIB isolate has 20% frequency in clade B. Almost all T cells primed by this peptide also recognized the most frequent variant KgLGISYGRKKRRQR (50% frequency in clade B, also present in consensus A1, B, C, D, F1, F2). 3 more variants KgLGISYGsKKRRQR, KALGISnGRKKRRQR, KgLGIyYGRKKRRQR (10% frequency each) were recognized to a lesser extent.
- Based on binding data and experiments with HLA-DR transfected L cells, this peptide was restricted to DR11, DRB5 and DR3. Using EBV cell lines, it was suggested that DR13 may be a restricting HLA for Tat 41-55.

HXB2 Location Tat (46–65)
Author Location Tat (46–65 LAI)
Epitope SYGRKKRRQRRRPPQGSQTH
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^d)
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Tat (56–70)
Author Location Tat (56–70 HTLV IIIB)
Epitope RRAHQNSQTHQASLS?
Subtype B
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA), macrophage activating lipopeptide-2 (MALP-2)
Species (MHC) mouse (H-2^d)
Assay type Cytokine production, proliferation, T-cell Elispot, Th support of CTL response
Keywords Th1, Th2
References Borsutzky *et al.* 2003

- BALB/c mice that were vaccinated intranasally with Tat protein plus mucosal adjuvant macrophage-activating lipopeptide-2 (MALP-2) had increased proliferative, antibody, and IFN-γ producing T-cell responses than did with Tat+IFA delivered by the i.p. route.
- IFA as adjuvant stimulated a Th2-dominant response pattern, and MALP-2 as adjuvant shifted to a Th1 response. Anti-Tat IgG1 dominated the Ab response with IFA, IgG2b dominated with MALP-2. In animals vaccinated with Tat+MALP-2, IFN-γ and IL-2 were the most prominent cytokines, with some IL-6. In contrast, in mice vaccinated with Tat+IFA, IL-6 was the dominant cytokine. Secreted IL-4, IL-5 and IL-10 were below the detection limit in both cases.

T-Helper CD4+

- The strongest proliferation of spenocytes was observed was after re-stimulation with residues 36-50 and 56-70.

HXB2 Location Tat (61–80)
Author Location Tat (61–80 LAI)
Epitope GSQTHQVSLSKQPTSQPRGD
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^d)
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally; rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Tat (65–80)
Author Location Tat (65–80 HXB2)
Epitope HQASLSKQPTSQPRGD
Epitope name D32
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DR2? plus others)
References Blazevic *et al.* 1993

- 9/14 (64%) of HIV-1 positive patients had proliferative T-cell responses associated with IL-2 production against at least one Tat-derived synthetic peptides of twelve overlapping 15-16 mer peptides spanning Tat. T cell proliferation was associated with IL-2 production.
- 3/12 Tat peptides were recognized.
- 3/14 HIV+ people recognized this peptide.
- An alpha-helix structure was predicted at residues 65-72, but charge patterns did not indicate it was an amphipathic helix, suggested to be most favorable for T-cell epitopes..
- This peptide contained epitopes restricted by several HLA DR alleles, although the frequency of DR2 was enriched (2/3) among the patients that recognized the peptide.

HXB2 Location Tat (67–86)
Author Location Tat (67–86 LAI)
Epitope VSLSKQPTSQPRGDPTGPKE
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^d)
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Tat
Author Location Tat
Epitope
Immunogen vaccine
Vector/Type: DNA, DNA with protein boost *Strain:* B clade LAI *HIV component:* Gag, Nef, Tat *Adjuvant:* IL-18
Species (MHC) mouse (H-2^d)
Keywords Th1, Th2
References Billaut-Mulot *et al.* 2001

- DNA vaccinated BALB/c mice primed and boosted with a multiepitopic vaccine with IL18 gave lymphoproliferative responses 7 weeks post immunization.
- Strong but non-lasting HIV-specific CTL responses were detected by a Cr-release assay and DNA prime + DNA boost was more effective than DNA prime + protein boost.
- Immunization with either the multiepitopic DNA or with the mixed DNA vaccine resulted in Th1 cytokines production (IL-2 and IFN-γ) in spleen cell cultures stimulated by Tat and Gag, while Th2 cytokines IL-4 and IL-10 production was not detectable.
- Co-administration of IL18 increased T-cell responses but decreased anti-HIV antibody levels.

HXB2 Location Tat
Author Location Tat
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Nef, Rev, Tat
Species (MHC) human
Keywords HAART, ART
References Calarota *et al.* 1999

- 9/9 HIV-1 + subjects were given one of three DNA vaccinations for nef, rev or tat, and novel proliferative and CTL responses were generated.
- The nef DNA immunization induced the highest and most consistent CTLp activity, IFN-γ production, and IL-6 and IgG responses.
- Highly active antiretroviral treatment (HAART) did not induce new HIV-specific CTL responses but reduced viral load, while DNA vaccination induced new immune responses but did not reduce viral load – thus this is a potentially complementary and promising combination.

HXB2 Location Tat
Author Location Tat
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *HIV component:* Nef, Rev, Tat *Adjuvant:* CpG immunostimulatory sequence (ISS)
Species (MHC) human
Keywords review, Th1
References Calarota & Wahren 2001

- This review discusses the cellular immune response, and comments on CpG induction of Th1 cytokines and enhanced immune responses, and HIV-1 DNA vaccine boosting of CTL and Th proliferative responses in asymptomatic HIV+ individuals.

HXB2 Location Tat
Author Location Tat
Epitope

Immunogen in vitro stimulation or selection
Species (MHC) human
Keywords dendritic cells, Th1, Th2
References Corinti *et al.* 2002

- In vitro delivery of recombinant Tat protein conjugated to red blood cells (RBCs) via avidin-biotin bridges (RBC-Tat) to human dendritic cells was compared to dendritic cells pulsed with rec Tat.
- Dendritic cells pulsed with RBC-Tat elicited specific and significantly stronger CD4+ and CD8+ T-cell responses and required 1250-fold less antigen than DCs stimulated with soluble Tat.
- Dendritic cells which were maturated in the presence of IFNgamma induced elevated IL-12 and TNF-alpha secretion. IFNgamma upregulated IP-10 and down regulated TARC, chemokines which attract Th1 and Th2 cells, respectively.

HXB2 Location Tat
Author Location Tat (IIIB, BH10)
Epitope
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human
Keywords epitope processing, vaccine-specific epitope characteristics, dendritic cells, Th1
References Fanales-Belasio *et al.* 2002b

- Biologically active HIV-1 Tat is readily taken up by monocyte-derived dendritic cells (MDDC) (and activated endothelial cells), but not other APCs. Tat must be in a native, non-oxidized conformation for efficient uptake. Tat upregulates MHC molecules, IL-12, TNFα, RANTES and MIP-1-α and MIP-1-β production which drives Th1 immune responses and enhances antigen presentation.
- Native Tat enhanced the antigen presentation of MDDC and boosted proliferative recall and allogeneic antigen responses, and the authors propose it could be used as an adjuvant to drive the immune response as well as an antigen.

HXB2 Location Tat
Author Location Tat
Epitope
Immunogen vaccine
Vector/Type: DNA, protein *HIV component:* Tat *Adjuvant:* aluminum hydroxide, Ribi adjuvant (MPL+TDM) (RIBI)
Species (MHC) macaque
Assay type Cytokine production, Delayed-type hypersensitivity (DTH)
Keywords review, early-expressed proteins, Th1
References Fanales-Belasio *et al.* 2002a

- HIV-1 Tat protein has several virtues vaccine component. It is an early expressed protein, and though variable, contains consverved T-cell and B-cell epitopes that allow cross-clade recognition. It is efficiently taken up by monocyte-derived dendritic cells (MDDCs) and in this context can stimulate Th1 immune responses. A Tat based vaccine can elicit an immune response that can control primary infection in monkeys that are in early stage of in infection with SHIV89.6P.

HXB2 Location Tat
Author Location Tat (1–72)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: protein, nanoparticle *Strain:* B clade BRU *HIV component:* Tat *Adjuvant:* aluminum hydroxide, lipid A
Species (MHC) mouse
Donor MHC H-2d
Assay type Cytokine production, proliferation
Keywords Th1, Th2, adjuvant comparison, vaccine antigen design
References Cui *et al.* 2004

- Mice were subcutaneously injected on day 0 and 14 with either Alum and Tat (Th2 control) or Lipid A-adjuvanted Tat (Th1 control), or Tat coated anionic nanoparticles. Analysis of Ab and cytokine release in splenocytes (day 28) showed both IgG and IgM Ab responses; immunization with Tat-coated nanoparticles induced a Th1-biased immune response.
- IFN gamma responses were 3.3-fold stronger with Tat and either Lipid-A or coated nanoparticles than with Tat and Alum.

III-B-14 Rev Helper/CD4+ T-cell epitopes

HXB2 Location Rev (9–23)
Author Location Rev (9–23 HXB2)
Epitope DEELIRTVRLIKLLY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Blazevic *et al.* 1995

- One of four peptides that stimulates in PBLs from HIV-1 + donors both CD4+ Th cell proliferation and CTL to autologous targets incubated with peptide were stimulated.

HXB2 Location Rev (11–27)
Author Location Rev (11–276 clade B consensus)
Epitope ELLKTVRLIKFLYQSNP
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (DRB1*0101, DRB1*0301, DRB1*0401, DRB1*0405, DRB1*0701, DRB1*1101, DRB1*1302, DRB1*1501)
Country Brazil
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 brazilian HIV-1 chronically infected individuals.

T-Helper CD4+

- While the reacting peptide was ELLKTVRLIKFLYQSNP, shorter LLKTVRLIKFLYQ peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

HXB2 Location Rev (14–30)
Author Location Rev (14–30 B Consensus)
Epitope KTVRLIKFLYQSNPPPS
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location Rev (16–35)
Author Location Rev (16–35 LAI)
Epitope VRLIKFLYQSNPPPNPEGTR
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^d)
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Rev (25–39)
Author Location Rev (25–39 HXB2)
Epitope SNPPPNPEGTRQARR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Blazevic *et al.* 1995

- One of four peptides that stimulates in PBLs from HIV-1 + donors both CD4+ Th cell proliferation and CTL to autologous targets incubated with peptide were stimulated.

HXB2 Location Rev (31–50)
Author Location Rev (31–50 LAI)
Epitope PEGTRQARRNRRRRWRERQR
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^d)
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Rev (33–48)
Author Location Rev (33–48 HXB2)
Epitope GTRQARRNRRRRWRER
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Blazevic *et al.* 1995

- One of four peptides that stimulates in PBLs from HIV-1 + donors both CD4+ Th cell proliferation and CTL to autologous targets incubated with peptide were stimulated.

HXB2 Location Rev (41–56)
Author Location Rev (41–56 HXB2)
Epitope RRRRWRERQRQIHSIS
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Blazevic *et al.* 1995

- One of four peptides that stimulates in PBLs from HIV-1 + donors both CD4+ Th cell proliferation and CTL to autologous targets incubated with peptide were stimulated.

HXB2 Location Rev (76–95)
Author Location Rev (76–95 LAI)
Epitope PPLERLTLDCNEDCGTSGTQ
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^b)
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Rev (96–116)
Author Location Rev (96–116 LAI)
Epitope GVGSPQILVESPTVLESGTKE
Subtype B

Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^d)
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Rev
Author Location Rev
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Rev
Species (MHC) mouse
Keywords HAART, ART
References Chan *et al.* 1998

- Rev M10 is a construct that was introduced into mice through a genetic vaccination.
- Rev was used to test for down-regulation of HIV-1 in infected cells as a method for gene therapy – in the course of this study, Rev-specific IL-2 producing Th cells developed in the mice.

HXB2 Location Rev
Author Location Rev
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Nef, Rev, Tat
Species (MHC) human
Keywords HAART, ART
References Calarota *et al.* 1999

- 9/9 HIV-1 + subjects were given one of three DNA vaccinations for nef, rev or tat, and novel proliferative and CTL responses were generated.
- The nef DNA immunization induced the highest and most consistent CTLp activity, IFN-γ production, and IL-6 and IgG responses.
- Highly active antiretroviral treatment (HAART) did not induce new HIV-specific CTL responses but reduced viral load, while DNA vaccination induced new immune responses but did not reduce viral load – thus this is a potentially complementary and promising combination.

HXB2 Location Rev
Author Location Rev
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *HIV component:* Nef, Rev, Tat *Adjuvant:* CpG immunostimulatory sequence (ISS)
Species (MHC) human
Keywords review, Th1
References Calarota & Wahren 2001

- This review discusses the cellular immune response, and comments on CpG induction of Th1 cytokines and enhanced immune responses, and HIV-1 DNA vaccine boosting of CTL and Th proliferative responses in asymptomatic HIV+ individuals.

HXB2 Location Rev
Author Location Rev
Epitope
Immunogen vaccine
Vector/Type: DNA with CMV promotor *Strain:* B clade MN *HIV component:* Env, Rev *Adjuvant:* Bupivacaine
Species (MHC) human
Keywords early-expressed proteins
References MacGregor *et al.* 2002

- A phase I clinical trial of a HIV-1 Env and Rev DNA vaccine with a CMV promoter was conducted and Th proliferative, CTL and Elispot responses monitored. The construct was modified for safety and included no LTRs or packaging signals. The vaccine strategy was safe, and elicited strong CD4-T cell responses, but not CD8 T-cell responses. Rev elicited strong Th responses, and is a early produced protein so may confer advantages.
- With a 300 ug dose, 4/6 individuals had a lymphocyte proliferation (LP) responses to gp120, 3/6 to Rev.
- With a 1000 ug dose, 4/6 individuals had a LP and 2/6 had IFNgamma Elispot responses to gp160; 3/6 had LP, and 4/6 had IFNgamma Elispot responses to Rev.
- No responses to three specific CTL epitopes were observed by Elispot in individuals with appropriate HLA. Some cytotoxic activity against whole protein was observed that was CD4+ T-cell mediated.

III-B-15 Vpu Helper/CD4+ T-cell epitopes

HXB2 Location Vpu (6–20)
Author Location Vpu (6–20 clade B consensus)
Epitope `VLAIVALVVATIIAI`
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human
Country Brazil
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 brazilian HIV-1 chronically infected individuals.

HXB2 Location Vpu (19–34)
Author Location Vpu (19–34)
Epitope `AIVVWSIVLIEYRKIL`
Immunogen HIV-1 infection

T-Helper CD4+

Species (MHC) human
References Ranki *et al.* 1997
- T-cell response to this epitope persisted after seroreversion.

HXB2 Location Vpu (20–41)
Author Location
Epitope AIWWSIVFIEYRKILRQRKIDR
Epitope name HIV-VAX-1056
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005
- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 1/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was VFIEYRKIL.

HXB2 Location Vpu
Author Location Vpu
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Nef, Vif, Vpu
Species (MHC) mouse (H-2^d)
Keywords subtype comparisons, Th1
References Ayyavoo *et al.* 2000
- Splenocytes from BALB/c mice immunized with pVVN-P DNA were incubated with Vif, Vpu or Nef antigens for 3 days and assayed for IL-4 and IFN-γ levels.
- Antigen stimulation increased IFN-γ production in pVVN-P immunized mice, indicating a Th1 response.
- IL-4 production was not significantly changed after antigen stimulation compared to control levels.
- Cross-clade CTL activity was also observed: A, B clade, CRF01(AE) clade antigens could serve as targets for the B clade immunization stimulated CTL – an HIV-1 AC recombinant, however, did not stimulate a CTL response, but was expressed at lower levels on the target cell.

III-B-16 gp160 Helper/CD4+ T-cell epitopes

HXB2 Location gp160 (19–31)
Author Location gp160 (19–31 clade B consensus)
Epitope TMLLGMLMICSAA
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (DRB1*0101, DRB1*0405, DRB1*1101)
Country Brazil
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References Fonseca *et al.* 2006
- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 brazilian HIV-1 chronically infected individuals.
- While the reacting peptide was TMLLGMLMICSAA, shorter MLLGMLMICSA peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

HXB2 Location gp160 (30–51)
Author Location gp120 (30–51 IIIB)
Epitope ATEKLWVTVYYGVPVWKEATTT?
Epitope name A1
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994
- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 2/15 responders recognized this peptide, mean SI = 4.6.

HXB2 Location gp160 (31–45)
Author Location Env (31–45 HXB2)
Epitope TEKLWVTVYYGVPVW
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DP4)
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, epitope processing, computational epitope prediction, dendritic cells
References Cohen *et al.* 2006
- Motif-based quantitative matrices binding predictions, binding assays and cellular assays were used to identify 4 HLA-DP4 epitopes by scanning the whole HIV-1 genome.
- 21 peptides were predicted to bind HLA-DP4, 17 of them did bind in binding assays, 6 of them were good binders. Of the 6 good binders, 4 peptides primed peptide-specific CD4+ T cell lines restricted to HLA-DP4 molecules.

HXB2 Location gp160 (31–48)
Author Location Env
Epitope VGLNWVTVYYGVPVWKEA
Subtype C
Immunogen vaccine

T-Helper CD4+

Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, previously described as VYYGVPVWKEA, and found within peptides VGLNWVTVYYGVPVWKEA and WVTVYYGVPVWKGAT elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (31–50)
Author Location gp120 (30–49 89.6)
Epitope KEKTWVTIYYGVPVWREATT
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 2 out 7 individuals responded to this peptide.

HXB2 Location gp160 (32–44)
Author Location gp120 (39–51)
Epitope EQLWVTVYYGVPV
Immunogen vaccine
Vector/Type: peptide
Species (MHC) mouse (H-2^{bxk})
References Sastry & Arlinghaus 1991

- Peptides induced T-cell proliferative response to immunizing peptide and to gp160.

HXB2 Location gp160 (35–49)
Author Location Env
Epitope WVTVYYGVPVWKGAT
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, previously described as VYYGVPVWKEA, and found within peptides VGLNWVTVYYGVPVWKEA and WVTVYYGVPVWKGAT elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (38–48)
Author Location gp120 (45–55)
Epitope VYYGVPVWKEA
Immunogen vaccine
Vector/Type: peptide
Species (MHC) mouse (H-2^{bxk}, H-2^{sxd})
References Sastry & Arlinghaus 1991

- Peptides induced T-cell proliferative response to immunizing peptide and to gp160.

HXB2 Location gp160 (38–48)
Author Location Env (45–55)
Epitope VYYGVPVWKEA
Immunogen vaccine
Vector/Type: peptide
Species (MHC) macaque
References Nehete *et al.* 1993

- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice.
- Proliferative response to this peptide was observed in 3/3 immunized rhesus monkeys.

HXB2 Location gp160 (38–48)
Author Location Env (45–55)
Epitope VYYGVPVWKEA

Immunogen HIV-1 infection
Species (MHC) human, chimpanzee
References Nehete *et al.* 1998b

- Seven out of nine HIV-infected chimpanzees and eight out of seventeen HIV-positive humans exhibited positive proliferative responses to this conserved peptide (peptide 104) – no HIV negative individuals showed a response.
- This peptide, along with 4 other peptides from conserved regions of envelope, can induce proliferative responses to HIV and may be useful for vaccines.
- Peptide 104 elicited proliferative responses in inbred mouse strains and outbred rhesus monkeys in previous study by same group.

HXB2 Location gp160 (41–54)
Author Location gp120 (48–61)
Epitope GVPVWKEATTLFC
Immunogen vaccine
Vector/Type: peptide
Species (MHC) mouse (H-2^{sxd})
References Sastry & Arlinghaus 1991

- Peptides induced T-cell proliferative response to immunizing peptide and to gp160.

HXB2 Location gp160 (41–54)
Author Location Env (48–60)
Epitope GVPVWKEATTLFC
Immunogen vaccine
Vector/Type: peptide
Species (MHC) macaque
References Nehete *et al.* 1993

- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice.
- Despite the proliferative response to this peptide in mice, no response was observed in 3 rhesus monkeys.

HXB2 Location gp160 (41–60)
Author Location gp120 (40–59 89.6)
Epitope GVPVWREATTTLFCASDAKA
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse (H-2^{d})
Keywords immunodominance
References Dai *et al.* 2001

- Promiscuous immunodominant epitopes in gp120 were mapped by overlapping peptides in CBA/J H-2^{k} and BALB/c H-2^{d} mice, and all were found to be in the outer domain, proximal to regions of structural disorder indicated by the crystal structure or by sequence divergence.
- This peptide was recognized by 10/10 BALB/c with an average SI of 6.4, the strongest reaction among BALB/c mice, but not by CBA/J mice, but recognized well not by CBA/J mice, so is considered to be uniquely immunodominant for H-2^{d}
- Uniquely immunodominant sequences tended to be in the inner domain of the protein.

HXB2 Location gp160 (41–60)
Author Location gp120 (41–60)
Epitope GVPVWKEATTTLFCASDAKA
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) mouse (H-2^{d})
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- GVPVWKEATTTLFCASDAKA is a previously known epitope that is a part of TCI fragment TVYYGVPVWKEATTTLFCASDAKAY in this vaccine construct.

HXB2 Location gp160 (41–60)
Author Location gp120 (40–59 89.6)
Epitope GVPVWREATTTLFCASDAKA
Epitope name Peptide 2
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse
Donor MHC H-2k, H2-d
Keywords epitope processing, immunodominance
References Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was highly reactive in 10/10 BALB/c mice tested, but only in 5/10 CBA/J mice.

HXB2 Location gp160 (41–60)
Author Location gp120 (40–59 89.6)
Epitope GVPVWREATTTLFCASDAKA
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

T-Helper CD4+

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 1 out 7 individuals responded to this peptide.

HXB2 Location gp160 (42–61)
Author Location gp120 (42–61 IIIB)
Epitope VPVWKEATTTLFCASDAKAY?
Epitope name A2
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 2/15 responders recognized this peptide, mean SI = 6.6.

HXB2 Location gp160 (47–61)
Author Location Env
Epitope GATTTLFCASDAKAY
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, not previously described, and found within peptides GATTTLFCASDAKAY and TTLFCASKAKAYDTE elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (50–64)
Author Location Env
Epitope TTLFCASKAKAYDTE
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, not previously described, and found within peptides GATTTLFCASDAKAY and TTLFCASKAKAYDTE elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (51–70)
Author Location gp120 (50–69 89.6)
Epitope TLFCASDAKAYDTEVHNVWA
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.

T-Helper CD4+

- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 1 out 7 individuals responded to this peptide.

HXB2 Location gp160 (52–71)
Author Location gp120 (52–71 IIIB)
Epitope LFCASDAKAYDTEVHNVWAT?
Epitope name A3
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 3/15 responders recognized this peptide, mean SI = 4.3.

HXB2 Location gp160 (61–80)
Author Location gp120 (60–79 89.6)
Epitope YDTEVHNVWATHACVPTDPN
Epitope name Peptide 4
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse
Donor MHC H-2k, H2-d
Keywords epitope processing, immunodominance
References Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was highly reactive in 4/10 BALB/c mice tested, but only in 1/10 CBA/J mice.

HXB2 Location gp160 (61–80)
Author Location gp120 (60–79 89.6)
Epitope YDTEVHNVWATHACVPTDPN
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 1 out 7 individuals responded to this peptide.

HXB2 Location gp160 (62–80)
Author Location gp120 (62–80 IIIB)
Epitope DTEVHNVWATHACVPTDPN?
Epitope name A4
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 3.5.

HXB2 Location gp160 (62–81)
Author Location gp120 (MN)
Epitope DTEVHNVWATQACVPTDPNP
Epitope name DP20
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DR)
Assay type Cytokine production, proliferation, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords HAART, ART, acute/early infection, cross-presentation by different HLA
References Malhotra *et al.* 2003

- 92 acute- or early-HIV infected subjects were tested for Env- and Gag-specific Th responses. There was an overall low probability of detecting HIV-1-specific Th responses, Env responses were rare and (5%) and only detected very early in infection, probably reflecting a low frequency of response and impaired lymophoproliferative capacity, not viral escape.

T-Helper CD4+

Gag-specific Th responses were observed more frequently (16%), were found throughout the acute and early infection phases, and predominated after ARV therapy.
- This epitope is one of six Env-specific Th responses detected in one patient 11 days post-infection that were studied in detail. The CD4+ clones showed MHC-restricted cytotoxicity and secreted high levels of cytokines when stimulated. These Th reponses were not detected at subsequent time points, despite the Env specific Th cells being maintained as detected by TCR clonal transcripts, and the epitope sequence being maintained in Env.
- This peptide showed bound to HLA-DRB1*0101.

HXB2 Location gp160 (65–75)
Author Location gp120 (72–82)
Epitope AHKVWATHACV
Immunogen vaccine
Vector/Type: peptide
Species (MHC) mouse (H-2^{bxk}, H-2^{sxd})
References Sastry & Arlinghaus 1991
- Peptides induced T-cell proliferative response to immunizing peptide and to gp160.

HXB2 Location gp160 (71–85)
Author Location Env
Epitope THACVPADPNPQEMV
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008
- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, previously described as CVPTDPNPQEW, and found within peptide THACVPADPNPQEMV elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (74–85)
Author Location gp120 (81–92)
Epitope CVPTNPVPQEVV
Immunogen vaccine
Vector/Type: peptide
Species (MHC) mouse (H-2^{bxk}, H-2^{sxd})
References Sastry & Arlinghaus 1991
- Peptides induced T-cell proliferative response to immunizing peptide and to gp160.

HXB2 Location gp160 (74–85)
Author Location gp120 (74–85 LAI)
Epitope CVPTDPNPQEVV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989
- Stimulates T-cell proliferation in HIV-infected donors.

HXB2 Location gp160 (80–99)
Author Location gp120 (51–70 HXB2)
Epitope NPQEVVLVNTENFNMWKND
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human
Keywords TCR usage
References Li Pira *et al.* 1998
- Clonal heterogeneity was broad for a recall response to tetanus toxoid or PPD, but oligoclonal to primary HIV antigens, dominated in this case by TCR Vβ 13 usage.
- Donor of PBMC that recognized this epitope had HLA-DR alleles 2 and 7.

HXB2 Location gp160 (81–100)
Author Location gp120 (80–99 89.6)
Epitope PQEVVLGNVTENFNMWKNNM
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse (H-2^{k})
Keywords immunodominance
References Dai *et al.* 2001
- Promiscuous immunodominant epitopes in gp120 were mapped by overlapping peptides in CBA/J H-2^{k} and BALB/c H-2^{d} mice, and all were found to be in the outer domain, proximal to regions of structural disorder indicated by the crystal structure or by sequence divergence.
- This peptide was recognized by 10/10 CBA/J with an average SI of 8.2, and not by BALB/c mice, so is considered to be uniquely immunodominant for H-2^{k}
- Uniquely immunodominant sequences tended to be in the inner domain of the protein.

HXB2 Location gp160 (81–100)
Author Location gp120 (80–99 89.6)
Epitope PQEVVLGNVTENFNMWKNNM
Epitope name Peptide 6
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse
Donor MHC H-2k
Keywords epitope processing, immunodominance
References Dai *et al.* 2001

T-Helper CD4+

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was not reactive in any BALB/c mice tested (0/10), but was highly reactive in all (10/10) CBA/J mice.

HXB2 Location gp160 (81–100)
Author Location gp120 (80–99 89.6)
Epitope PQEVVLGNVTENFNMWKNNM
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 1 out 7 individuals responded to this peptide.

HXB2 Location gp160 (81–101)
Author Location gp120 (81–101 IIIB)
Epitope PQEVVLVNVTENFNMWKNDMV?
Epitope name B1
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 2/15 responders recognized this peptide, mean SI = 5.1.

HXB2 Location gp160 (87–101)
Author Location Env
Epitope ENVTENFNMWKNEMV
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, previously described as PQEWLVNVTENFNMWKNDMV, and found within peptides ENVTENFNMWKNEMV and ENFNMWKNEMVNQMQ elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (91–105)
Author Location Env
Epitope ENFNMWKNEMVNQMQ
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, previously described as PQEWLVNVTENFNMWKNDMV, and found within peptides ENVTENFNMWKNEMV and ENFNMWKNEMVNQMQ elicited immune response.

- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (91–110)
Author Location gp120 (90–109 89.6)
Epitope ENFNMWKNNMVDQMHEDIIS
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 1 out 7 individuals responded to this peptide.

HXB2 Location gp160 (92–101)
Author Location gp120 (90–100 W6.ID)
Epitope YFNMWKNNMV
Immunogen vaccine
Vector/Type: protein *Strain:* B clade W61D *HIV component:* gp120 *Adjuvant:* MPL-SE adjuvant, QS21
Species (MHC) human
References Jones *et al.* 1999

- An HIV seronegative volunteer was vaccinated with rgp120 and a QS21/MPL adjuvant and HIV-1 specific T-cell lines were isolated.
- One T-cell clone reacts with two overlapping peptides, and the region of overlap is: YFNMWKNNMV.
- The first 20-mer peptide that this clone reacts with is PQEVVLGNVTEYFNMWKNNMV, and the IIIB version of this peptide does not induce proliferation in the T-cell line that responds to the W61D version: IIIB: pqevvlVnvteNfDmwknDmv.

HXB2 Location gp160 (92–111)
Author Location gp120 (92–111 W6.ID)
Epitope YFNMWKNNMVDQMHEDIISL
Immunogen vaccine
Vector/Type: protein *Strain:* B clade W61D *HIV component:* gp120 *Adjuvant:* MPL-SE adjuvant, QS21
Species (MHC) human
References Jones *et al.* 1999

- An HIV seronegative volunteer was vaccinated with rgp120 and a QS21/MPL adjuvant and HIV-1 specific T-cell lines were isolated.
- The IIIB version of this peptide does not induce proliferation in the T-cell line that responds to the W61D version of the peptide NfDmwknDmvEqmhediisl.
- Six T-cell lines react with this peptide, but some of these can also be stimulated by other gp120 peptides located in different regions of gp120.

HXB2 Location gp160 (99–113)
Author Location Env
Epitope EMVNQMQEDVISLWD
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, previously not described was found within peptide EMVNQMQEDVISLWD and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (101–120)
Author Location gp120 (100–119 89.6)
Epitope VDQMHEDIISLWDESLKPCV
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.

- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 1 out 7 individuals responded to this peptide.

HXB2 Location gp160 (101–126)
Author Location gp120 (101–126)
Epitope VEQMHEDIISLWDQSLKPCVKLTPLC
Immunogen vaccine
Vector/Type: protein *HIV component:* gp160
Species (MHC) mouse (H-2^{k})
References Sjolander *et al.* 1996
- Study showing that T-cell determinants from glycoproteins can be dependent on the glycosylation of the protein.

HXB2 Location gp160 (102–114)
Author Location gp120 (109–121)
Epitope EQMHEDIISLWDQ
Immunogen vaccine
Vector/Type: peptide
Species (MHC) mouse (H-2^{bxk})
References Sastry & Arlinghaus 1991
- Peptides induced T-cell proliferative response to immunizing peptide and to gp160.

HXB2 Location gp160 (102–116)
Author Location gp160 (109–123 IIIB)
Epitope EQMHEDIISLWDQSL
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^{b}, H-2^{d})
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a
- B10.D2 (H-$2A^{d}$, E^{d}) and B10.A(R5) (H-$2A^{b}$, E^{b}) mice immunized with rec gp160 showed a proliferative response to EQMHEDIISLWDQSL.
- EQMHEDIISLWDQSLKPCVK encompasses several murine Th epitopes including HEDIISLWDQSLK and is referred to as a "multideterminant region" or cluster peptide.

HXB2 Location gp160 (102–116)
Author Location gp120 (109–123 IIIB)
Epitope EQMHEDIISLWDQSL
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^{d}, H-2^{i5})
References Hale *et al.* 1989
- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

HXB2 Location gp160 (102–121)
Author Location gp160 (109–128 IIIB)
Epitope EQMHEDIISLWDQSLKPCVK
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) human, mouse (H-2^{k}, H-2^{s})
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a
- EQMHEDIISLWDQSLKPCVK encompasses several murine Th epitopes and is referred to as a "multideterminant region" or cluster peptide.
- Six multideterminant region cluster peptides were evaluated Th responses in different MHC/HLA backgrounds after vaccination of mice with gp160, or in infected people.
- This cluster peptide elicited proliferative responses in cells from vaccinated B10.BR mice (H-$2A^{k}$, E^{k}) and B10.S(9R) mice (H-$2A^{s}$, E^{s}), while shorter peptides from within this region stimulated H-2^{k}, H-2^{d} and H-2^{b} responses, but not H-2^{s}
- IL-2 production was observed in response to this peptide in 64% (23/36) of asymptomatic HIV-infected individuals.

HXB2 Location gp160 (102–121)
Author Location gp120 (102–121 IIIB)
Epitope EQMHEDIISLWDQSLKPCVK?
Epitope name B3
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994
- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 5.9.

HXB2 Location gp160 (105–117)
Author Location gp120 (112–124 IIIB)
Epitope HEDIISLWDQSLK
Epitope name T2
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^{k})
References Hale *et al.* 1989
- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

HXB2 Location gp160 (105–117)
Author Location gp160 (112–124 IIIB)
Epitope HEDIISLWDQSLK
Immunogen vaccine

T-Helper CD4+

Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^k)
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- B10.BR (H-$2A^k$, E^k) mice immunized with rec gp160 showed a strong proliferative response to three overlapping peptides, QMHEDIISLWDQSL, HEDIISLWDQSLK, and DIISLWDQSLKPCVK, and HEDIISLWDQSLK is common to between them.
- EQMHEDIISLWDQSLKPCVK encompasses several murine Th epitopes including HEDIISLWDQSLK and is referred to as a "multideterminant region" or cluster peptide.

HXB2 Location gp160 (105–117)
Author Location gp120 (112–124 BH10)
Epitope `HEDIISLWDQSLK`
Epitope name T2
Immunogen computer prediction
Species (MHC) mouse (H-2^k, H-2^s)
References Cease *et al.* 1987

- 1 of 2 functional epitopes identified using an amphipathic helix epitope prediction algorithm.

HXB2 Location gp160 (105–117)
Author Location gp120 (112–124 IIIB)
Epitope `HEDIISLWDQSLK`
Epitope name T2
Immunogen HIV-1 infection
Species (MHC) human
References Clerici *et al.* 1997

- Used in a study of pentoxifylline's influence on HIV specific T-cells.

HXB2 Location gp160 (105–117)
Author Location gp120 (112–124 BH10)
Epitope `HEDIISLWDQSLK`
Epitope name T2
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) human
References Berzofsky *et al.* 1988

- Proliferative response to T1 and T2 peptides in 14 immunized, uninfected humans.

HXB2 Location gp160 (105–117)
Author Location gp120 (112–124 IIIB)
Epitope `HEDIISLWDQSLK`
Epitope name T2
Immunogen HIV-1 infection
Species (MHC) human
References Clerici *et al.* 1989

- IL-2 production detection of Th lymphocytes from asymptomatic HIV-positive individuals.

HXB2 Location gp160 (105–117)
Author Location gp120 (112–124 IIIB)
Epitope `HEDIISLWDQSLK`
Epitope name T2
Immunogen HIV-1 infection
Species (MHC) human
References Clerici *et al.* 1991a

- Peptides stimulate Th cell function and CTL activity in similar patient populations.

HXB2 Location gp160 (105–117)
Author Location gp120 (112–124)
Epitope `HEDIISLWDQSLK`
Epitope name T2
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) human
References Clerici *et al.* 1991b

- Immunizing uninfected individuals with rgp160 results in stronger Th response than does natural infection.

HXB2 Location gp160 (105–117)
Author Location gp120 (112–124 IIIB)
Epitope `HEDIISLWDQSLK`
Epitope name T2
Immunogen
Species (MHC) human
References Clerici *et al.* 1992

- Cell-mediated immune response to HIV-1 peptides in HIV-1 exposed seronegative men.

HXB2 Location gp160 (105–117)
Author Location gp120 (112–124 IIIB)
Epitope `HEDIISLWDQSLK`
Epitope name T2
Immunogen vaccine
Vector/Type: peptide prime with protein boost *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) macaque
References Hosmalin *et al.* 1991

- Peptide priming to induce T-cell help enhances antibody response to gp160 immunization.

HXB2 Location gp160 (105–117)
Author Location gp120 (112–124 IIIB)
Epitope `HEDIISLWDQSLK`
Epitope name T2
Immunogen
Species (MHC) human
References Pinto *et al.* 1995

- CTL activity analyzed in parallel with Th reactivity in exposed but uninfected health care workers.

HXB2 Location gp160 (105–117)
Author Location gp120 (112–124 IIIB)
Epitope `HEDIISLWDQSLK`
Epitope name T2
Immunogen HIV-1 infection
Species (MHC) human
References Kaul *et al.* 1999

- Kenyan sex workers that remained seronegative were found to frequently have HIV-env peptide specific Th responses detected by an IL-2 assay (11/20 cases) and mucosal genital tract anti-HIV IgA (16/21 cases)
- Helper epitopes used in this study were noted to be previously described Clerici *et al.* [1989], and were not explicitly described in Kaul *et al.* [1999]

HXB2 Location gp160 (105–117)
Author Location gp120
Epitope HEDIISLWDQSLK
Epitope name T2
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human
Keywords subtype comparisons, responses in children, mother-to-infant transmission
References Kuhn *et al.* 2001a

- In a S. African perinatal transmission study, 33% (33/86) of cord blood samples from infants with seropositive mothers produced T-helper responses (measured by a bioassay measuring IL2 production in a murine cell line and confirmed with a proliferation assay) against a peptide cocktail containing Th epitopes P18 MN, P18 IIIB, T1, T2, and TH4.
- The mothers were predominantly infected with subtype C, but the T help response was detectable in a number of cord blood samples despite using peptides based on B subtype reagents.
- 3/33 infants with cord blood T help responses to Env were infected *in utero*, 2/33 were lost to follow up, and 28/33 were not infected. 6/53 of the infants with cord blood that was unresponsive to Env peptide stimulation were infected before delivery, and 8/47 contracted HIV intrapartum or via breast-feeding.
- Measurable HIV specific T help responses elicited in the immunologically immature newborn, possibly in response to *in utero* exposure, are associated with a protective natural immunity that helps block mother-infant transmission of HIV-1.

HXB2 Location gp160 (105–117)
Author Location Env (112–124 IIIB)
Epitope HEDIISLWDQSLK
Epitope name T2
Subtype B
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC)
Assay type Cytokine production
Keywords mother-to-infant transmission
References Clerici *et al.* 1993a

- Cord blood samples in 8/23 infants with HIV+ mothers showed IL-2 production in response to peptides from HIV-1 gp1260, demonstrating that Th cell priming to HIV env determinants can occur in utero. HIV-specific Th immunity in utero may be protective, as none of the 8 with HIV-1 specific Th activity became infected, while 3/15 infants with no detectable Th activited were infected.
- PBL from 10/21 of the mothers showed HIV-1 specific Th activity through IL-2 production in response to Env peptides.

HXB2 Location gp160 (105–117)
Author Location Env (IIIB)
Epitope HEDIISLWDQSLK
Epitope name T2
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC)
Assay type Cytokine production
References Clerici *et al.* 1994a

- Six of eight HIV-exposed health care workers had transient HIV-specific T-helper responses after percutaneous exposure to HIV, responding to two or more Env peptides among the set T1, T2, Th4.1, P18IIIB and P18MN. Responses were lost after 12-56 weeks. The HIV-specific Th responses occurred without seroconversion or PCR evidence for infection.
- Six of the eight HIV-exposed individuals responded to two or more peptides, whereas, only one individual exposed to HIV-negative blood responded to one peptide.

HXB2 Location gp160 (105–117)
Author Location HIV-1 (IIIB)
Epitope HEDIISLWDQSLK
Epitope name T2
Subtype B
Immunogen HIV-1 infection
Species (MHC)
Assay type Cytokine production
References Clerici *et al.* 1994b

- IL-10-specific mRNA was upregulated in PBMC from asymptomatic, HIV-infected (HIV+) patients, and was particularly high in those with severely compromised Th cells function. Th response to HIV peptides *in vitro* could be restored by IL-10 Ab.

HXB2 Location gp160 (105–117)
Author Location Env (112–124)
Epitope HEDIISLWDQSLK
Epitope name T2
Immunogen HIV-1 infection
Species (MHC) human
Assay type proliferation
Keywords responses in children, mother-to-infant transmission
References Kuhn *et al.* 2001b

- T helper proliferative responses in cord blood at delivery to a cocktail of HIV envelope peptides were infrequent (1/41) among infants whose HIV-positive mothers received antiretroviral prophylaxis at delivery to prevent transmission. Responses were 10 times more frequent among infants of HIV-seropositive women who had no antiretroviral treatment (7/29). Reductions of HIV-specific responses occurred despite persistance of detectable HIV RNA in the mothers at delivery.
- The reduction of Th responses in newborns raises the possibility that anti-retrovial exposure during pregnancy may block subsequent immune protection. The authors point two relevant citations that showed ARV exposed infants had a more rapid course of progression (Kuhn *et al.*, JID 182:104 (2000)), but were at no greater risk of infection due to subsequent breast feeding (Ditrame *et al.*, Lancet 354:2050 (1999)).

HXB2 Location gp160 (105–117)
Author Location Env (gp160) (105–117)
Epitope HEDIISLWDQSLK

T-Helper CD4+

Epitope name TH2
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type proliferation
Keywords responses in children, variant cross-recognition or cross-neutralization
References Meddows-Taylor *et al.* 2004

- Viral isolates (gp160) from 16 vertically HIV-1 infected children (8 T-helper cell Env responders and 8 non-responders) were analyzed for variation after comparison with Env peptide sequences (conserved regions T1, T2 and TH4.1, hypervariable regions P18 MN and P181 IIIB) used for in vitro stimulation.
- T2 was the most conserved of the 5 peptides studied.
- No correlation between the age, clinical category (mild or severe), HIV-1 viral load and the degree of epitope variation was established.

HXB2 Location gp160 (105–123)
Author Location gp120 (112–130 IIIB)
Epitope HEDIISLWDQSLKPCVKLT
Immunogen
Species (MHC) human
References Furci *et al.* 1997

- 9/11 exposed-uninfected individuals in this study had a proliferative response to a C5 peptide, but none reacted with this previously defined epitope.

HXB2 Location gp160 (108–119)
Author Location gp120 (108–119 LAI)
Epitope IISLWDQSLKPC
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

HXB2 Location gp160 (108–119)
Author Location
Epitope IISLWDQSLKPC
Immunogen
Species (MHC)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 45/51 Brazilian sequences.

HXB2 Location gp160 (110–125)
Author Location gp120 (110–125)
Epitope SLWDQSLKPCVKLTPL
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Caruso *et al.* 1997

- As HIV-1-infected individuals progress to disease, T-cells show reduced ability to proliferate in response to HIV antigen, but retain the ability to express the activation antigens CD25 and CD71.
- The ability to express activation markers in response to HIV is retained, but the response to tetanus toxoid recall antigen is lost.
- This study investigated CD25 and CD71 expression in PBMC from patients at various stages of progression, measuring the response to *in vitro* stimulation by peptide cocktail containing four antigenic Env peptides, or p17 and p24.

HXB2 Location gp160 (110–125)
Author Location
Epitope SLWDQSLKPCVKLTPL
Immunogen
Species (MHC)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 47/51 Brazilian sequences.

HXB2 Location gp160 (111–123)
Author Location gp120 (118–130)
Epitope LWDQSLKPCVKLT
Immunogen vaccine
Vector/Type: peptide
Species (MHC) macaque
References Nehete *et al.* 1993

- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice.
- Proliferative response to this peptide was observed in 3/3 immunized rhesus monkeys.

HXB2 Location gp160 (111–130)
Author Location gp120 (110–129 89.6)
Epitope LWDESLKPCVKLTPLCVTLN
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five

residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 1 out 7 individuals responded to this peptide.

HXB2 Location gp160 (112–130)
Author Location gp120 (112–130 IIIB)
Epitope WDQSLKPCVKLTPLCVSLK?
Epitope name B4
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994
- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 3/15 responders recognized this peptide, average SI = 4.4.

HXB2 Location gp160 (112–141)
Author Location gp120 (112–141 NL43)
Epitope WDQSLKPCVKLTPLCVSLKCTDLGNATNTN
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43 *HIV component:* gp120, gp160
Species (MHC) human
References Sitz *et al.* 1999
- There was a great breadth of proliferative response to env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients.
- Over 35% of vaccinees had a stimulation index of greater than 5 to this peptide.

HXB2 Location gp160 (115–126)
Author Location gp120 (115–126 LAI)
Epitope SLKPCVKLTPLC
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989
- Stimulates T-cell proliferation in HIV-infected donors.

HXB2 Location gp160 (115–129)
Author Location gp120 (115–129 LAI)
Epitope SLKPCVKLTPLCVSL
Subtype B
Immunogen peptide-HLA interaction
Species (MHC) human (DR)
Keywords binding affinity
References Gaudebout *et al.* 1997
- Peptide bound to both HLA-DR*1101 and HLA-DR*0401 with high affinity.
- Because of the distinctive binding pockets of HLA-DR*1101 and HLA-DR*0401, peptides that bound both were considered candidates for promiscuous HLA-DR binding.

HXB2 Location gp160 (119–133)
Author Location Env
Epitope CVKLTPLCVTLECRN
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008
- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, previously not described was found within peptide CVKLTPLCVTLECRN and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (121–140)
Author Location gp120 (120–139 89.6)
Epitope KLTPLCVTLNCTNLNITKNT
Epitope name Peptide 10
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse
Donor MHC H-2d
Keywords epitope processing, immunodominance
References Dai *et al.* 2001
- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was highly reactive in 5/10 BALB/c mice tested, but not in and (0/10) CBA/J mice.

HXB2 Location gp160 (121–141)

Author Location gp120 (131–151 IIIB)
Epitope KLTPLCVSLKCTDLKNDTNTN?
Epitope name C1
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 3/15 responders recognized this peptide, average SI = 3.9.

HXB2 Location gp160 (122–141)
Author Location gp120 (121–140 MN)
Epitope LTPLCVTLNCTDLRNTTNTN
Epitope name 1931
Subtype B
Immunogen vaccine
Vector/Type: DNA, protein *Strain:* B clade MN *HIV component:* gp120 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) guinea pig
Keywords vaccine-specific epitope characteristics, Th1
References Chattergoon *et al.* 2002

- Hartley guinea pigs were intradermally injected with either recombinant protein or plasmid expressed gp120 and monitored for delayed type hypersensivity (DTH) responses after vaccination, which are related to Th1 T-cell responses. CFA did not augment responses in animals vaccinated with plasmid.
- A total of 7 gp120 peptides elicited a delayed type hypersensivity (DTH) response after vaccination, out of a set of 60 overlapping peptides that spanned gp120. The vaccine delivery system, DNA versus rec protein, resulted in the recognition of distinct peptides.
- 3/5 animals vaccinated with rec gp120 responded by DTH to this peptide, while 0/6 vaccinated with plasmid gp120 DNA responded.

HXB2 Location gp160 (122–141)
Author Location gp120 (122–141 IIIB)
Epitope LTPLCVSLKCTDLKNDTNTN?
Epitope name B5
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- 1/15 responders recognized this peptide, SI = 3.1.

HXB2 Location gp160 (136–155)
Author Location gp120 (141–160 MN)
Epitope NSTAWNNSNSEGTIKGGEMK
Epitope name 1932
Subtype B
Immunogen vaccine
Vector/Type: DNA, protein *Strain:* B clade MN *HIV component:* gp120 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) guinea pig
Keywords vaccine-specific epitope characteristics, Th1
References Chattergoon *et al.* 2002

- Hartley guinea pigs were intradermally injected with either recombinant protein or plasmid expressed gp120 and monitored for delayed type hypersensivity (DTH) responses after vaccination, which are related to Th1 T-cell responses. CFA did not augment responses in animals vaccinated with plasmid.
- A total of 7 gp120 peptides elicited a delayed type hypersensivity (DTH) response after vaccination, out of a set of 60 overlapping peptides that spanned gp120. The vaccine delivery system, DNA versus rec protein, resulted in the recognition of distinct peptides.
- 4/5 animals vaccinated with rec gp120 responded by DTH to this peptide, as did 2/6 vaccinated with plasmid gp120 DNA.

HXB2 Location gp160 (138–158)
Author Location gp120 (140–159 89.6)
Epitope TNPTSSSWGMMEKGEIKNCS
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 1 out 7 individuals responded to this peptide.

HXB2 Location gp160 (138–159)
Author Location gp120 (141–160 W6.ID)
Epitope TTSNGWTGEIRKGEIKNCSF

T-Helper CD4+

Immunogen vaccine
Vector/Type: protein *Strain:* B clade W61D *HIV component:* gp120 *Adjuvant:* MPL-SE adjuvant, QS21
Species (MHC) human
References Jones *et al.* 1999

- An HIV seronegative volunteer was vaccinated with rgp120 and a QS21/MPL adjuvant and HIV-1 specific T-cell lines were isolated.
- The IIIB version of this peptide does not induce proliferation in the T-cell line that responds to the W61D version of the peptide: IIIB: ttsnSSGRMIMEgeikncsf.

HXB2 Location gp160 (142–161)
Author Location gp120 (142–161 IIIB)
Epitope SSSGRMIMEKGEIKNCSFNI?
Epitope name C2
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords immunodominance
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- Five peptides were recognized most frequently: C2 (aa 142-161), C3 (aa 152-171), C5 (aa 172-191), E5 (aa 272-291) and G4 (aa 380-393). The first three were in or near V2, the other two were proximal to the V3 and V4 loops.
- 4/15 responders recognized this immunodominant peptide, average SI = 4.3.

HXB2 Location gp160 (147–168)
Author Location gp120 (152–173 NL43)
Epitope MMMEKGEIKNCSFNISTSIRGK
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43 *HIV component:* gp120, gp160
Species (MHC) human
References Sitz *et al.* 1999

- There was a great breadth of proliferative response to env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients.
- Over 50% of vaccinees had a stimulation index of greater than 5 to this peptide.

HXB2 Location gp160 (149–168)
Author Location gp120 (150–169 89.6)
Epitope MEKGEIKNCSFYITTSIRNK
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 1 out 7 individuals responded to this peptide.

HXB2 Location gp160 (152–171)
Author Location gp120 (152–171 IIIB)
Epitope GEIKNCSFNISTSIRGKVQK?
Epitope name C3
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords immunodominance
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- Five peptides were recognized most frequently: C2 (aa 142-161), C3 (aa 152-171), C5 (aa 172-191), E5 (aa 272-291) and G4 (aa 380-393). The first three were in or near V2, the other two were proximal to the V3 and V4 loops.
- 4/15 responders recognized this immunodominant peptide, average SI = 4.4.

HXB2 Location gp160 (155–169)
Author Location gp120 (160–174 LAI)
Epitope KNCSFNISTSIRGKV
Subtype B
Immunogen
Species (MHC) human (DR)
Keywords binding affinity
References Gaudebout *et al.* 1997

- Peptide binds to both HLA-DR*1101 and HLA-DR*0401 with high affinity.
- Because of the distinctive binding pockets of HLA-DR*1101 and HLA-DR*0401, peptides that bound both were considered candidates for promiscuous HLA-DR binding.

T-Helper CD4+

HXB2 Location gp160 (155–169)
Author Location Env (UG92005)
Epitope KNCSFNITTELIDKK
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^{b})
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This epitope is located in the V2 region of UG92005 (UG, clade D) and the hybridoma that recognized it used Vβ5.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^{b} transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^{b} restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (156–170)
Author Location Env
Epitope NCSFNATTVVRDRDQ
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, previously not described was found within peptides NCSFNATTVVRDRDQ and NATTVVRDRKQTVYA and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (159–178)
Author Location gp120 (160–179 89.6)
Epitope FYITTSIRNKVKKEYALFNR
Epitope name Peptide 14
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse
Donor MHC H-2k, H2-d
Keywords epitope processing, immunodominance
References Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was highly reactive in 6/10 BALB/c mice tested, and in 4/10 CBA/J mice.

HXB2 Location gp160 (160–174)
Author Location Env
Epitope NATTVVRDRKQTVYA
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.

- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, previously not described was found within peptides NCSFNATTVVRDRDQ and NATTVVRDRKQTVYA and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (162–181)
Author Location gp120 (162–181 IIIB)
Epitope `STSIRGKVQKEYAFFYKLDI`
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* Env
Species (MHC) macaque
References Lekutis *et al.* 1997
- HIV-1 env DNA vaccine induced Th cell response to this epitope in a rhesus monkeys.

HXB2 Location gp160 (162–182)
Author Location gp120 (162–182 IIIB)
Epitope `STSIRGKVQKEYAFFYKLDII?`
Epitope name C4
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994
- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 3.3.

HXB2 Location gp160 (166–185)
Author Location gp120 (MN)
Epitope `RDKMQKEYALLYKLDIVSID`
Epitope name RD20
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type Cytokine production, proliferation, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords HAART, ART, acute/early infection
References Malhotra *et al.* 2003
- 92 acute- or early-HIV infected subjects were tested for Env- and Gag-specific Th responses. There was an overall low probability of detecting HIV-1-specific Th responses, Env responses were rare and (5%) and only detected very early in infection, probably reflecting a low frequency of response and impaired lymophoproliferative capacity, not viral escape. Gag-specific Th responses were observed more frequently (16%), were found throughout the acute and early infection phases, and predominated after ARV therapy.
- This epitope is one of six Env-specific Th responses detected in one patient 11 days post-infection that were studied in detail.These Th reponses were not detected at subsequent time points, despite the Env specific Th cells being maintained as detected by TCR clonal transcripts, and the epitope sequence being maintained in Env.

HXB2 Location gp160 (169–188)
Author Location gp120 (170–189 89.6)
Epitope `VKKEYALFNRLDVVPIENTN`
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008
- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 2 out 7 individuals responded to this peptide.

HXB2 Location gp160 (169–189)
Author Location gp120 (141–160 W6.ID)
Epitope `VQKEYALFYNLDVVPIDDDNA`
Immunogen vaccine
Vector/Type: protein *Strain:* B clade W61D *HIV component:* gp120 *Adjuvant:* MPL-SE adjuvant, QS21
Species (MHC) human
References Jones *et al.* 1999
- An HIV seronegative volunteer was vaccinated with rgp120 and a QS21/MPL adjuvant and HIV-1 specific T-cell lines were isolated.
- The IIIB version of this peptide does not induce proliferation in the T-cell line that responds to the W61D version of the peptide ——F–K–II—N-TT vqkeyaFfyKldIIpidNdTT.
- Two T-cell lines react specifically with this peptide.

HXB2 Location gp160 (172–186)
Author Location Env
Epitope `VYALFYRLDIVPLTK`
Subtype C
Immunogen vaccine

T-Helper CD4+

Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol

Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, previously not described was found within peptides VYALFYRLDIVPLTK and FYRLDIVPLTKNYS and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (172–191)
Author Location gp120 (172–191 IIIB)
Epitope EYAFFYKLDIIPIDNDTTSY
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* Env
Species (MHC) macaque
References Lekutis *et al.* 1997

- HIV-1 env DNA vaccine induced Th cell response to this epitope in a rhesus monkey.

HXB2 Location gp160 (172–191)
Author Location gp120 (172–191 IIIB)
Epitope EYAFFYKLDIIPIDNDTTSY?
Epitope name C5
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords immunodominance
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 nonresponders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- Five peptides were recognized most frequently: C2 (aa 142-161), C3 (aa 152-171), C5 (aa 172-191), E5 (aa 272-291) and G4 (aa 380-393). The first three were in or near V2, the other two were proximal to the V3 and V4 loops.
- 4/15 responders recognized this immunodominant peptide, average SI = 7.4.

HXB2 Location gp160 (174–185)
Author Location gp160 (174–185 clade B consensus)
Epitope ALFYKLDVVPID
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (DRB1*0101, DRB1*0401, DRB1*0405, DRB1*0701, DRB1*1101, DRB1*1302)
Country Brazil
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 brazilian HIV-1 chronically infected individuals.
- While the reacting peptides was ALFYKLDVVPID, shorter FYKLDVVPID peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

HXB2 Location gp160 (175–189)
Author Location Env (UG92005)
Epitope LFYKLDVVQIDNSTN
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This epitope is located in the V2 region of UG92005 (UG, clade D) and the Vβ usage of the TCR was not determined.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.

T-Helper CD4+

- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (176–189)
Author Location Env
Epitope `FYRLDIVPLTKNYS`
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, previously not described was found within peptides VYALFYRLDIVPLTK and FYRLDIVPLTKNYS and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (186–208)
Author Location Env
Epitope `NDNTSYRLISCNTSVITQACPKV`
Epitope name HIV_env_DRB0101_3
Subtype M
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type T-cell Elispot
Keywords computational epitope prediction
References De Groot *et al.* 2004

- Bioinformatic tools (EpiMatrix and Conservatrix) were employed to predict 9 highly conserved and promiscuous class II restricted T helper epitopes from HIV-1 env sequences for a cross-clade polyepitope vaccine. 10/34 HIV-1 infected patients induced Th1 immune responses to 8/9 study peptides.
- 5/34 subjects tested responded to this peptide.
- Class II peptides containing putative epitopes were selected to favor DRB0101 presentation, as there is a transgenic mouse model for this allele for future vaccine studies. The highest scoring DRB0101 sequence of this peptide was YRLISCNTS.

HXB2 Location gp160 (186–215)
Author Location gp120 (191–220 NL43)
Epitope `NDTTSYTLTSCNTSVITQACPKVSFEPIPI`
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43 *HIV component:* gp120, gp160
Species (MHC) human
References Sitz *et al.* 1999

- There was a great breadth of proliferative response to env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients.
- Over 30% of vaccinees had a stimulation index of greater than 5 to this peptide.

HXB2 Location gp160 (188–201)
Author Location gp160 (188–201 clade B consensus)
Epitope `NTSYRLISCNTSVI`
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (DRB1*0101, DRB1*0401, DRB1*0405, DRB1*0701, DRB1*1101, DRB1*1302, DRB1*1501, DRB5*0101)
Country Brazil
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 brazilian HIV-1 chronically infected individuals.
- While the reacting peptide was NTSYRLISCNTSVI, shorter YRLISCNTSVI peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

HXB2 Location gp160 (188–207)
Author Location gp120 (190–209 89.6)
Epitope `NTKYRLISCNTSVITQACPK`
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse (H-2^k)
Keywords immunodominance

T-Helper CD4+

References Dai *et al.* 2001

- Promiscuous immunodominant epitopes in gp120 were mapped by overlapping peptides in CBA/J H-2^k and BALB/c H-2^d mice, and all were found to be in the outer domain, proximal to regions of structural disorder indicated by the crystal structure or by sequence divergence.
- This peptide was recognized by 9/10 CBA/J with an average SI of 9.8, one of the two immunodominant peptides in CBA/J mice, and not by BALB/c mice, so is considered to be uniquely immunodominant for H-2^k
- Uniquely immunodominant sequences tended to be in the inner domain of the protein.

HXB2 Location gp160 (188–207)
Author Location gp120 (89.6)
Epitope `NTKYRLISCNTSVITQACPK`
Epitope name Peptide 17
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse
Donor MHC H-2k, H2-d
Keywords epitope processing, immunodominance
References Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was reactive in only 1/10 BALB/c mice tested, but was one of the most reactive in CBA/J mice, reacting with 9/10 mice.

HXB2 Location gp160 (188–207)
Author Location gp120 (190–209 89.6)
Epitope `NTKYRLISCNTSVITQACPK`
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 1 out 7 individuals responded to this peptide.

HXB2 Location gp160 (190–212)
Author Location Env (185–215)
Epitope `SYRLISCNTSVITQACPKVSFEP`
Epitope name HIV_env_DRB0101_62
Subtype M
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type T-cell Elispot
Keywords computational epitope prediction
References De Groot *et al.* 2004

- Bioinformatic tools (EpiMatrix and Conservatrix) were employed to predict 9 highly conserved and promiscuous class II restricted T helper epitopes from HIV-1 env sequences for a cross-clade polyepitope vaccine. 10/34 HIV-1 infected patients induced Th1 immune responses to 8/9 study peptides.
- 1/34 subjects tested responded to this peptide.
- Class II peptides containing putative epitopes were selected to favor DRB0101 presentation, as there is a transgenic mouse model for this allele for future vaccine studies.The highest scoring DR B0101 sequence of this peptide was NTSVITQA.

HXB2 Location gp160 (192–211)
Author Location gp120 (192–211 IIIB)
Epitope `KLTSCNTSVITQACPKVSFE?`
Epitope name D2
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 3.6.

HXB2 Location gp160 (193–218)
Author Location gp120 (193–218)
Epitope `LTSCNSVITQACPKVSFEPIPIHYC`
Immunogen vaccine
Vector/Type: protein *HIV component:* gp160
Species (MHC) mouse (H-2^b, H-2^d)
References Sjolander *et al.* 1996

- Study showing that T-cell determinants from glycoproteins can be dependent on the glycosylation of the protein.

HXB2 Location gp160 (194–208)
Author Location Env
Epitope `INCNTSAITQACPKV`

T-Helper CD4+

Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, INCNTSAITQACPKV was previously described as peptide KLTSCNTSVITQACPKVSFE and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (198–212)
Author Location Env (1007)
Epitope `TSVITQACPKVSFEP`
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This epitope is located in the C2 region of 1007 (US, clade B) and the Vβ usage of the TCRs for two clonotypes was Vβ3 and Vβ8.1-2.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (198–215)
Author Location Env (1007)
Epitope `TSVITQACPKVSFEPIPI`
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This epitope is located in the C2 region of 1007 (US, clade B) and the Vβ usage of the TCR was Vβ6.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (198–217)

Author Location gp120 (200–219 89.6)
Epitope TSVITQACPKVSFQPIPIHY
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 2 out 7 individuals responded to this peptide.

HXB2 Location gp160 (199–211)
Author Location gp120 (204–216)
Epitope SVITQACSKVSFE
Immunogen vaccine
Vector/Type: peptide
Species (MHC) mouse (H-2^{bxk}, H-2^{sxd})
References Sastry & Arlinghaus 1991

- Peptides induced T-cell proliferative response in mice representing four haplotypes.

HXB2 Location gp160 (199–211)
Author Location Env (204–216)
Epitope SVITQACSKVSFE
Immunogen vaccine
Vector/Type: peptide
Species (MHC) macaque
References Nehete *et al.* 1993

- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice.
- A weak or transient proliferative response to this peptide was observed in 3/3 immunized rhesus monkeys.

HXB2 Location gp160 (199–211)
Author Location Env (204–216)
Epitope SVITQACSKVSFE
Immunogen HIV-1 infection
Species (MHC) human, chimpanzee
References Nehete *et al.* 1998b

- HIV-infected chimpanzees and HIV-positive patients show positive proliferative responses to multiple peptides from five conserved regions of the HIV-1 Env.

HXB2 Location gp160 (200–214)
Author Location gp120 (205–219 LAI)
Epitope VITQACPKVSFEPIP
Subtype B
Immunogen peptide-HLA interaction
Species (MHC) human (DR)
Keywords binding affinity
References Gaudebout *et al.* 1997

- Peptide binds to both HLA-DR*1101 and HLA-DR*0401 with high affinity.
- Because of the distinctive binding pockets of HLA-DR*1101 and HLA-DR*0401, peptides that bound both were considered candidates for promiscuous HLA-DR binding.

HXB2 Location gp160 (201–212)
Author Location Env (1007)
Epitope ITQACPKVSFEP
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This epitope is located in the C2 region of 1007 (US, clade B) and the Vβ usage of the TCR was Vβ3.
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (TSVITQACPKVSFEP and ITQACPKVSFEPIPI)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (201–215)

Author Location
Epitope ITQACPKVSFEPIPI
Subtype B, D
Immunogen vaccine
Vector/Type: DNA prime with protein boost *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140
Species (MHC) mouse
Assay type Cytokine production
Keywords epitope processing
References Sealy *et al.* 2008

- Murine hybridomas with known Env peptide specificities were tested for IL-2 production following stimulation with autologous splenocytes exposed to HIV-1-infected CXCR4 GHOST cells. Hybridomas were originally derived from C57BL/6 mice immunized with a prime-boost regimen. Antigen-processing potentials in the mouse system were studied.
- The presence of a target sequence within HIV-1 did not ensure T-cell reactivity. Subtype of immunogen used to elicit T-cell reactivity also did not predict T-cell responsiveness.
- ITQACPKVSFEPIPI was the target sequence for hybridoma 1007P1-22.1 and the sequence was identical to HIV-1 pNL43 sequence infecting GHOST cells. The hybridoma was responsive to ITQACPKVSFEPIPI.
- ITQACPKVSFEPIPI was located in the vicinity of two antiparallel beta sheets. Further mapping of hybridoma target epitopes showed that hybridoma 1007P1-22.1 responded to peptides containing the QACPKVSFEP or QACPKITFEP sequence.

HXB2 Location gp160 (206–220)
Author Location Env (1007)
Epitope PKVSFEPIPIHYCAP
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing
References Surman *et al.* 2001

- This epitope is located in the C2 region of 1007 (US, clade B) and 12 hybridomas recognized the peptide with Vβ usage of Vβ4,6,7,8.1-2,8.3,11,12 and others not determined.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (206–220)
Author Location Env (gp160)
Epitope PKVSFEPIPIHYCAP
Subtype B, D
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* Env *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^b)
Assay type Cytokine production, CD4 T-cell Elispot - IFNγ
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization, vaccine antigen design
References Zhan *et al.* 2004

- To develop a polyvalent Env vaccine, subtype specific B and D T-helper epitopes were identified, and mixtures of strain 1007, clade B, or UG92005, clade D envelopes were given to C57BL/6J mice. Mice were intramuscularly immunized with recombinant DNA, then intraperitoneally with rVV and finally with env protein in CFA. A dilution of 1/100 could still elicit type specific responses, and responses persisted with different prime boost combinations.
- Priming with 1007 and UG92005 env's induced both Env-specific (SNNTVGNPIILPCRI and AMYAPPIAGLIQCSS) and cross-reactive (PKVSFEPIPIHYCAP, C2, GNIRQAHCNVSKAKW, V3-C3) Th responses in murine spleen cells.

HXB2 Location gp160 (206–220)
Author Location Env
Epitope PKVTFDPIPIHYCTP
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design

T-Helper CD4+

References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, PKVSFEPIPIHYCAPAG-FAILKCNN was found within peptides PKVTFDPIPIHYCTP and FDPIPIHYCTPAGYA and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (206–225)
Author Location gp120 (211–230 MN)
Epitope `PKISFEPIPIHYCAPAGFAI`
Epitope name 1957
Subtype B
Immunogen vaccine
Vector/Type: DNA, protein *Strain:* B clade MN *HIV component:* gp120 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) guinea pig
Keywords vaccine-specific epitope characteristics, Th1
References Chattergoon *et al.* 2002

- Hartley guinea pigs were intradermally injected with either recombinant protein or plasmid expressed gp120 and monitored for delayed type hypersensivity (DTH) responses after vaccination, which are related to Th1 T-cell responses. CFA did not augment responses in animals vaccinated with plasmid.
- A total of 7 gp120 peptides elicited a delayed type hypersensivity (DTH) response after vaccination, out of a set of 60 overlapping peptides that spanned gp120. The vaccine delivery system, DNA versus rec protein, resulted in the recognition of distinct peptides.
- 5/5 animals vaccinated with rec gp120 responded by DTH to this peptide, as did 2/6 vaccinated with plasmid gp120 DNA.

HXB2 Location gp160 (206–230)
Author Location gp120 (206–230)
Epitope `PKVSFEPIPIHYCAPAGFAILKCNN`
Immunogen vaccine
Vector/Type: protein *HIV component:* gp160
Species (MHC) mouse (H-2^b, H-2^d)
References Sjolander *et al.* 1996

- Study showing that T-cell determinants from glycoproteins can be dependent on the glycosylation of the protein.

HXB2 Location gp160 (208–218)
Author Location Env (UG92005)
Epitope `ITFEPIPIHYC`
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing
References Surman *et al.* 2001

- This epitope is located in the C2 region of UG92005 (UG, clade D) and its was recognized by two hybridomas with Vβ usage Vβ12 and not determined.
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (PKITFEPIPIHYCAP and ITFEPIPIHYCAPAG)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (208–222)
Author Location Env (UG92005)
Epitope `ITFEPIPIHYCAPAG`
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This epitope is located in the C2 region of UG92005 (UG, clade D) and it was recognized by five hybridomas with Vβ usage Vβ5, 8.2, 12 and not determined.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.

- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (208–222)
Author Location
Epitope `ITFEPIPIHYCAPAG`
Subtype B, D
Immunogen vaccine
Vector/Type: DNA prime with protein boost *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140
Species (MHC) mouse
Assay type Cytokine production
Keywords epitope processing
References Sealy *et al.* 2008

- Murine hybridomas with known Env peptide specificities were tested for IL-2 production following stimulation with autologous splenocytes exposed to HIV-1-infected CXCR4 GHOST cells. Hybridomas were originally derived from C57BL/6 mice immunized with a prime-boost regimen. Antigen-processing potentials in the mouse system were studied.
- The presence of a target sequence within HIV-1 did not ensure T-cell reactivity. Subtype of immunogen used to elicit T-cell reactivity also did not predict T-cell responsiveness.
- ITFEPIPIHYCAPAG was the target sequence for hybridoma UGP1-81 and differed in 2 residues from HIV-1 pNL43 sequence infecting GHOST cells (vsFEPIPHYGAPAG was the peptide in HIV-1 pNL43 sequence). Nevertheless, the hybridoma was responsive to ITFEPIPIHYCAPAG.
- ITFEPIPIHYCAPAG was located in the vicinity of two antiparallel beta sheets. Further mapping of hybridoma target epitopes showed that hybridoma UGP1-81 responded to peptides containing the VSFEPIPIHYCAP or ITFEPIPIHYCAP sequence.

HXB2 Location gp160 (208–227)
Author Location gp120 (210–229 89.6)
Epitope `VSFQPIPIHYCVPAGFAMLK`
Epitope name Peptide 19
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse
Donor MHC H-2k, H2-d
Keywords epitope processing, immunodominance
References Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was reactive in 6/10 BALB/c mice tested, and in 6/10 CBA/J mice.

HXB2 Location gp160 (208–227)
Author Location gp120 (210–229 89.6)
Epitope `VSFQPIPIHYCVPAGFAMLK`
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 2 out 7 individuals responded to this epitope.

HXB2 Location gp160 (209–220)
Author Location gp120 (MN)
Epitope `SFEPIPIHYCAP`
Epitope name SP12
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DR)
Assay type Cytokine production, proliferation, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords HAART, ART, vaccine-specific epitope characteristics, acute/early infection, cross-presentation by different HLA

T-Helper CD4+

References Malhotra *et al.* 2003

- 92 acute- or early-HIV infected subjects were tested for Env- and Gag-specific Th responses. There was an overall low probability of detecting HIV-1-specific Th responses, Env responses were rare and (5%) and only detected very early in infection, probably reflecting a low frequency of response and impaired lymophoproliferative capacity, not viral escape. Gag-specific Th responses were observed more frequently (16%), were found throughout the acute and early infection phases, and predominated after ARV therapy.
- This epitope is one of six Env-specific Th responses detected in one patient 11 days post-infection that were studied in detail. The CD4+ clones showed MHC-restricted cytotoxicity and secreted high levels of cytokines when stimulated. These Th reponses were not detected at subsequent time points, despite the Env specific Th cells being maintained as detected by TCR clonal transcripts, and the epitope sequence being maintained in Env.
- Seven out of 12 clones recognized this conserved C3 region of gp120. Clone one was mapped to the optimal epitope and was found to be presented by HLA-DR. The peptide showed promiscuous binding to DRB1*0101, DRB1*0401, DRB1*1302, DRB1*0701, DRB1*0901, DRB4*0101, DRB5*0101.

HXB2 Location gp160 (210–218)
Author Location Env (186–194 1035)
Epitope FEPIPIHYC
Subtype B
Immunogen vaccine
Vector/Type: vaccinia prime with gp120 boost *Strain:* B clade 1035 *HIV component:* Env *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse
Assay type proliferation, T-cell Elispot
Keywords epitope processing, vaccine-induced epitopes, escape, TCR usage, optimal epitope
References Zhan *et al.* 2003

- A very narrow Th response was stimulated in C57BL/6 mice vaccinated with vaccinia expressed HIV-1 env clone 1035. Five of seven different Th hybridomas isolated from five immunized mice immunized reacted with the peptide PKVSFEPIPIHYCAP, located in the C2 region of gp120. TCR Vβ usage indicated each of the clones was unique. Splenic populations from other C57BL/6 mice immunized with 1035 env confirmed that the gp120 specific T-helper response was focused on the PKVSFEPIPIHYCAP peptide. The authors suggest the protein structural context may contribute to the immunodominance of this peptide.
- The minimal epitope was mapped for one of the hybridomas, and was FEPIPIHYC.
- The natural variant, fDpipihyc, did not stimulate a response in three of the hybridomas.

HXB2 Location gp160 (210–223)
Author Location gp120 (215–228)
Epitope FEPIPIHYCAFPGF
Immunogen vaccine
Vector/Type: peptide
Species (MHC) mouse (H-2^{bxk})
References Sastry & Arlinghaus 1991

- Peptides induced T-cell proliferative response to immunizing peptide and to gp160.

HXB2 Location gp160 (210–224)
Author Location Env
Epitope FDPIPIHYCTPAGYA
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, PKVSFEPIPIHYCAPAGFAILKCNN was found within peptides PKVTFDPIPIHYCTP and FDPIPIHYCTPAGYA and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (211–225)
Author Location
Epitope EPIPIHYCAPAGFAI
Subtype B, D
Immunogen vaccine
Vector/Type: DNA prime with protein boost *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140
Species (MHC) mouse
Assay type Cytokine production
Keywords epitope processing
References Sealy *et al.* 2008

- Murine hybridomas with known Env peptide specificities were tested for IL-2 production following stimulation with autologous splenocytes exposed to HIV-1-infected CXCR4 GHOST cells. Hybridomas were originally derived from C57BL/6 mice immunized with a prime-boost regimen. Antigen-processing potentials in the mouse system were studied.
- The presence of a target sequence within HIV-1 did not ensure T-cell reactivity. Subtype of immunogen used to elicit T-cell reactivity also did not predict T-cell responsiveness.
- EPIPIHYCAPAGFAI was the target sequence for hybridoma 1007P1-89 and precisely matched HIV-1 pNL43 sequence infecting GHOST cells. The hybridoma was not responsive to EPIPIHYCAPAGFAI.

T-Helper CD4+

HXB2 Location gp160 (212–231)
Author Location gp120 (221–240 W6.ID)
Epitope PIPIHYCAPAGFAILKCNNK
Immunogen vaccine
Vector/Type: protein *Strain:* B clade W61D *HIV component:* gp120 *Adjuvant:* MPL-SE adjuvant, QS21
Species (MHC) human
References Jones *et al.* 1999

- An HIV seronegative volunteer was vaccinated with rgp120 and a QS21/MPL adjuvant and HIV-1 specific T-cell lines were isolated.
- Two T-cell lines react specifically with this peptide.

HXB2 Location gp160 (212–231)
Author Location gp120 (212–231 IIIB)
Epitope PIPIHYCAPAGFAILKCNNK?
Epitope name D4
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 3/15 responders recognized this peptide, average SI = 4.2.

HXB2 Location gp160 (214–220)
Author Location Env (1007)
Epitope PIHYCAP
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This epitope is located in the C2 region of 1007 (US, clade B) and the Vβ usage of the TCR was not determined.
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (PKVSFEPIPIHYCAP and PIHYCAPAGFAILKC)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (215–225)
Author Location Env (1007)
Epitope IHYCAPAGFAI
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This epitope is located in the C2 region of 1007 (US, clade B) and the Vβ usage of the TCR was not determined.
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (EPIPIHYCAPAGFAI and IHYCAPAGFAILKCN)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.

- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (216–225)
Author Location Env (UG92005)
Epitope HYCAPAGFAI
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This epitope is located in the C2 region of UG92005 (UG, clade D) and Vβ usage of its TCR was not determined.
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (EPIPIHYCAPAGFAI and HYCAPAGFAILKCND)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (218–237)
Author Location gp120 (220–239 89.6)
Epitope CVPAGFAMLKCNNKTFNGSG
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 1 out 7 individuals responded to this peptide.

HXB2 Location gp160 (220–234)
Author Location gp120 (225–240 SF2)
Epitope PAGFAILKCNNKTFN
Immunogen in vitro stimulation or selection
Species (MHC)
References Manca *et al.* 1993

- T-cell line derived from unprimed, uninfected individual.
- Responds to APC pulsed with either synthetic peptide or gp120.
- Human MAbs 448-D and 450-D enhance APC gp120 uptake and presentation.

HXB2 Location gp160 (220–234)
Author Location gp120 (IIIB)
Epitope PAGFAILKCNNKTFN
Epitope name pep24
Immunogen vaccine
Vector/Type: Streptococcus gordonii *HIV component:* gp120
Species (MHC) human
Keywords immunodominance
References Pozzi *et al.* 1994

- This previously described immunodominant Th cell epitope was fused to the streptococcal surface protein M6 (emm-6.1), for expression on the surface of the bacterium Streptococcus gordonii.
- Recombinant bacteria showed efficient MHC class II mediated presentation of gp120 to T-cells by stimulation of a proliferative response in a human T cell clone specific for pep24.

HXB2 Location gp160 (220–235)
Author Location gp120 (IIIB)
Epitope PAGFAILKCNNKTFNY
Immunogen in vitro stimulation or selection
Species (MHC) human (DR2)
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.
- gp120 priming induced T-cells that recognize this peptide.

HXB2 Location gp160 (220–235)
Author Location gp120 (220–235 HXB2)
Epitope PAGFAILKCNNKTFNY
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DR2)
Keywords escape
References Guzman *et al.* 1998

- Listeria monocytogenes, an intracellular pathogen which is ingested by macrophages and can escape from the phagosome to replicate in the cytoplasm, was used successfully as carrier to deliver this gp120 epitope to CD4+ T-cells.

HXB2 Location gp160 (220–235)
Author Location gp120 (191–205 HXB2)
Epitope PAGFAILKCNNKTFNY
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DR2)
References Fenoglio *et al.* 1999

- gp120 pep24 epitope exhibited antagonistic activity against proliferation of gp120-specific T-cells when flanked by unrelated amino acid sequence.
- The glutathione S-transferase (GST)-peptide system can be used to display peptides; antigenicity was maintained when this peptide was expressed at the C-term end, but antagonism resulted when this peptide was expressed at the N-term end.

HXB2 Location gp160 (222–241)
Author Location gp120 (222–241 IIIB)
Epitope GFAILKCNNKTFNGTGPCTN?
Epitope name D5
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 2/15 responders recognized this peptide, average SI = 4.8.

HXB2 Location gp160 (223–231)
Author Location gp120 (194–202 HXB2)
Epitope FAILKCNNK
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DR2, DR6)
References Manca *et al.* 1996

- Epitope was the minimal stimulatory sequence defined for two Th lines stimulated *in vitro*.
- One Th line was stimulated by gp120, one by a Glutathione-S-transferase (GST)-peptide fusion.
- Alanine substitutions at position 914, 196, and 202 abrogated activity for the GST-peptide stimulated line, but not for a gp120 stimulated line.
- Constructs combining GST and the PAGFAILKCNNKTFNY gp120 peptide at the C-term end of GST stimulated Th cells but not at the N-term end.

HXB2 Location gp160 (223–231)
Author Location gp120 (194–202 HXB2)
Epitope FAILKCNNK
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DR2, DR6)
References Manca *et al.* 1996

- Epitope was the minimal stimulatory sequence defined for two Th lines stimulated *in vitro*.
- One Th line was stimulated by p66, one by a Glutathione-S-transferase (GST)-peptide fusion protein.
- Alanine substitutions at position 914, 196, and 202 abrogated activity for the GST-peptide stimulated line, but not for a gp120 stimulated line.
- Constructs linking GST to the PAGFAILKCNNKTFNY gp120 peptide at the C-term end of GST stimulated Th cells, constructs linking at the N-term end did not.
- The C and N termini of GST are not intrinsically permissive or non-permissive, presentation is epitope specific (see SSTVNDIQKLV for contrast)

HXB2 Location gp160 (223–231)
Author Location gp120 (237–245 SF2, HXB2)
Epitope FAILKCNNK
Immunogen
Species (MHC) mouse (H-2^{d})
Keywords subtype comparisons, immunodominance
References Fenoglio *et al.* 2000

- This peptide is an immunodominant Th epitope in BALB/c mice.
- Substitutions in positions 237, 241, 243, 244 with Ala all cause reduced recognition.
- Most natural analogs they tested did not cross-react, including peptides based on clade A, B, C, D, E and O sequences.
- Position 237 and 244 when substituted with Ala cause an antagonistic response and the natural analogues of this epitope to loose antigenicity.
- Some of the naturally occurring variants also cause an antagonistic response.

HXB2 Location gp160 (223–231)
Author Location gp120 (238–246 HXB2)

T-Helper CD4+

Epitope FAILKCNNK
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human
Keywords TCR usage
References Li Pira *et al.* 1998

- Clonal heterogeneity was broad for a recall response to tetanus toxoid or PPD, but oligoclonal to primary HIV antigens, dominated in this case by TCR Vβ 22 usage.
- Donor of PBMC that recognized this epitope had HLA-DR alleles 2 and 6.
- The only (detected) immunogenic variant of this epitope was derived from strain NOF (YAILKCNNK)

HXB2 Location gp160 (228–246)
Author Location gp120 (230–248 89.6)
Epitope CNNKTFNGSGPCTNVSTVQ
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 1 out 7 individuals responded to this peptide.

HXB2 Location gp160 (230–245)
Author Location gp120 (IIIB)
Epitope NKTFNGKGPCTNVSTY
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

HXB2 Location gp160 (232–251)
Author Location gp120 (232–251 IIIB)
Epitope TFNGTGPCTNVSTVQCTHGI?
Epitope name E1
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 3/15 responders recognized this peptide, average SI = 3.9.

HXB2 Location gp160 (235–247)
Author Location gp120 (240–252)
Epitope GTGPCTNVSTVQC
Immunogen vaccine
Vector/Type: peptide
Species (MHC) macaque
References Nehete *et al.* 1993

- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice.
- Proliferative response to this peptide was observed in 1/3 immunized rhesus monkeys, with a weak transient response in the other two.

HXB2 Location gp160 (238–257)
Author Location gp120 (240–249 89.6)
Epitope PCTNVSTVQCTHGIRPVVST
Epitope name Peptide 22
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse
Donor MHC H-2d
Keywords epitope processing, immunodominance
References Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was highly reactive in 6/10 BALB/c mice tested, but not in any (0/10) CBA/J mice.

HXB2 Location gp160 (238–257)
Author Location gp120 (238–257 89.6)
Epitope PCTNVSTVQCTHGIRPVVST
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 3 out 7 individuals responded to this peptide.

HXB2 Location gp160 (240–255)
Author Location gp120 (IIIB)
Epitope TNVSTVQCTHGRPIY
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.

HXB2 Location gp160 (242–261)
Author Location gp120 (242–261 IIIB)
Epitope VSTVQCTHGIRPVVSTQLLL
Immunogen SHIV infection
Species (MHC) macaque (DRB1*0406)
References Lekutis & Letvin 1997

- A novel C2 region Th epitope was described in SHIV-89.6 infected Macaca mulatta.

HXB2 Location gp160 (242–261)
Author Location gp120 (242–261 IIIB)
Epitope VSTVQCTHGIRPVVSTQLLL?
Epitope name E2
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 3.4.

HXB2 Location gp160 (244–266)
Author Location Env
Epitope TVQCTHGIRPVVSTQLLLNGSLA
Epitope name HIV_env_DRB0101_11
Subtype M
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type T-cell Elispot
Keywords computational epitope prediction
References De Groot *et al.* 2004

- Bioinformatic tools (EpiMatrix and Conservatrix) were employed to predict 9 highly conserved and promiscuous class II restricted T helper epitopes from HIV-1 env sequences for a cross-clade polyepitope vaccine. 10/34 HIV-1 infected patients induced Th1 immune responses to 8/9 study peptides.
- 1/34 subjects tested responded to this peptide.
- Class II peptides containing putative epitopes were selected to favor DRB0101 presentation, as there is a transgenic mouse model for this allele for future vaccine studies. The highest scoring DR B0101 sequence of this peptide was RPVVSTQL.

HXB2 Location gp160 (246–268)
Author Location Env (438–460)
Epitope QCTHGIRPVVSTQLLLNGSLAEE
Epitope name HIV_env_DRB0101_02
Subtype M
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type T-cell Elispot
Keywords computational epitope prediction
References De Groot *et al.* 2004

- Bioinformatic tools (EpiMatrix and Conservatrix) were employed to predict 9 highly conserved and promiscuous class II restricted T helper epitopes from HIV-1 env sequences for a cross-clade polyepitope vaccine. 10/34 HIV-1 infected patients induced Th1 immune responses to 8/9 study peptides.
- 1/34 subjects tested responded to this peptide.
- Class II peptides containing putative epitopes were selected to favor DRB0101 presentation, as there is a transgenic mouse model for this allele for future vaccine studies. The highest scoring DRB0101 sequence within this peptide was PVVSTQLLL.

HXB2 Location gp160 (248–267)
Author Location gp120 (250–269 89.6)
Epitope THGIRPVVSTQLLLNGSLAE
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.

- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 1 out 7 individuals responded to this peptide.

HXB2 Location gp160 (250–265)
Author Location gp120 (IIIB)
Epitope GIRPIVSTQLLLNGSC
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

HXB2 Location gp160 (252–271)
Author Location gp120 (252–271 IIIB)
Epitope RPVVSTQLLLNGSLAEEEVV?
Epitope name E3
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, average SI = 7.4.

HXB2 Location gp160 (258–277)
Author Location gp120 (260–279 89.6)
Epitope QLLLNGSLAEEDIVIRSENF
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.

- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 1 out 7 individuals responded to this peptide.

HXB2 Location gp160 (262–281)
Author Location gp120 (262–281 IIIB)
Epitope NGSLAEEEVVIRSVNFTDNA?
Epitope name E4
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 2/15 responders recognized this peptide, average SI = 3.1.

HXB2 Location gp160 (264–287)
Author Location gp120 (269–292 NL43)
Epitope SLAEEEVVIRSANFTDNAKTIIVQ
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43
HIV component: gp120, gp160
Species (MHC) human
References Sitz *et al.* 1999

- There was a great breadth of proliferative response to env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients.
- 50% of vaccinees had a stimulation index of greater than 5 to this peptide.

HXB2 Location gp160 (268–287)
Author Location gp120 (270–289 89.6)
Epitope EDIVIRSENFTDNAKTIIVQ
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.

T-Helper CD4+

- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 1 out 7 individuals responded to this peptide.

HXB2 Location gp160 (269–283)
Author Location gp120 (269–283 IIIB, B10)
Epitope `EVVIRSANFTDNAKT`
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location gp160 (269–291)
Author Location Env
Epitope `EVVIRSENFTNNAKTIIVQLNES`
Epitope name HIV_env_DRB0101_7
Subtype M
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type T-cell Elispot
Keywords computational epitope prediction
References De Groot *et al.* 2004

- Bioinformatic tools (EpiMatrix and Conservatrix) were employed to predict 9 highly conserved and promiscuous class II restricted T helper epitopes from HIV-1 env sequences for a cross-clade polyepitope vaccine. 10/34 HIV-1 infected patients induced Th1 immune responses to 8/9 study peptides.
- 1/34 subjects tested responded to this peptide.
- Class II peptides containing putative epitopes were selected to favor DRB0101 presentation, as there is a transgenic mouse model for this allele for future vaccine studies. The highest scoring DRB0101 sequence of this peptide was NFTNNAKTI.

HXB2 Location gp160 (270–285)
Author Location gp120 (IIIB)
Epitope `VVIRSDNFTNNAKTIC`
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

HXB2 Location gp160 (272–291)
Author Location gp120 (272–291 IIIB)
Epitope `IRSVNFTDNAKTIIVQLNTS?`
Epitope name E5
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords immunodominance
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- Five peptides were recognized most frequently: C2 (aa 142-161), C3 (aa 152-171), C5 (aa 172-191), E5 (aa 272-291) and G4 (aa 380-393). The first three were in or near V2, the other two were proximal to the V3 and V4 loops.
- 4/15 responders recognized this immunodominant peptide, average SI = 5.0.

HXB2 Location gp160 (274–288)
Author Location gp120 (274–288 IIIB, B10)
Epitope `SANFTDNAKTIIVQL`
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location gp160 (274–296)
Author Location Env
Epitope `SENFTNNAKIIIVQLNESVVINV`
Epitope name HIV_env_DRB0101_5
Subtype M
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type T-cell Elispot
Keywords computational epitope prediction
References De Groot *et al.* 2004

- Bioinformatic tools (EpiMatrix and Conservatrix) were employed to select 9 highly conserved and promiscuous class II restricted T helper epitopes from HIV-1 env sequences for a cross-clade vaccine. 10/34 HIV-1 infected patients induced Th1 immune responses to the 9 study peptides.
- 1/26 subjects tested responded to this peptide.
- Class II peptides containing putative epitopes were selected to favor DRB0101 presentation, as there is a transgenic mouse model for this allele for future vaccine studies. The highest scoring DRB0101 sequence of this peptide was AKIIIVQLN.

HXB2 Location gp160 (276–295)
Author Location gp120 (MN)
Epitope `NFTDNAKTIIVHLNESVQIN`
Epitope name NN20
Subtype B
Immunogen HIV-1 infection

Species (MHC) human
Assay type Cytokine production, proliferation, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords acute/early infection
References Malhotra *et al.* 2003

- 92 acute- or early-HIV infected subjects were tested for Env- and Gag-specific Th responses. There was an overall low probability of detecting HIV-1-specific Th responses, Env responses were rare and (5%) and only detected very early in infection, probably reflecting a low frequency of response and impaired lymophoproliferative capacity, not viral escape. Gag-specific Th responses were observed more frequently (16%), were found throughout the acute and early infection phases, and predominated after ARV therapy.
- This epitope is one of six Env-specific Th responses detected in one patient 11 days post-infection that were studied in detail.These Th reponses were not detected at subsequent time points, despite the Env specific Th cells being maintained as detected by TCR clonal transcripts, and the epitope sequence being maintained in Env.

HXB2 Location gp160 (280–296)
Author Location gp120 (IIIB)
Epitope NAKTIIVQLNESVAIC
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

HXB2 Location gp160 (288–307)
Author Location gp120 (290–309 89.6)
Epitope LNESVVINCTRPNNNTRRRL
Epitope name Peptide 27
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse
Donor MHC H-2k, H2-d
Keywords epitope processing, immunodominance
References Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was reactive in only 1/10 BALB/c mice tested, but reacted in 8/10 CBA/J mice.

HXB2 Location gp160 (288–307)
Author Location gp120 (290–309 89.6)
Epitope LNESVVINCTRPNNNTRRRL
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 2 out 7 individuals responded to this peptide.

HXB2 Location gp160 (289–297)
Author Location gp120 (292–300 SF2)
Epitope NESVAINCT
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF2 *HIV component:* gp120
Species (MHC) human
References Botarelli *et al.* 1991

- A non-glycosylated form of SF2 gp120, env 2-3, was used as an immunogen – 20% of T-cell clones do not recognize the glycosylated form.

HXB2 Location gp160 (290–306)
Author Location gp120 (296–312 LAI)
Epitope SVVEINCTRPNNNTRKS
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

HXB2 Location gp160 (290–314)
Author Location Env
Epitope ESVVINCTRPNNNTRRSIHIGPG
Epitope name HIV_env_DRB0101_14
Subtype M
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type T-cell Elispot
Keywords computational epitope prediction
References De Groot *et al.* 2004

- Bioinformatic tools (EpiMatrix and Conservatrix) were employed to predict 9 highly conserved and promiscuous class II restricted T helper epitopes from HIV-1 env sequences for a cross-clade polyepitope vaccine. 10/34 HIV-1 infected patients induced Th1 immune responses to 8/9 study peptides.

T-Helper CD4+

- 1/34 subjects tested responded to this peptide.
- Class II peptides containing putative epitopes were selected to favor DRB0101 presentation, as there is a transgenic mouse model for this allele for future vaccine studies.The highest scoring DR B0101 sequence of this peptide was TRPNNNTRR.

HXB2 Location gp160 (292–310)
Author Location gp120 (292–310 IIIB)
Epitope VEINCTRPNNNTRKRIRIQ?
Epitope name F1
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- Only 1/15 responders recognized this peptide, but it had the highest SI in the study of 9.9.

HXB2 Location gp160 (296–307)
Author Location gp120 (301–324 RF)
Epitope CTRPNNNTRKSI
Immunogen HIV-1 infection
Species (MHC)
Keywords epitope processing
References de Lorimier *et al.* 1994

- Proton NMR spectroscopy was employed to analyze the solution conformation of a hybrid peptide, T1-SP10RF, in order to better understand the immunogenicity of its' T helper (KQIINMWQEVGKAMYA, CTRPNNNTRKSI), CTL (SITKGPGRVIYATG) and B-cell epitopes (RKSITKGPGRVIYATG).
- This epitope embedded in the T1-SP10RF peptide does not form a helical amphipathic conformation. It lacks random-coil conformations, and this may make a peptide less susceptible to complete proteolytic degredation and be favored within epitopes.

HXB2 Location gp160 (296–314)
Author Location gp120 (303–321 IIIB)
Epitope CTRPNNNTRKSIRIQRGPG(Y)
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB
Species (MHC) goat
References Palker *et al.* 1989

- Goats were immunized with peptides containing V3 type-specific neutralizing determinants coupled to T1.

HXB2 Location gp160 (297–321)
Author Location gp120 (302–324 MN)
Epitope TRPNYNKRKRIHIGPGRAFYTTK
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade MN
HIV component: V3
Species (MHC) mouse (H-2^d)
References Oscherwitz *et al.* 1999b

- Epitope presented as a tandem repeat (eight copies) elicits stronger B-cell and T-cell responses than the epitope presented as a single copy.
- This study indicates that the increased response was not due to neodeterminants created at the junction of the peptides, but rather due to an epitope density effect, increased immunogenicity through a high ratio of epitope to protein.

HXB2 Location gp160 (297–330)
Author Location Env (303–335 BX08)
Epitope TRPNNNTRKSIHIGPGRAFYATGEIIGDIRQAH
Immunogen vaccine
Vector/Type: lipopeptide
Species (MHC) human
References Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 6/10 reacted to this peptide.
- 9/12 tested mounted a CTL responses to at least one of the six peptides, each of the six peptides elicited a CTL response in at least one individual – this peptide was particularly immunogenic, eliciting a CTL response in five vaccinees.
- None of the 12 tested had an IgG response to gp120 or gp160 and vaccinees could be differentiated from HIV-1 seropositive individuals with a commercial HIV detection kit – no neutralizing antibodies were observed.

HXB2 Location gp160 (298–307)
Author Location Env (UG92005)
Epitope RPYNNTRKGI
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This epitope is located in the V3 region of UG92005 (UG, clade D) and was recognized by a hybridoma with Vβ usage not determined.
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (TINCTRPYNNTRKGI and RPYNNTRKGIHIGPG)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.

T-Helper CD4+

- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (298–319)
Author Location gp120 (300–319 89.6)
Epitope RPNNNTRRRLSIGPGRAFYA
Epitope name Peptide 28
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse
Donor MHC H-2k, H2-d
Keywords epitope processing, immunodominance
References Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was reactive in 7/10 BALB/c mice tested, and in 5/10 CBA/J mice.

HXB2 Location gp160 (298–319)
Author Location gp120 (300–319 89.6)
Epitope RPNNNTRRRLSIGPGRAFYA
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 4 out 7 individuals responded to this peptide.

HXB2 Location gp160 (301–325)
Author Location gp120 (IIIB)
Epitope NNTRKSIRIQRGPGRAFVTIGKIGN
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* Env, Rev *Adjuvant:* QS21
Species (MHC) mouse
Keywords Th1
References Sasaki *et al.* 1998

- The env response is what is being sought, but co-expression of rev is required.
- Intramuscular versus nasal vaccination with DNA vaccine with a QS-21 adjuvant was studied.
- QS-21 enhanced the IgG2a response mediated via Th1 cytokines IFN-γ and IL-2 and delayed type hypersensitivity (DTH) in response to the V3 peptide was measured by a foot pad swelling test Sasaki *et al.* [1998]

HXB2 Location gp160 (302–315)
Author Location gp120 (307–322 IIIB)
Epitope NTRKSIRIQRGPGR
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* V3
Species (MHC) mouse
References Goodman-Snitkoff *et al.* 1990

- Identification of putative Th epitopes that can stimulate an antibody response in peptide-immunized mice.

HXB2 Location gp160 (302–321)
Author Location gp120 (302–321 IIIB)
Epitope NTRKRIRIQRGPGRAFVTIG?
Epitope name F2
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.

- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 5.6.

HXB2 Location gp160 (302–327)
Author Location gp120 (307–332 MN)
Epitope `NKRKRIHIGPGRAFYTTKNIIGTIR`
Subtype B
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade MN *HIV component:* V3 *Adjuvant:* Montanide (ISA 51)
Species (MHC) mouse
References Anderson *et al.* 2001

- Hypervariable epitope constructs (HECs) are degenerative peptide cocktails that are made in a single peptide synthesis reaction. Vaccination with a V3 degenerative peptide cocktail containing 64 distinct peptides, NTRK-[SR]-I-[HR]-IGPG-[RQ]-AFY-[AT]-TG-[DE]-IG-[DN]-IRQ, elicited broader and more durable Th responses than the MN V3 peptide alone in BALB/c mice immunized and boosted with V3 peptides, although the MN peptide elicited a transient MN-specific V3 response.

HXB2 Location gp160 (303–319)
Author Location gp120 (subtype C)
Epitope `(CKR)KIHIGPGQAFYT`
Subtype C
Immunogen HIV-1 infection
Species (MHC) mouse (H-2^b, H-2^d, H-2^k, H-2^s)
Keywords Th1
References Ahluwalia *et al.* 1997

- A V3 loop peptide modified to resemble an Indian form (GPGQ) was incorporated into ISCOMS (immune stimulating complexes) or liposomes, and used to immunize mice – the IgG2a/IgG2b Ab response was enhanced by the presentation in the ISCOM suggestive of a Th1 response.

HXB2 Location gp160 (305–321)
Author Location gp120 (312–329)
Epitope `(CG)KSIRIQRGPGRAFVTIG`
Immunogen HIV-1 infection
Species (MHC) human
References Adams *et al.* 1997

- Used as positive control in study examining T-cell response to four p24 Gag peptides.

HXB2 Location gp160 (308–321)
Author Location gp120 (MN)
Epitope `RIHIGPGRAFYTTK`
Epitope name SP10
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade MN *HIV component:* V3
Species (MHC) mouse (H-2^d)
References Klinman *et al.* 1995

- Hybrid T1-V3 peptide activates IL-4 and IL-6 in a dose dependent manner.
- 10-mer from V3 contributes to this response.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope `RIQRGPGRAFVTIGK`
Epitope name P18
Immunogen HIV-1 infection
Species (MHC) human (DR)
References Baier *et al.* 1995

- Linked HIV-1 T1 and P18 peptides to anti-HLA-DR and IgD Fab fragments to enhance uptake by antigen presenting cells thus increase immunogenicity.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope `RIQRGPGRAFVTIGK`
Epitope name P18
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2 A^d)
References Takahashi *et al.* 1990

- Induces both class II restricted CD4+ Th cells, and class I restricted CD8+ CTL.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope `RIQRGPGRAFVTIGK`
Epitope name P18
Immunogen peptide-HLA interaction
Species (MHC) mouse (H-2 I-A^d)
References Takeshita *et al.* 1995

- Binds Class II H-2 I-A^d requiring riqrgPgRaFvti, and Class I H-2 D^d, requiring iGPgRaFvtI.

HXB2 Location gp160 (308–322)
Author Location Env (IIIB)
Epitope `RIQRGPRAFVTIGK`
Epitope name P18
Immunogen vaccine
Vector/Type: DNA with CMV promotor *Strain:* B clade IIIB *HIV component:* gp160, Rev *Adjuvant:* MIP-1α
Species (MHC) mouse (H-2^d)
Keywords Th1
References Lu *et al.* 1999

- MIP-1a expression plasmid co-inoculated with a DNA vaccine consisting of HIV-1 pCMV160IIIB and pcREV enhanced the HIV-specific T-cell immune response as measured by a CTL test against using V3 peptide pulsed targets, and a DTH test to V3 peptide.
- The IgG1/IgG2a response was lowered with co-inoculation of MIP-1 alpha, suggesting it preferentially elicits a Th1 response.

HXB2 Location gp160 (308–322)
Author Location gp120 (308–322 IIIB)
Epitope `RIHIGPGRAFYTTKN`

T-Helper CD4+

Immunogen
Species (MHC) human
References Furci *et al.* 1997

- 9/11 exposed-uninfected individuals in this study had a proliferative response to a C5 peptide, but only 1/11 exposed-uninfected individuals recognized this peptide.
- 1/18 unexposed-uninfected controls could recognize this peptide.
- Erroneously documented as IIIB sequence - most likely MN peptide.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Epitope name P18
Immunogen vaccine
Vector/Type: peptide
Species (MHC) macaque
References Nehete *et al.* 1993

- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice.
- Despite the proliferative response to this peptide in mice and humans, no response was observed in 3 rhesus monkeys.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Epitope name P18
Immunogen HIV-1 infection
Species (MHC) human
Keywords responses in children, Th1, Th2
References Wasik *et al.* 1997

- The breadth and intensity of the CTL response and the type of Th response was studied in seven rapidly progressing HIV-1 + infants.
- IL-2 and γ IFN production from Th1 cells correlated with the CTLp frequency against HIV-1 Gag, Env, Nef and Pol.
- IL-4 production from Th2 cells was inversely correlated with the CTLp frequency.
- The HIV-1 + children with strong CTL responses had levels of anti-CD3 MAb induction of Th1 cells comparable to uninfected children.
- The children that did not mount a good CTL response had dramatically decreased numbers of Th1 relative to Th2 cells.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Epitope name P18
Immunogen HIV-1 infection
Species (MHC) human
Keywords responses in children, kinetics, Th1
References Wasik *et al.* 2000

- Th responses measured by IL-2 responses to P18 and T1 in HIV-1 infected infants were undetectable at less than 1 month of age, and remained low in children with AIDS symptoms, but increased with age in children with slowly progressive disease.
- The kinetics and intensity of the CTL activity during the first year of life was related to the child's ability to make Th1 responses.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Epitope name P18
Immunogen
Species (MHC) human
References Pinto *et al.* 1995

- CTL activity analyzed in parallel with Th reactivity in exposed but uninfected health care workers.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 MN)
Epitope RIHIGPGRAFYTTKN
Epitope name P18
Immunogen
Species (MHC) human
References Pinto *et al.* 1995

- CTL activity analyzed in parallel with Th reactivity in exposed but uninfected health care workers.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Epitope name P18
Immunogen HIV-1 infection
Species (MHC) human
References Clerici *et al.* 1989

- IL-2 production detection of Th lymphocytes from asymptomatic HIV-positive individuals.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Epitope name P18
Immunogen HIV-1 infection
Species (MHC) human
References Clerici *et al.* 1991a

- Peptides stimulate Th cell function and CTL activity in similar patient populations.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Epitope name P18
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) human
References Clerici *et al.* 1991b

- Immunizing uninfected individuals with rgp160 results in stronger Th response than does natural infection.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Epitope name P18
Immunogen

T-Helper CD4+

Species (MHC) human
References Clerici *et al.* 1992
- Cell-mediated immune response to HIV-1 peptides in HIV-1 exposed seronegative men.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Epitope name P18
Immunogen HIV-1 infection
Species (MHC) human
References Clerici *et al.* 1997
- used in a study of the influence of pentoxifylline on HIV specific T-cells.

HXB2 Location gp160 (308–322)
Author Location gp120 (MN)
Epitope RIHIGPGRAFYTTKN
Immunogen
Species (MHC) human
References Clerici *et al.* 1992
- Epitope P18 MN: Cell-mediated immune response to HIV-1 peptides in HIV-1 exposed seronegative men.

HXB2 Location gp160 (308–322)
Author Location gp160 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Epitope name P18
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human
Keywords immunodominance
References Wasik *et al.* 1999
- IL-2 responses associated with beta-chemokine expression were detectable at birth in the majority of uninfected infants born to HIV+ mothers, declining by age 6 months.
- In both uninfected and infected infants of HIV-positive mothers, responses to the T1 peptide (KQIINMWQEVGKAMYA) were more frequent than responses to P18.
- T1 is a highly conserved epitope, whereas P18 has a higher mutation rate due to its location in the immunodominant V3 loop region.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Epitope name P18
Immunogen HIV-1 infection
Species (MHC) human
References Kaul *et al.* 1999
- Kenyan sex workers that remained seronegative were found to frequently have HIV-env peptide specific Th responses detected by an IL-2 assay (11/20 cases) and mucosal genital tract anti-HIV IgA (16/21 cases)
- Helper epitopes used in this study were noted to be previously described Clerici *et al.* [1989], and were not explicitly described in Kaul *et al.* [1999]

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Epitope name P18
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human
Keywords subtype comparisons, responses in children, mother-to-infant transmission
References Kuhn *et al.* 2001a
- In a S. African perinatal transmission study, 33% (33/86) of cord blood samples from infants with seropositive mothers produced T-helper responses (measured by a bioassay measuring IL2 production in a murine cell line and confirmed with a proliferation assay) against a peptide cocktail containing Th epitopes P18 MN, P18 IIIB, T1, T2, and TH4.
- The mothers were predominantly infected with subtype C, but the T help response was detectable in a number of cord blood samples despite using peptides based on B subtype reagents.
- 3/33 infants with cord blood T help responses to Env were infected *in utero*, 2/33 were lost to follow up, and 28/33 were not infected. 6/53 of the infants with cord blood that was unresponsive to Env peptide stimulation were infected before delivery, and 8/47 contracted HIV intrapartum or via breastfeeding.
- Measurable HIV specific T help responses elicited in the immunologically immature newborn, possibly in response to *in utero* exposure, are associated with a protective natural immunity that helps block mother-infant transmission of HIV-1.

HXB2 Location gp160 (308–322)
Author Location gp120 (315–329 MN)
Epitope RIHIGPGRAFYTTKN
Epitope name P18
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human
Keywords subtype comparisons, responses in children, mother-to-infant transmission
References Kuhn *et al.* 2001a
- In a S. African perinatal transmission study, 33% (33/86) of cord blood samples from infants with seropositive mothers produced T-helper responses (measured by a bioassay measuring IL2 production in a murine cell line and confirmed with a proliferation assay) against a peptide cocktail containing Th epitopes P18 MN, P18 IIIB, T1, T2, and TH4.
- The mothers were predominantly infected with subtype C, but the T help response was detectable in a number of cord blood samples despite using peptides based on B subtype reagents.
- 3/33 infants with cord blood T help responses to Env were infected *in utero*, 2/33 were lost to follow up, and 28/33 were not infected. 6/53 of the infants with cord blood that was unresponsive to Env peptide stimulation were infected before delivery, and 8/47 contracted HIV intrapartum or via breastfeeding.
- Measurable HIV specific T help responses elicited in the immunologically immature newborn, possibly in response to *in utero* exposure, are associated with a protective natural immunity that helps block mother-infant transmission of HIV-1.

HXB2 Location gp160 (308–322)
Author Location Env (315–329 IIIB)
Epitope RIQRGPGRAFVTIGK
Epitope name P18IIIB
Immunogen HIV-1 infection, HIV-1 exposed seronegative

Species (MHC)
Assay type Cytokine production
Keywords mother-to-infant transmission
References Clerici *et al.* 1993a

- Cord blood samples in 8/23 infants with HIV+ mothers showed IL-2 production in response to peptides from HIV-1 gp1260, demonstrating that Th cell priming to HIV env determinants can occur in utero. HIV-specific Th immunity in utero may be protective, as none of the 8 with HIV-1 specific Th activity became infected, while 3/15 infants with no detectable Th activited were infected.
- PBL from 10/21 of the mother showed HIV-1 specific Th activity through IL-2 production in response to Env peptides.

HXB2 Location gp160 (308–322)
Author Location Env (MN)
Epitope RIHIGPGRAFYTTKN
Epitope name P18MN
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC)
Assay type Cytokine production
Keywords mother-to-infant transmission
References Clerici *et al.* 1993a

- Cord blood samples in 8/23 infants with HIV+ mothers showed IL-2 production in response to peptides from HIV-1 gp1260, demonstrating that Th cell priming to HIV env determinants can occur in utero. HIV-specific Th immunity in utero may be protective, as none of the 8 with HIV-1 specific Th activity became infected, while 3/15 infants with no detectable Th activited were infected.
- PBL from 10/21 of the mother showed HIV-1 specific Th activity through IL-2 production in response to Env peptides.

HXB2 Location gp160 (308–322)
Author Location Env (IIIB)
Epitope RIQRGPGRAFVTIGK
Epitope name P18IIIB
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC)
Assay type Cytokine production
References Clerici *et al.* 1994a

- Six of eight HIV-exposed health care workers had transient HIV-specific T-helper responses after percutaneous exposure to HIV, responding to two or more Env peptides among the set T1, T2, Th4.1, P18IIIB and P18MN. Responses were lost after 12-56 weeks. The HIV-specific Th responses occurred without seroconversion or PCR evidence for infection.
- Six of the eight HIV-exposed individuals responded to two or more peptides, whereas, only one individual exposed to HIV-negative blood responded to one peptide.

HXB2 Location gp160 (308–322)
Author Location Env (MN)
Epitope RIHIGPGRAFYTTKN
Epitope name P18MN
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC)
Assay type Cytokine production
References Clerici *et al.* 1994a

- Six of eight HIV-exposed health care workers had transient HIV-specific T-helper responses after percutaneous exposure to HIV, responding to two or more Env peptides among the set T1, T2, Th4.1, P18IIIB and P18MN. Responses were lost after 12-56 weeks. The HIV-specific Th responses occurred without seroconversion or PCR evidence for infection.
- Six of the eight HIV-exposed individuals responded to two or more peptides, whereas, only one individual exposed to HIV-negative blood responded to one peptide.

HXB2 Location gp160 (308–322)
Author Location HIV-1 (IIIB)
Epitope RIQRGPGRAFVTIGK
Epitope name P18IIIB
Subtype B
Immunogen HIV-1 infection
Species (MHC)
Assay type Cytokine production
References Clerici *et al.* 1994b

- IL-10-specific mRNA was upregulated in PBMC from asymptomatic, HIV-infected (HIV+) patients, and was particularly high in those with severely compromised Th cells function. Th response to HIV peptides *in vitro* could be restored by IL-10 Ab.

HXB2 Location gp160 (308–322)
Author Location HIV-1 (MN)
Epitope RIHIGPGRAFYTTKN
Epitope name P18MN
Subtype B
Immunogen HIV-1 infection
Species (MHC)
Assay type Cytokine production
References Clerici *et al.* 1994b

- IL-10-specific mRNA was upregulated in PBMC from asymptomatic, HIV-infected (HIV+) patients, and was particularly high in those with severely compromised Th cells function. Th response to HIV peptides *in vitro* could be restored by IL-10 Ab.

HXB2 Location gp160 (308–322)
Author Location Env (315–329)
Epitope RIHIGPGRAFYTTKN
Epitope name P18 MN
Immunogen HIV-1 infection
Species (MHC) human
Assay type Cytokine production
Keywords mother-to-infant transmission
References Kuhn *et al.* 2001b

- The proliferative responses in cord blood at delivery to a cocktail of HIV Envelope peptides were infrequent (1/41) among infants whose HIV-positive mothers received antiretroviral prophylaxis at delivery to prevent transmission. Responses were 10 times more frequent among infants of HIV-seropositive women who had no antiretroviral treatment (7/29). Reductions of HIV-specific responses occurred despite persistance of detectable HIV RNA in the mothers at delivery.

- The reduction of Th responses in newborns raises the possibility that anti-retrovial exposure during pregnancy may block subsequent immune protection. The authors point two relevant citations that showed ARV exposed infants had a more rapid course of progression (Kuhn *et al.*, JID 182:104 (2000)), but were at no greater risk of infection due to subsequent breast feeding (Ditrame *et al.*, Lancet 354:2050 (1999)).

HXB2 Location gp160 (308–322)
Author Location Env (315–329 IIIB)
Epitope `RIQRGPGRAFVTIGK`
Epitope name P18 IIB
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type proliferation
Keywords responses in children, mother-to-infant transmission
References Kuhn *et al.* 2001b

- T helper proliferative responses in cord blood at delivery to a cocktail of HIV envelope peptides were infrequent (1/41) among infants whose HIV-positive mothers received antiretroviral prophylaxis at delivery to prevent transmission. Responses were 10 times more frequent among infants of HIV-seropositive women who had no antiretroviral treatment (7/29). Reductions of HIV-specific responses occurred despite persistance of detectable HIV RNA in the mothers at delivery.
- The reduction of Th responses in newborns raises the possibility that anti-retrovial exposure during pregnancy may block subsequent immune protection. The authors point two relevant citations that showed ARV exposed infants had a more rapid course of progression (Kuhn *et al.*, JID 182:104 (2000)), but were at no greater risk of infection due to subsequent breast feeding (Ditrame *et al.*, Lancet 354:2050 (1999)).

HXB2 Location gp160 (308–322)
Author Location Env (gp160) (317–331 MN)
Epitope `RIHIGPGRAFYTTKN`
Epitope name P18
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type proliferation
Keywords responses in children, variant cross-recognition or cross-neutralization
References Meddows-Taylor *et al.* 2004

- Viral isolates (gp160) from 16 vertically HIV-1 infected children (8 T-helper cell Env responders and 8 non-responders) were analyzed for variation after comparison with Env peptide sequences (conserved regions T1, T2 and TH4.1, hypervariable regions P18 MN and P181 IIIB) used for in vitro stimulation.
- No correlation between the age, clinical category (mild or severe), HIV-1 viral load and the degree of epitope variation was established.

HXB2 Location gp160 (308–322)
Author Location Env (gp160) (317–331 IIIB)
Epitope `RIQRGPGRAFVTIGK`
Epitope name P18
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type proliferation
Keywords responses in children
References Meddows-Taylor *et al.* 2004

- Viral isolates (gp160) from 16 vertically HIV-1 infected children (8 T-helper cell Env responders and 8 non-responders) were analyzed for variation after comparison with Env peptide sequences (conserved regions T1, T2 and TH4.1, hypervariable regions P18 MN and P181 IIIB) used for in vitro stimulation.
- No correlation between the age, clinical category (mild or severe), HIV-1 viral load and the degree of epitope variation was established.

HXB2 Location gp160 (308–327)
Author Location gp120 (306–325 MN)
Epitope `RIHIGPGRAFYTTKNIIGIT`
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101)
References Hayball *et al.* 1997

- Tandem repeated presentation of epitope enhances binding to class II molecule and therefore induction of T-cell proliferation.
- Tandem peptides are thought to enhance proliferation through improved recruiting of CD4 to the activation complex, which can counter-balance gp120's sequestering of CD4 and consequential inhibition of a proliferative response.

HXB2 Location gp160 (309–323)
Author Location gp120 (309–323 IIIB, B10)
Epitope `EQRGPGRAFVTIGKI`
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location gp160 (309–325)
Author Location gp120 (314–330)
Epitope `IQRGPGRAFVTIGKIGN`
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Caruso *et al.* 1997

- As HIV-1-infected individuals progress to disease, T-cells show reduced ability to proliferate in response to HIV antigen, but retain the ability to express the activation antigens CD25 and CD71.
- The ability to express activation markers in response to HIV is retained, but the response to tetanus toxoid recall antigen is lost.
- This study investigated CD25 and CD71 expression in PBMC from patients at various stages of progression, measuring the response to *in vitro* stimulation by peptide cocktail containing four antigenic Env peptides, or p17 and p24.

HXB2 Location gp160 (310–328)
Author Location gp120 (310–329 89.6)
Epitope SIGPGRAFYARRNIIGDIRQ
Epitope name Peptide 29
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse
Donor MHC H-2k, H2-d
Keywords epitope processing, immunodominance
References Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was reactive in 2/10 BALB/c mice tested, and in 8/10 CBA/J mice.

HXB2 Location gp160 (310–328)
Author Location gp120 (310–329 89.6)
Epitope SIGPGRAFYARRNIIGDIRQ
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 2 out 7 individuals responded to this peptide.

HXB2 Location gp160 (311–319)
Author Location
Epitope RGPGRAFVT
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade BH10 *HIV component:* gp120 *Adjuvant:* GM-CSF
Species (MHC) mouse
References Barouch *et al.* 2002

- gp120 encoding DNA co-injected with a plasmid carrying GMCSF gave meager CD4+ T-cell responses in BALB/c mice relative to bicistronic gp120 and GMCSF cloned into the same vector and expressed from the same promoter.
- The bicistronic gp120/GM-CSF vaccine induced an approximately 10-fold increase of CD4+ T cell proliferative responses to gp120, as well as a significant increase in IL-2, IL-4, IL-10, IFN-γ and GM-CSF production, compared to immunization with the monocistronic pVIJ-gp120 with GMCSF. The enhanced proliferative responses were substantiated by CD4+ T-cell Elispot.
- Both mono and bicistronic DNA vaccines induced similar CTL responses directed against the H-2Dd restricted P18 peptide RGPRAFTVTI in murine splenocytes despite the enhanced proliferative responses.

HXB2 Location gp160 (311–320)
Author Location gp120 (IIIB)
Epitope RGPGPAFVTI
Immunogen vaccine
Vector/Type: DNA with CMV promotor *Strain:* B clade IIIB *HIV component:* gp160, Rev *Adjuvant:* IL-2
Species (MHC) mouse (H-2^d)
Keywords Th1
References Xin *et al.* 1998

- Intranasal immunization with IL-2 expression plasmid in addition to DNA vaccine amplifies cellular response to antigen, probably via activation of Th type 1 (Th1) cells.

HXB2 Location gp160 (311–320)
Author Location gp120 (IIIB)
Epitope RGPGPAFVTI
Immunogen vaccine
Vector/Type: DNA with CMV promotor *Strain:* B clade IIIB *HIV component:* gp160, Rev *Adjuvant:* IL-15
Species (MHC) mouse (H-2^d)
Keywords Th1
References Xin *et al.* 1999

- Intranasal immunization with IL-15 expression plasmid in addition to DNA vaccine increases DTH response and CTL activity to the antigen, and decreases the serum IgG1 to IgG2a ratio, enhancing Th type 1 (Th1) cell-mediated immunity.
- Expression of IL-2 or IL-15 can enhance Th1 response to the vaccine, but they to do not appear to elicit a synergistic response.

HXB2 Location gp160 (311–320)
Author Location gp120 (IIIB)
Epitope RGPGPAFVTI
Immunogen vaccine
Vector/Type: DNA with CMV promotor *Strain:* B clade IIIB *HIV component:* gp160, Rev *Adjuvant:* CD40
Species (MHC) mouse (H-2^d)
Keywords Th1, Th2
References Ihata *et al.* 1999

T-Helper CD4+

- CD40L expression increases DTH, and Th1-dependent responses based on enhanced IgG2a titers, with no lowering of IgG1 titers.
- Elispot assay indicated co-injection with hCD40L resulted in greater numbers of IFN-γ producing Th1cells, as well as increased IL-4 producing Th2 cells.
- Results suggest hCD40L enhance both Th1 and Th2 cells, and such a pattern of induction is unique among adjuvants, as most adjuvants increase either Th1 or Th2.

HXB2 Location gp160 (311–322)
Author Location Env (IIIB)
Epitope `RGPGRAFVTIGK`
Immunogen vaccine
Vector/Type: DNA with CMV promotor *Strain:* B clade IIIB *HIV component:* gp160, Rev *Adjuvant:* GM-CSF
Species (MHC) mouse (H-2^d)
Keywords Th1, Th2
References Kusakabe *et al.* 2000

- The timing of delivery of the pGM-CSF expression plasmid for intramuscular DNA pCMV160IIIB/REV vaccination impacts the Th response, maximizing Th2 responses when administered 3 days prior to the DNA vaccine, and Th1 responses when administered 3 days after the DNA vaccine.

HXB2 Location gp160 (314–328)
Author Location gp120 (314–328 IIIB, B10)
Epitope `GRAFVTIGKIGNMRQ`
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location gp160 (314–341)
Author Location gp120 (319–346 NL43)
Epitope `GRAFVTIGKIGNMRQAHCNISRAKWNAT`
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43 *HIV component:* gp120, gp160
Species (MHC) human
References Sitz *et al.* 1999

- There was a great breadth of proliferative response to env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients.
- More than 25% of vaccinees had a stimulation index of greater than 5 to this peptide.

HXB2 Location gp160 (315–328)
Author Location Env (UG92005)
Epitope `RAYYTTNIVGNIRQ`
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This epitope is located in the V3 region of UG92005 (UG, clade D) and was recognized by two hybridomas with Vβ usage not determined, but one used Vα 8.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (317–331)
Author Location gp120 (324–338 IIIB)
Epitope `FVTIGKIGNMRQAHC`
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^d, H-2^k)
References Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

HXB2 Location gp160 (317–331)
Author Location gp160 (324–338 IIIB)
Epitope `FVTIGKIGNMRQAHC`
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^d, H-2^k)
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- B10.BR (H-2A^k, E^k) and B10.D2 (H-2A^d, E^d) mice immunized with rec gp160 showed a proliferative response to this peptide.

T-Helper CD4+

- FVTIGKIGNMRQAHCNISRAKWNNTLKQIDSKL encompasses several murine Th epitopes including FVTIGKIGNMRQAHC and is referred to as a "multi-determinant region" or cluster peptide.

HXB2 Location gp160 (317–336)
Author Location gp120 (321–340 MN)
Epitope YTTKNIIGTIRQAHCNSRA
Epitope name 1987
Subtype B
Immunogen vaccine
Vector/Type: DNA, protein *Strain:* B clade MN *HIV component:* gp120 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) guinea pig
Keywords vaccine-specific epitope characteristics, Th1
References Chattergoon *et al.* 2002

- Hartley guinea pigs were intradermally injected with either recombinant protein or plasmid expressed gp120 and monitored for delayed type hypersensivity (DTH) responses after vaccination, which are related to Th1 T-cell responses. CFA did not augment responses in animals vaccinated with plasmid.
- A total of 7 gp120 peptides elicited a delayed type hypersensivity (DTH) response after vaccination, out of a set of 60 overlapping peptides that spanned gp120. The vaccine delivery system, DNA versus rec protein, resulted in the recognition of distinct peptides.
- 4/5 animals vaccinated with rec gp120 responded by DTH to this peptide, as did 4/6 vaccinated with plasmid gp120 DNA.

HXB2 Location gp160 (317–349)
Author Location gp160 (324–356 IIIB)
Epitope FVTIGKIGNMRQAHCNISRAKWNNTLKQIDSKL
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) human, mouse (H-2^d, H-2^k)
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- FVTIGKIGNMRQAHCNISRAKWNNTLKQIDSKL encompasses several murine Th epitopes and is referred to as a "multideterminant region" or cluster peptide.
- Six multideterminant region cluster peptides were evaluated Th responses in different MHC/HLA backgrounds after vaccination of mice with gp160, or in infected people.
- This cluster peptide elicited proliferative responses in cells from B10.BR mice (H-2A^k, E^k) and B10.D2 mice (H-2A^d, E^d), but shorter peptides from within this region stimulated H-2^k, H-2^d, H-2^b and H-2^s responses.
- IL-2 production in response to this peptide was observed in 58% (21/36) of asymptomatic HIV-infected individuals.

HXB2 Location gp160 (319–333)
Author Location Env
Epitope TGDIIGDIRQAHCNI
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, TGDIIGDIRQAHCNI was previously described as peptide GRAFVTIGKIGNMRQAHCNISRAKWNAT and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (319–338)
Author Location gp120 (320–339 89.6)
Epitope RRNIIGDIRQAHCNISRAKW
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse (H-2^d, H-2^k)
Keywords immunodominance
References Dai *et al.* 2001

- Promiscuous immunodominant epitopes in gp120 were mapped by overlapping peptides in CBA/J H-2^k and BALB/c H-2^d mice, and all were found to be in the outer domain, proximal to regions of structural disorder indicated by the crystal structure or by sequence divergence.
- This peptide was recognized by 7/10 CBA/J and 7/10 BALB/c mice with SI > 4, averaging 6.3 and 4.8, and is considered to be promiscuously immunodominant.
- Uniquely immunodominant sequences tended to be in the inner domain of the protein.

HXB2 Location gp160 (319–338)
Author Location gp120 (320–339 89.6)
Epitope RRNIIGDIRQAHCNISRAKW
Epitope name Peptide 30
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse
Donor MHC H-2k, H2-d
Keywords epitope processing, immunodominance
References Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was highly reactive in 7/10 BALB/c mice tested, and in 7/10 CBA/J mice and was considered one of the 3 immunodominant peptides identified that were shared in both mouse strains: RRNIIGDIRQAHCNISRAKW, NNTLQQIVIKLREKFRNKTI, GTNGTEGNDIITLQCRIKQI.

HXB2 Location gp160 (319–338)
Author Location gp120 (320–339 89.6)
Epitope `RRNIIGDIRQAHCNISRAKW`
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 5 out 7 individuals responded to this peptide.

HXB2 Location gp160 (321–336)
Author Location gp120 (IIIB)
Epitope `RIIGDIRKAHCNISRY`
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

HXB2 Location gp160 (322–336)
Author Location Env (1007)
Epitope `IIGDIRQAHCNISRE`
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This epitope is located in the V3 region of 1007 (US, clade B) and was recognized by three hybridomas with Vβ usage Vβ 6 and not determined.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (322–336)
Author Location Env (UG92005)
Epitope `IVGNIRQAHCNVSKA`
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This epitope is located in the V3 region of UG92005 (UG, clade D) and was recognized by three hybridomas with Vβ usage Vβ 6, 8.1, and not determined.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4

T-Helper CD4+

weeks later boosted again with purified protein in Freund's adjuvant.

- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (322–336)
Author Location Env (UG92005)
Epitope IVGNIRQAHCNVSKA
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This epitope is located in the V3 region of UG92005 (UG, clade D) and was recognized by three hybridomas with Vβ usage Vβ 6, 8.1, and not determined.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
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- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (322–336)
Author Location
Epitope IIGDIRQAHCNISRE
Subtype B, D
Immunogen vaccine
Vector/Type: DNA prime with protein boost
Strain: B clade 1007, D clade UG92005
HIV component: gp140
Species (MHC) mouse
Assay type Cytokine production
Keywords epitope processing
References Sealy *et al.* 2008

- Murine hybridomas with known Env peptide specificities were tested for IL-2 production following stimulation with autologous splenocytes exposed to HIV-1-infected CXCR4 GHOST cells. Hybridomas were originally derived from C57BL/6 mice immunized with a prime-boost regimen. Antigen-processing potentials in the mouse system were studied.
- The presence of a target sequence within HIV-1 did not ensure T-cell reactivity. Subtype of immunogen used to elicit T-cell reactivity also did not predict T-cell responsiveness.
- IIGDIRQAHCNISRE was the target sequence for hybridoma 1007P3-11 and differed in 4 residues from HIV-1 pNL43 sequence infecting GHOST cells. The hybridoma was not responsive.

HXB2 Location gp160 (322–341)
Author Location gp120 (322–341 IIIB)
Epitope KIGNMRQAHCNISRAKWNNT?
Epitope name F4
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 7.6.

HXB2 Location gp160 (324–336)
Author Location Env (UG92005)
Epitope GNIRQAHCNVSKA
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This epitope is located in the V3 region of UG92005 (UG, clade D) and was recognized by two hybridoma with Vβ usage Vβ8.2 and not determined.
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (IVGNIRQAHCNVSKA and GNIRQAHCN-VSKAKW)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (324–338)
Author Location Env (UG92005)
Epitope GNIRQAHCNVSKAKW
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This epitope is located in the V3 region of UG92005 (UG, clade D) and was recognized by eleven hybridomas with Vβ usage Vβ5, 7, 8.1, 8.2, 11 and not determined – a Vβ 8.1's and Vβ 8.2 also were shown to use Vα 8, and one of the ND used Vα 2.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (324–338)
Author Location gp120 (V3)
Epitope GNIRQAHCNVSKAKW
Subtype B, D
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* Env *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^b)
Assay type Cytokine production, CD4 T-cell Elispot - IFNγ
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization, vaccine antigen design
References Zhan *et al.* 2004

- To develop a polyvalent Env vaccine, subtype specific B and D T-helper epitopes were identified, and mixtures of strain 1007, clade B, or UG92005, clade D envelopes were given to C57BL/6J mice. Mice were intramuscularly immunized with recombinant DNA, then intraperitoneally with rVV and finally with env protein in CFA. A dilution of 1/100 could still elicit type specific responses, and responses persisted with different prime boost combinations.

T-Helper CD4+

- Priming with 1007 and UG92005 env's induced both Env-specific (SNNTVGNPIILPCRI and AMYAPPIAGLIQCSS) and cross-reactive (PKVSFEPIPIHYCAP, C2, GNIRQAHC-NVSKAKW, V3-C3) Th responses in murine spleen cells.

HXB2 Location gp160 (327–341)
Author Location gp120 (327–341 HXB2)
Epitope RQAHCNISRAKWNNT
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2 *HIV component:* gp120
Species (MHC) mouse (I-A^{d})
References Warren & Thomas 1992

- Minimum epitope and MHC restriction determined for CTL clone that recognizes the N-terminal flank of the V3 loop.

HXB2 Location gp160 (327–346)
Author Location gp120 (331–350 MN)
Epitope RQAHCNISRAKWNDILRQIV
Epitope name 1988
Subtype B
Immunogen vaccine
Vector/Type: DNA, protein *Strain:* B clade MN *HIV component:* gp120 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) guinea pig
Keywords vaccine-specific epitope characteristics, Th1
References Chattergoon *et al.* 2002

- Hartley guinea pigs were intradermally injected with either recombinant protein or plasmid expressed gp120 and monitored for delayed type hypersensivity (DTH) responses after vaccination, which are related to Th1 T-cell responses. CFA did not augment responses in animals vaccinated with plasmid.
- A total of 7 gp120 peptides elicited a delayed type hypersensivity (DTH) response after vaccination, out of a set of 60 overlapping peptides that spanned gp120. The vaccine delivery system, DNA versus rec protein, resulted in the recognition of distinct peptides.
- 4/5 animals vaccinated with rec gp120 responded by DTH to this peptide, and 2/6 responded that were vaccinated with plasmid gp120 DNA.

HXB2 Location gp160 (329–348)
Author Location gp120 (330–349 89.6)
Epitope AHCNISRAKWNNTLQQIVIK
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 2 out 7 individuals responded to this peptide.

HXB2 Location gp160 (330–350)
Author Location gp120 (330–349 IIIB)
Epitope HCNISRAKWNNTLKQIASKLR?
Epitope name F5
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 3/15 responders recognized this peptide, average SI = 5.5.

HXB2 Location gp160 (331–345)
Author Location gp120 (IIIB)
Epitope CNISRAQWNNTLEQI
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

HXB2 Location gp160 (332–354)
Author Location gp120 (337–359 NL43)
Epitope NISRAKWNATLKQIASKLREQFG
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43 *HIV component:* gp120, gp160
Species (MHC) human
References Sitz *et al.* 1999

- There was a great breadth of proliferative response to env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients.
- More than 30% of vaccinees had a stimulation index of greater than 5 to this peptide.

HXB2 Location gp160 (335–349)
Author Location gp160 (342–356 IIIB)
Epitope RAKWNNTLKQIDSKL
Immunogen vaccine

T-Helper CD4+

Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^b, H-2^k, H-2^s)
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- B10.BR (H-$2A^k$, E^k), B10.A(5R) (H-$2A^b$, E^b) and B10.S(9R) (H-$2A^s$, E^s) mice immunized with rec gp160 showed a proliferative response to this peptide.
- FVTIGKIGNMRQAHCNISRAKWNNTLKQIDSKL encompasses several murine Th epitopes including RAKWNNTLKQIDSKL and is referred to as a "multideterminant region" or cluster peptide.

HXB2 Location gp160 (335–349)
Author Location gp120 (342–356 IIIB)
Epitope `RAKWNNTLKQICSKL`
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^{i5}, H-2^k, H-2^{t4})
References Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

HXB2 Location gp160 (337–356)
Author Location gp120 (341–360 MN)
Epitope `KWNDTLRQIVSKLKEQFKNK`
Epitope name 1989
Subtype B
Immunogen vaccine
Vector/Type: DNA, protein *Strain:* B clade MN *HIV component:* gp120 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) guinea pig
Keywords vaccine-specific epitope characteristics, Th1
References Chattergoon *et al.* 2002

- Hartley guinea pig were intradermally injected with either recombinant protein or plasmid expressed gp120 and monitored for delayed type hypersensivity (DTH) responses after vaccination, which are related to Th1 T-cell responses. CFA did not augment responses in animals vaccinated with plasmid.
- A total of 7 gp120 peptides elicited a delayed type hypersensivity (DTH) response after vaccination, out of a set of 60 overlapping peptides that spanned gp120. The vaccine delivery system, DNA versus rec protein, resulted in the recognition of distinct peptides.
- 3/5 animals vaccinated with rec gp120 responded by DTH to this peptide, and 2/6 responded that were vaccinated with plasmid gp120 DNA.

HXB2 Location gp160 (339–359)
Author Location gp120 (340–359 89.6)
Epitope `NNTLQQIVIKLREKFRNKTI`
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse (H-2^d, H-2^k)
Keywords immunodominance
References Dai *et al.* 2001

- Promiscuous immunodominant epitopes in gp120 were mapped by overlapping peptides in CBA/J H-2^k and BALB/c H-2^d mice, and all were found to be in the outer domain, proximal to regions of structural disorder indicated by the crystal structure or by sequence divergence.
- This peptide was recognized by 4/10 CBA/J and 6/10 BALB/c mice with SI > 4, averaging 4.9 and 5.5 and is considered to be promiscuously immunodominant.
- Uniquely immunodominant sequences tended to be in the inner domain of the protein.

HXB2 Location gp160 (339–359)
Author Location gp120 (340–359 89.6)
Epitope `NNTLQQIVIKLREKFRNKTI`
Epitope name Peptide 32
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse
Donor MHC H-2k, H2-d
Keywords epitope processing, immunodominance
References Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was reactive in 6/10 BALB/c mice tested, and in 4/10 CBA/J mice and was considered one of the 3 immunodominant peptides identified that were shared in both mouse strains: RRNIIGDIRQAHCNISRAKW, NNTLQQIVIKLREKFRNKTI, GTNGTEGNDIITLQCRIKQI.

HXB2 Location gp160 (339–359)
Author Location gp120 (340–359 89.6)
Epitope `NNTLQQIVIKLREKFRNKTI`
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.

T-Helper CD4+

- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 4 out 7 individuals responded to this peptide.

HXB2 Location gp160 (341–356)
Author Location gp120 (IIIB)
Epitope `TLEQIVKKLREQFGNC`
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

HXB2 Location gp160 (342–361)
Author Location gp120 (342–361 IIIB)
Epitope `LKQIASKLREQFGNNKTIIF?`
Epitope name G1
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 2/15 responders recognized this peptide, average SI = 6.0.

HXB2 Location gp160 (344–357)
Author Location gp120 (346–359)
Epitope `QIVKKLREQFGNNK`
Immunogen HIV-1 infection
Species (MHC) human
References Krowka *et al.* 1990

- Conjugation of HIV peptides to liposomes and rIL-2 stimulation may enhance cell-mediated responses.

HXB2 Location gp160 (349–368)
Author Location gp120 (350–369 89.6)
Epitope `LREKFRNKTIAFNQSSGGD`
Epitope name Peptide 33
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse
Donor MHC H-2k, H2-d
Keywords epitope processing, immunodominance
References Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was reactive in 3/10 BALB/c mice tested, and in 5/10 CBA/J mice.

HXB2 Location gp160 (349–368)
Author Location gp120 (350–368 89.6)
Epitope `LREKFRNKTIAFNQSSGGD`
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 2 out 7 individuals responded to this peptide.

HXB2 Location gp160 (350–370)
Author Location gp120 (350–370 IIIB)
Epitope `REQFGNNKTIIFKQSSGGDPE?`
Epitope name G2
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, average SI = 3.2.

HXB2 Location gp160 (353–360)
Author Location gp120 (355–362 IIIB)
Epitope FGNNKTII
Immunogen SHIV infection
Species (MHC) macaque
References Lekutis & Letvin 1997
- C3 region minimal epitope determined through fine epitope mapping.
- Cell line was lost prior to confirmation of MHC requirements.

HXB2 Location gp160 (360–379)
Author Location gp120 (360–379 89.6)
Epitope AFNQSSGGDPEIVMHSFNCG
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008
- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 1 out 7 individuals responded to this peptide.

HXB2 Location gp160 (363–372)
Author Location gp120 (368–377 LAI)
Epitope QSSGGDPEIV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989
- Stimulates T-cell proliferation in HIV-infected donors.

HXB2 Location gp160 (364–378)
Author Location gp120 (364–378 IIIB, B10)
Epitope SSGGKPEIVTHSFNC
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a
- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location gp160 (369–383)
Author Location gp120 (369–383 IIIB, B10)
Epitope PEIVTHSFNCGGEFF
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a
- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location gp160 (380–393)
Author Location gp120 (380–393 IIIB)
Epitope GEFFYCNSTQLFNS?
Epitope name G4
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords immunodominance
References Geretti *et al.* 1994
- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- Five peptides were recognized most frequently: C2 (aa 142-161), C3 (aa 152-171), C5 (aa 172-191), E5 (aa 272-291) and G4 (aa 380-393). The first three were in or near V2, the other two were proximal to the V3 and V4 loops.
- 4/15 responders recognized this immunodominant peptide, average SI = 4.4.

HXB2 Location gp160 (380–401)
Author Location gp120 (380–399 89.6)
Epitope GEFFYCNTAQLFNSTWNVTGN
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008
- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 1 out 7 individuals responded to this peptide.

HXB2 Location gp160 (381–395)
Author Location gp120 (IIIB)
Epitope EFFYCNTTQLFNNTW
Immunogen in vitro stimulation or selection

Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

HXB2 Location gp160 (388–402)
Author Location Env (388–402 HXB2)
Epitope TQLFNSTWFNSTWST
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DP4)
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, epitope processing, computational epitope prediction, dendritic cells
References Cohen *et al.* 2006

- Motif-based quantitative matrices binding predictions, binding assays and cellular assays were used to identify 4 HLA-DP4 epitopes by scanning the whole HIV-1 genome.
- 21 peptides were predicted to bind HLA-DP4, 17 of them did bind in binding assays, 6 of them were good binders. Of the 6 good binders, 4 peptides primed peptide-specific CD4+ T cell lines restricted to HLA-DP4 molecules.

HXB2 Location gp160 (391–405)
Author Location gp120 (IIIB)
Epitope FNNTWRLNHTEGTKGC
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

HXB2 Location gp160 (392–411)
Author Location gp120 (392–411 IIIB)
Epitope NSTWFNSTWSTEGSNNTEGS?
Epitope name G5
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 9.3.

HXB2 Location gp160 (394–408)
Author Location gp120 (394–408 IIIB, B10)
Epitope TWFNSTWSTKGSNNT
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location gp160 (399–413)
Author Location gp120 (399–413 IIIB, B10)
Epitope TWSTKGSNNTEGSDT
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location gp160 (404–423)
Author Location gp120 (400–419 89.6)
Epitope GTNGTEGNDIITLQCRIKQI
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse (H-2^d, H-2^k)
Keywords immunodominance
References Dai *et al.* 2001

- Promiscuous immunodominant epitopes in gp120 were mapped by overlapping peptides in CBA/J H-2^k and BALB/c H-2^d mice, and all were found to be in the outer domain, proximal to regions of structural disorder indicated by the crystal structure or by sequence divergence.
- This peptide was recognized by 4/10 CBA/J and 6/10 BALB/c mice with SI > 4, averaging 4.9 and 5.5 and is considered to be promiscuously immunodominant.
- Uniquely immunodominant sequences tended to be in the inner domain of the protein.

HXB2 Location gp160 (404–423)
Author Location gp120 (400–419 89.6)
Epitope GTNGTEGNDIITLQCRIKQI
Epitope name Peptide 38
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse
Donor MHC H-2k, H2-d
Keywords epitope processing, immunodominance
References Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.

- This peptide was reactive in 8/10 BALB/c mice tested, and in 6/10 CBA/J mice, and was considered one of the 3 immunodominant peptides identified that were shared in both mouse strains: RRNIIGDIRQAHCNISRAKW, NNTLQQIVIKLREKFRNKTI, GTNGTEGNDIITLQCRIKQI.

HXB2 Location gp160 (404–423)
Author Location gp120 (400–419 89.6)
Epitope GTNGTEGNDIITLQCRIKQI
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 3 out 7 individuals responded to this peptide.

HXB2 Location gp160 (405–420)
Author Location Env (1007)
Epitope SNNTVGNPIILPCRI
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This epitope is located in the V4C4 region of 1007 (US, clade B) and was recognized by 13 hybridomas with Vβ usage Vβ 4, 7, 8.1, 8.2, 10, 12 and not determined – one of the Vβ 8.2 was shown to utilize Vα 2.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (405–420)
Author Location Env (gp160) (1007)
Epitope SNNTVGNPIILPCRI
Subtype B
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* Env *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^b)
Assay type Cytokine production, CD4 T-cell Elispot - IFNγ
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization, vaccine antigen design
References Zhan *et al.* 2004

- To develop a polyvalent Env vaccine, subtype specific B and D T-helper epitopes were identified, and mixtures of strain 1007, clade B, or UG92005, clade D envelopes were given to C57BL/6J mice. Mice were intramuscularly immunized with recombinant DNA, then intraperitoneally with rVV and finally with env protein in CFA. A dilution of 1/100 could still elicit type specific responses, and responses persisted with different prime boost combinations.
- T-cell hybridoma 1007P3-23 was isolated from mice immunized with 1007, and it recognized the peptide SNNTVGNPIILPCRI of the V4/C4 region. The minimal, core peptide recognized by 10007P3-23 was NPIIL, a sequence not found in UG92005, which has a deletion in the core, so that the equivalent region in the D isolate is NNET—ITLQCRI
- Priming mixtures of 1007 and UG92005 induced both Env-specific (SNNTVGNPIILPCRI and AMYAPPIAGLIQCSS) and cross-reactive (PKVSFEPIPIHYCAP, C2, GNIRQAHCNVSKAKW, V3-C3) Th responses in murine spleen cells.

HXB2 Location gp160 (410–424)
Author Location Env
Epitope SSSIITIPCRIKQII
Subtype C
Immunogen vaccine

T-Helper CD4+

Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, previously not described was found within peptide SSSIITIPCRIKQII and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (410–429)
Author Location gp120 (410–429 PV22)
Epitope `GSDTITLPCRIKQFINMWQE`
Immunogen HIV-1 infection
Species (MHC) human (DR4)
References Callahan *et al.* 1990

- Synthetic peptides representing natural variants were used to test for recognition in the context DR4.

HXB2 Location gp160 (410–429)
Author Location gp120 (410–429 PV22)
Epitope `GSDTITLPCRIKQFINMWQE`
Immunogen HIV-1 infection
Species (MHC) human (DR4(Dw10))
References Polydefkis *et al.* 1990

- Human CD4+ T-cell clones lyse recombinant vaccinia virus-infected cells that synthesize envelope gp160.

HXB2 Location gp160 (412–431)
Author Location gp120 (412–431 IIIB)
Epitope `DTITLPCRIKQIINMWQKVG?`
Epitope name H2
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 5.7.

HXB2 Location gp160 (414–428)
Author Location Env
Epitope `ITIPCRIKQIINMWQ`
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, DTITLPCRIKQIINMWQKVG was found within peptides ITIPCRIKQIINMWQ and CRIKQIINMWQEVGR and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (414–433)
Author Location gp120 (410–429 89.6)
Epitope `ITLQCRIKQIINMWQKVGKA`
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.

- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 6 out 7 individuals responded to this peptide.

HXB2 Location gp160 (416–431)
Author Location gp120 (IIIB)
Epitope LPCRIKQIINMWQEVY
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

HXB2 Location gp160 (418–432)
Author Location Env
Epitope CRIKQIINMWQEVGR
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, DTITLPCRIKQIINMWQKVG was found within peptides ITIPCRIKQIINMWQ and CRIKQIINMWQEVGR and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (418–436)
Author Location Env (417–435)
Epitope CRIKQIINMWQGVGKAMYA
Immunogen HIV-1 infection
Species (MHC) human, chimpanzee
References Nehete *et al.* 1998b

- HIV-infected chimpanzees and HIV-positive patients show positive proliferative responses to multiple peptides from five conserved regions of the HIV-1 Env.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen HIV-1 infection
Species (MHC) human (DR)
References Baier *et al.* 1995

- Linked HIV-1 T1 and P18 peptides to anti-HLA-DR and anti-IgD Fab fragments to enhance uptake by antigen presenting cells and thus increase immunogenicity.

HXB2 Location gp160 (421–436)
Author Location
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen vaccine
Vector/Type: canarypox prime with recombinant protein boost *HIV component:* gp120
Species (MHC) human (DRB1*13)
Donor MHC DRB1*01, DRB1*13
Assay type proliferation
Keywords optimal epitope
References Okazaki *et al.* 2006

- KQIINMWQEVGKAMYA-specific human CD4+ T-cell line from a healthy Caucasian American volunteer immunized with a canarypox virus vector expressing gp120 and boosted with recombinant gp120 was developed and found to be restricted to DRβ1*13. Epitope enhancement with different amino acid substitutions was studied.
- Likely binding core for KQIINMWQEVGKAMYA was determined as WQEVGKAMY, based on single A or S substitutions that diminished recognition, and proliferation assay data using truncated peptides.
- HLA binding motif was studied using substituted peptides in anchor positions 1,4,6,9 from the N-terminus of WQEVGKAMY. In position 1, CD4+ response was reduced by kqiinm[w/ai]QEVGKAMYa substitutions, but not by kqiinm[w/f]QEVGKAMYa substitution suggesting a requirement of aromatic amino acid. In position 4, CD4 response was reduced by kqiinmMWQE[v/af]GKAMYa substitutions, but enhanced by kqiinmWQE[v/i]GKAMYa substitution, suggesting a requirement of aliphatic amino avid. In position 6, response was reduced by kqiinmWQEVG[k/ae]AMYa substitutions, but was enhanced by positively charged R substitution (kqiinmWQEVG[k/r]AMYa). In position 9, all peptides substituted with small, aromatic, or aliphatic amino acids (kqiinmWQEVGKAM[y/afi]a) induced enhanced response.
- The altered KQIINMWQE[v/i]GKAMYA peptide produced higher IFN-γ production that the original peptide, suggesting greater CD4 T-cell activation in a Th1 functional response.
- Triple substituted peptide KQIINMWQE[v/i]G[k/r]AM[y/a]A shifted the peak proliferative response to lower concentrations.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB
Species (MHC) mouse (H-2^d)

T-Helper CD4+

References Klinman *et al.* 1995
- Hybrid T1-V3 peptide activates IL-4 and IL-6 in a dose dependent manner.

HXB2 Location gp160 (421–436)
Author Location
Epitope KQIINMWQEVGKAMYA
Epitope name N16
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) mouse (H-2^d)
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008
- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- Peptide N16, KQIINMWQEVGKAMYA, was used as a specific antigen for ELISpot positive control. N16 was previously known to induce T-helper responses not only in mice but also in humans and monkeys. It is a previously known epitope that is a part of TCI fragment RIKQIINMWQEVGKAMYAPPISGQIR in this vaccine construct.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB
Species (MHC) mouse (H-2^k)
References Ahlers *et al.* 1997b
- first identified Th epitope in HIV.
- Alanine at position 436 (instead of E in wild-type) enhances MHC binding and antigenicity of peptide by several orders of magnitude.
- Vaccines with a CTL epitope linked to a more potent helper epitope yielded greatly enhanced CTL response relative to the wildtype helper epitope.
- T1 peptide linked to CTL epitopes in four vaccine constructs used to immunize mice: KQIINMWQEVGKAMYAPPISGQIRRIQRGPGRAFVTIGK, KQIINMWQEVGKAMYAPPISGQIRRIQRGPGRAFVTI, KQIINMWQAVGKAMYAPPISGQIRRIQRGPGRAFVTIGK, KQIINMWQAVGKAMYAPPISGQIRRIQRGPGRAFVTI.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB, B10)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen computer prediction
Species (MHC) mouse (H-2^d, H-2^k, H-2^s)
References Cease *et al.* 1987
- 1 of 2 functional epitopes identified using an amphipathic helix epitope prediction algorithm.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^d, H-2^k, H-2^{t4})
References Hale *et al.* 1989
- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

HXB2 Location gp160 (421–436)
Author Location gp160 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^d, H-2^k, H-2^s)
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a
- B10.BR (H-$2A^k$, E^k), B10.D2 (H-$2A^d$, E^d) and B10.S(9R) (H-$2A^s$, E^s) mice immunized with rec gp160 showed a proliferative response to this peptide.
- KQIINMWQEVGKAMYAPPISGQIR encompasses several murine Th epitopes including KQIINMWQEVGKAMYA and is referred to as a "multideterminant region" or cluster peptide.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB
Species (MHC) mouse (H-2Eα $E\beta^k$)
References Boehncke *et al.* 1993
- C3H $H2^k$ mice were used for immunization in the study because H-2^k mice are particularly good T1 responders – T1 can be presented by Eα $E\beta^k$ but not Eα $E\beta^b$ – the nature of the T1 class II molecular interaction was thoroughly explored.
- Alanine substitutions across peptide did not negatively affect MHC binding or effective presentation of epitope, except at three critical residues (432N, 435Q, 439K), however substitutions with larger side chains often diminished activity – only a few amino acids were found to be critical for class II interaction and for maintaining T-cell receptor specificity.
- A gain in potency was observed when 436E was replaced with A, suggesting that substitutions in positions that interfere with binding might allow the design of a more potent vaccine.

HXB2 Location gp160 (421–436)

HXB2 Location gp160 (421–436)
Author Location Env (421–436 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen vaccine
Vector/Type: peptide *Strain:* modified B clade IIIB *HIV component:* Env
Species (MHC) mouse (H-2E^k)
Assay type Cytokine production, Th support of CTL response
Keywords binding affinity, Th1
References Ahlers *et al.* 2001

- BALB/c and A.AL were immunized with an Env-peptide vaccine construct containing the CTL epitope P18IIIB and a T helper epitope.
- Substitution of Glu (wt) to Ala, kqiinmwqAvgkamya, caused increased affinity for MHC class II Ek. This resulted in the upregulation of CD40L in the responding Th cells, and shifted the response towards Th1. Increased Th responses stimulated DCs to produce higher levels of IL-12, and B7-1 and B7-2, thus enhance CTL responses.
- The modified epitope, T1A, elicited stronger protection against increasing doses of viral challenge with vaccinia expressing HIV-1 IIIB gp120 compared to the wildtype epitope T1.

HXB2 Location gp160 (421–436)
Author Location gp120 (426–441 IIIB)
Epitope KQFINMWQEWGKAMYA
Immunogen
Species (MHC) human
References Furci *et al.* 1997

- Epitope T1 variant: 9/11 exposed-uninfected individuals in this study had a proliferative response to a C5 peptide, but none reacted with this previously defined epitope.
- IIIB position 435 listed as W in this epitope as opposed to V in the sequence.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–433 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen HIV-1 infection
Species (MHC) human
Keywords responses in children, kinetics, Th1
References Wasik *et al.* 2000

- Th responses measured by IL-2 responses to P18 and T1 in HIV-1 infected infants were undetectable at less than 1 month of age, and remained low in children with AIDS symptoms, but increased with age in children with slowly progressive disease.
- The kinetics and intensity of the CTL activity during the first year of life was related to the child's ability to make Th1 responses.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–433 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen HIV-1 infection
Species (MHC) human
Keywords responses in children, Th1, Th2
References Wasik *et al.* 1997

- The breadth and intensity of the CTL response and the type of Th response was studied in seven rapidly progressing HIV-1 + infants.
- IL-2 and γ IFN production from Th1 cells correlated with the CTLp frequency against HIV-1 Gag, Env, Nef and Pol.
- IL-4 production from Th2 cells was inversely correlated with the CTLp frequency.
- The HIV-1 + children with strong CTL responses had levels of anti-CD3 MAb induction of Th1 cells comparable to those of uninfected children.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) human
References Berzofsky *et al.* 1988

- Proliferative response to T1 and T2 peptides in 14 immunized, uninfected humans.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB
Species (MHC) goat
References Palker *et al.* 1989

- Goats immunized with peptides containing V3 type-specific neutralizing determinants coupled to T1.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen HIV-1 infection
Species (MHC) human
References Clerici *et al.* 1989

- IL-2 production detection of Th lymphocytes from asymptomatic HIV-positive individuals.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen HIV-1 infection
Species (MHC) human
References Clerici *et al.* 1991a

- Peptides stimulate Th cell function and CTL activity in similar patient populations.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA

Epitope name T1
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) human
References Clerici *et al.* 1991b

- Immunizing uninfected individuals with rgp160 results in stronger Th response than does natural infection.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen
Species (MHC) human
References Clerici *et al.* 1992

- Cell-mediated immune response to HIV-1 peptides in HIV-1 exposed seronegative men.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Immunogen vaccine
Vector/Type: bacteriophage coat protein *Strain:* B clade MN *HIV component:* V3
Species (MHC) mouse
References di Marzo Veronese *et al.* 1994

- Epitope T1 was engineered into a filamentous bacteriophage coat protein, and the Th epitope stimulated Ab production to the V3 loop.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB
Species (MHC) chimpanzee
References Haynes *et al.* 1993

- Hybrid T1-V3 peptide immunogenicity reduced when the fusogenic domain of gp41 was added.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen HIV-1 infection
Species (MHC) human
References Clerici *et al.* 1997

- Used in a study of the influence of pentoxifylline on HIV specific T-cells.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen
Species (MHC) human
References Pinto *et al.* 1995

- CTL activity analyzed in parallel with Th reactivity in exposed but uninfected health care workers.

HXB2 Location gp160 (421–436)
Author Location gp160 (428–433 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human
Keywords immunodominance
References Wasik *et al.* 1999

- IL-2 responses associated with beta-chemokine expression were detectable at birth in the majority of uninfected infants born to HIV+ mothers, declining by age 6 months.
- T1 peptide: In both uninfected and infected infants of HIV-positive mothers, responses to the T1 peptide were more frequent than responses to P18 (RIQRGPGRAFVTIGK)
- T1 is a highly conserved epitope, whereas P18 has a higher mutation rate due to its location in the immunodominant V3 loop region.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen HIV-1 infection
Species (MHC) human
References Kaul *et al.* 1999

- Kenyan sex workers that remained seronegative were found to frequently have HIV-env peptide specific Th responses detected by an IL-2 assay (11/20 cases) and mucosal genital tract anti-HIV IgA (16/21 cases)
- Helper epitopes used in this study were noted to be previously described Clerici *et al.* [1989], and were not explicitly described in Kaul *et al.* [1999]

HXB2 Location gp160 (421–436)
Author Location gp120 (MN)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *Strain:* B clade MN
Species (MHC) human
References Bartlett *et al.* 1998

- C4-V3 PV (polyvalent HIV envelope synthetic peptide immunogen) consisted of T1 helper epitope presented in tandem with a V3 loop CTL epitope from one of four different North American strains.
- This was a pilot phase I study involving vaccination of ten HIV-infected subjects who were HLA-B7-positive.
- Enhanced lymphoproliferative response to peptide was observed in 5/8 vaccinees – increase in neutralizing antibody responses in 4/8 vacinees.

HXB2 Location gp160 (421–436)
Author Location gp120
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human

Keywords subtype comparisons, responses in children, mother-to-infant transmission
References Kuhn *et al.* 2001a

- In a S. African perinatal transmission study, 33% (33/86) of cord blood samples from infants with seropositive mothers produced T-helper responses (measured by a bioassay measuring IL2 production in a murine cell line and confirmed with a proliferation assay) against a peptide cocktail containing Th epitopes P18 MN, P18 IIIB, T1, T2, and TH4.
- The mothers were predominantly infected with subtype C, but the T help response was detectable in a number of cord blood samples despite using peptides based on B subtype reagents.
- 3/33 infants with cord blood T help responses to Env were infected *in utero*, 2/33 were lost to follow up, and 28/33 were not infected. 6/53 of the infants with cord blood that was unresponsive to Env peptide stimulation were infected before delivery, and 8/47 contracted HIV intrapartum or via breastfeeding.
- Measurable HIV specific T help responses elicited in the immunologically immature newborn, possibly in response to *in utero* exposure, are associated with a protective natural immunity that helps block mother-infant transmission of HIV-1.

HXB2 Location gp160 (421–436)
Author Location gp120 (428–443 RF)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen HIV-1 infection
Species (MHC)
Keywords epitope processing
References de Lorimier *et al.* 1994

- Proton NMR spectroscopy was employed to analyze the solution conformation of a hybrid peptide, T1-SP10RF, in order to better understand the immunogenicity of its' T helper (KQIINMWQEVGKAMYA, CTRPNNNTRKSI), CTL (SITKGPGRVIYATG) and B-cell epitopes (RKSITKGPGRVIYATG).
- As a free peptide, the T1 segment, a T-helper epitope is in an extended conformation with nascent helical conformation. It may form a beta strand in native gp120, and a nonnative conformation may account for the inability of free T1 peptide to elicit antibody responses, in contrast to the T1 segment in native gp120. It lacks random-coil conformations, and it is suggested that this may make the peptide less susceptible to complete proteolytic degredation, and be favored within epitopes.

HXB2 Location gp160 (421–436)
Author Location Env (428–443 IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC)
Assay type Cytokine production
Keywords mother-to-infant transmission
References Clerici *et al.* 1993a

- Cord blood samples in 8/23 infants with HIV+ mothers showed IL-2 production in response to peptides from HIV-1 gp1260, demonstrating that Th cell priming to HIV env determinants can occur in utero. HIV-specific Th immunity in utero may be protective, as none of the 8 with HIV-1 specific Th activity became infected, while 3/15 infants with no detectable Th activited were infected.
- PBL from 10/21 of the mothers showed HIV-1 specific Th activity through IL-2 production in response to Env peptides.

HXB2 Location gp160 (421–436)
Author Location Env (IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC)
Assay type Cytokine production
References Clerici *et al.* 1994a

- Six of eight HIV-exposed health care workers had transient HIV-specific T-helper responses after percutaneous exposure to HIV, responding to two or more Env peptides among the set T1, T2, Th4.1, P18IIIB and P18MN. Responses were lost after 12-56 weeks. The HIV-specific Th responses occurred without seroconversion or PCR evidence for infection.
- Six of the eight HIV-exposed individuals responded to two or more peptides, whereas, only one individual exposed to HIV-negative blood responded to one peptide.

HXB2 Location gp160 (421–436)
Author Location HIV-1 (IIIB)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Subtype B
Immunogen HIV-1 infection
Species (MHC)
Assay type Cytokine production
References Clerici *et al.* 1994b

- IL-10-specific mRNA was upregulated in PBMC from asymptomatic, HIV-infected (HIV+) patients, and was particularly high in those with severely compromised Th cells function. Th response to HIV peptides *in vitro* could be restored by IL-10 Ab.

HXB2 Location gp160 (421–436)
Author Location Env (428–443)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type proliferation
Keywords responses in children, mother-to-infant transmission
References Kuhn *et al.* 2001b

- T helper proliferative responses in cord blood at delivery to a cocktail of HIV envelope peptides were infrequent (1/41) among infants whose HIV-positive mothers received antiretroviral prophylaxis at delivery to prevent transmission. Responses were 10 times more frequent among infants of HIV-seropositive women who had no antiretroviral treatment (7/29). Reductions of HIV-specific responses occurred despite persistance of detectable HIV RNA in the mothers at delivery.

T-Helper CD4+

- The reduction of Th responses in newborns raises the possibility that anti-retrovial exposure during pregnancy may block subsequent immune protection. The authors point two relevant citations that showed ARV exposed infants had a more rapid course of progression (Kuhn *et al.*, JID 182:104 (2000)), but were at no greater risk of infection due to subsequent breast feeding (Ditrame *et al.*, Lancet 354:2050 (1999)).

HXB2 Location gp160 (421–436)
Author Location Env (gp160) (421–436)
Epitope KQIINMWQEVGKAMYA
Epitope name T1
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type proliferation
Keywords responses in children, variant cross-recognition or cross-neutralization
References Meddows-Taylor *et al.* 2004

- Viral isolates (gp160) from 16 vertically HIV-1 infected children (8 T-helper cell Env responders and 8 non-responders) were analyzed for variation after comparison with Env peptide sequences (conserved regions T1, T2 and TH4.1, hypervariable regions P18 MN and P181 IIIB) used for in vitro stimulation.
- No correlation between the age, clinical category (mild or severe), HIV-1 viral load and the degree of epitope variation was established.

HXB2 Location gp160 (421–444)
Author Location gp120 (428–451 IIIB)
Epitope KQIIMNWQEVGKAMYAPPISGQIR
Epitope name T1
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB
Species (MHC) mouse (H-2^d)
References Shirai *et al.* 1996a

- Linked to a CTL epitope from hepatitis C virus, induced CD4+ helper cells producing IL-2.

HXB2 Location gp160 (421–444)
Author Location gp160 (428–451 IIIB)
Epitope KQIINMWQEVGKAMYAPPISGQIR
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) human, mouse (H-2^b, H-2^d, H-2^k, H-2^s)
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- KQIINMWQEVGKAMYAPPISGQIR encompasses several murine Th epitopes and is referred to as a "multideterminant region" or cluster peptide.
- Six multideterminant region cluster peptides were evaluated Th responses in different MHC/HLA backgrounds after vaccination of mice with gp160, or in infected people.
- This cluster peptide elicited proliferative responses in cells from all H-2 haplotypes tested: B10.BR mice (H-$2A^k$, E^k), B10.D2 mice (H-$2A^d$, E^d), B10.A(5R) mice (H-$2A^b$, E^b), and B10.S(9R) mice (H-$2A^s$, E^s)
- IL-2 production in response to this peptide was observed in 73% (8/11) of asymptomatic HIV-infected individuals.

HXB2 Location gp160 (421–444)
Author Location Env (gp160) (HIV-1 IIIB)
Epitope KQIINMWQEVGKAMYAPPISGQIR
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* Env *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72), Montanide (ISA 51)
Species (MHC) macaque
Assay type proliferation
Keywords mucosal immunity
References Belyakov *et al.* 2001

- Intrarectal vaccination with a Th and CTL peptide vaccine provided better protection against intrarectal challenge with pathogenic SHIV-Ku1 than subcutaneous administered vaccine. In some animals after the initial viremia, viral loads were diminished to undetectable levels in the blood and intestine, and CD4+ T cells were better preserved.
- The CD4 T-cell proliferative response correlated with the level of the CTL response.

HXB2 Location gp160 (423–440)
Author Location gp120 (428–445)
Epitope FINMWQEVGKAMYAPPIS
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Caruso *et al.* 1997

- As HIV-1-infected individuals progress to disease, T-cells show reduced ability to proliferate in response to HIV antigen, but retain the ability to express the activation antigens CD25 and CD71.
- The ability to express activation markers in response to HIV is retained, but the response to tetanus toxoid recall antigen is lost.
- This study investigated CD25 and CD71 expression in PBMC from patients at various stages of progression, measuring the response to *in vitro* stimulation by peptide cocktail containing four antigenic Env peptides, or p17 and p24.

HXB2 Location gp160 (424–438)
Author Location gp120 (424–438 IIIB, B10)
Epitope INMWQEVGKAMYAPP
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location gp160 (425–439)
Author Location gp160 (432–446 IIIB)
Epitope NMWQEVGKAMYAPPI
Immunogen vaccine

Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^s)
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- B10.S(9R) (H-2A^s, E^s) mice immunized with rec gp160 showed a proliferative response to this peptide.
- KQIINMWQEVGKAMYAPPISGQIR encompasses several murine Th epitopes including NMWQEVGKAMYAPPI and is referred to as a "multideterminant region" or cluster peptide.

HXB2 Location gp160 (425–439)
Author Location gp120 (432–446 IIIB)
Epitope `NMWQEVGKAMYAPPI`
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^{t4})
References Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

HXB2 Location gp160 (426–441)
Author Location gp120 (IIIB)
Epitope `MWQEVGKAMYAPPIGC`
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

HXB2 Location gp160 (430–444)
Author Location gp120 (437–451 IIIB)
Epitope `VGKAMYAPPISGQIR`
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^d, H-2^{i5}, H-2^k, H-2^{t4})
References Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

HXB2 Location gp160 (430–444)
Author Location gp120 (430–444)
Epitope `VGKAMYAPPISGQIR`
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) mouse (H-2^d, H-2^k)
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- VGKAMYAPPISGQIR is a previously known epitope that is a part of TCI fragment RIKQIINMWQEVGKAMYAPPISGQIR in this vaccine construct.

HXB2 Location gp160 (430–444)
Author Location gp160 (437–451 IIIB)
Epitope `VGKAMYAPPISGQIR`
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^b, H-2^d, H-2^k, H-2^s)
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in cells from all H-2 haplotypes tested: B10.BR mice (H-2A^k, E^k), B10.D2 mice (H-2A^d, E^d), B10.A(5R) mice (H-2A^b, E^b), and B10.S(9R) mice (H-2A^s, E^s)
- KQIINMWQEVGKAMYAPPISGQIR encompasses several murine Th epitopes including VGKAMYAPPISGQIR and is referred to as a "multideterminant region" or cluster peptide.

HXB2 Location gp160 (430–444)
Author Location Env
Epitope `VGRAMYAPPIKGNIT`
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.

- A CD4 helper Env epitope, VGKAMYAPPISGQIRCSS-NITGLL was found within peptides VGRAMYAPPIKGNIT, MYAPPIKGNITCKSN and PIKGNITCKSNITGL and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (430–453)
Author Location gp120 (430–453)
Epitope VGKAMYAPPISGQIRCSSNITGLL
Immunogen vaccine
Vector/Type: protein *HIV component:* gp160
Species (MHC) mouse (H-2^b)
Keywords epitope processing
References Sjolander *et al.* 1996

- Study demonstrates that T-cell determinants from glycoproteins can depend on the glycosylation of the protein.
- Peptide stimulation of an *in vitro* proliferative response required *in vivo* priming with glycosylated protein.
- Local glycosylation sites thought not to be part of the epitope, but may be important for epitope processing.

HXB2 Location gp160 (432–451)
Author Location gp120 (432–451 IIIB)
Epitope KAMYAPPISGQIRCSSNITG?
Epitope name H4
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 6.3.

HXB2 Location gp160 (433–447)
Author Location Env (UG92005)
Epitope AMYAPPIAGLIQCSS
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This epitope is located in the C4 region of UG92005 (UG, clade D) and was recognized by ten hybridomas with Vβ usage Vβ 6, 8.1, 8.2, 13, 14 and not determined – among the ND Vβ set, three Vαs were identified, Vα 2, 8, and 11.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (433–447)
Author Location Env (gp160) (UG92005)
Epitope AMYAPPIAGLIQCSS
Subtype D
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* Env *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^b)
Assay type Cytokine production, CD4 T-cell Elispot - IFNγ
Keywords vaccine-induced epitopes, variant cross-recognition or cross-neutralization, vaccine antigen design
References Zhan *et al.* 2004

- To develop a polyvalent Env vaccine, subtype specific B and D T-helper epitopes were identified, and mixtures of strain 1007, clade B, or UG92005, clade D envelopes were given to C57BL/6J mice. Mice were intramuscularly immunized with recombinant DNA, then intraperitoneally with rVV and finally with env protein in CFA. A dilution of 1/100 could still elicit type specific responses, and responses persisted with different prime boost combinations.
- T-cell hybridoma UGP2-17 was isolated from mice immunized with env sequence UG92005 (clade D), and it recognized the C4/V4 region peptide AMYAPPIAGLIQCSS. The minimal peptide recognized by 10007P3-23 was PPIAGLIQ, which matched only 5/8 residues in the B clade isolate, ppiRgQiK.

T-Helper CD4+

- Priming with 1007 and UG env's induced both Env-specific (SNNTVGNPIILPCRI and AMYAPPIAGLIQCSS) and cross-reactive (PKVSFEPIPIHYCAP, C2, GNIRQAHC-NVSKAKW, V3-C3) Th responses in murine spleen cells.

HXB2 Location gp160 (434–448)
Author Location Env
Epitope MYAPPIKGNITCKSN
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, VGKAMYAPPISGQIRCSS-NITGLL was found within peptides VGRAMYAPPIKGNIT, MYAPPIKGNITCKSN and PIKGNITCKSNITGL and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (434–453)
Author Location gp120 (430–449 89.6)
Epitope MYAPPITGQIRCSSNITGLL
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 1 out 7 individuals responded to this peptide.

HXB2 Location gp160 (436–451)
Author Location gp120 (IIIB)
Epitope APPIGGQISCSSNITY
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

HXB2 Location gp160 (438–452)
Author Location Env
Epitope PIKGNITCKSNITGL
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, VGKAMYAPPISGQIRCSS-NITGLL was found within peptides VGRAMYAPPIKGNIT, MYAPPIKGNITCKSN and PIKGNITCKSNITGL and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (438–460)
Author Location gp120 (443–465 NL43)
Epitope PISGQIRCSSNITGLLLTRDGGN
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43 *HIV component:* gp120, gp160
Species (MHC) human
References Sitz *et al.* 1999

- There was a great breadth of proliferative response to env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients.
- Close to 40% of vaccinees had a stimulation index of greater than 5 to this peptide.

T-Helper CD4+

HXB2 Location gp160 (439–448)
Author Location gp120 (151–160 W6.ID)
Epitope IGGQIRCSSN
Immunogen vaccine
Vector/Type: protein *Strain:* B clade W61D *HIV component:* gp120 *Adjuvant:* MPL-SE adjuvant, QS21
Species (MHC) human
References Jones *et al.* 1999

- HIV-1 specific T-cell lines isolated from an HIV seronegative volunteer vaccinated with rgp120 and a QS21/MPL adjuvant.
- One T-cell line responds to two overlapping peptides, and the region of overlap is IGGQIRCSSN.
- The IIIB version of the first reactive peptide, EVGKAMYAPPIGGQIRCSSN, has a single substitution and induces proliferation as well as the original W61D peptide: evgkamyappiSgqircssn.

HXB2 Location gp160 (439–461)
Author Location Env (438–460)
Epitope IRGQIRCSSNITGLLLTRDGGNN
Epitope name HIV_env_DRB0101_1
Subtype M
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type T-cell Elispot
Keywords computational epitope prediction
References De Groot *et al.* 2004

- Bioinformatic tools (EpiMatrix and Conservatrix) were employed to predict 9 highly conserved and promiscuous class II restricted T helper epitopes from HIV-1 env sequences for a cross-clade polyepitope vaccine. 10/34 HIV-1 infected patients induced Th1 immune responses to 8/9 study peptides.
- 2/28 subjects tested responded to this peptide.
- Class II peptides containing putative epitopes were selected to favor DRB0101 presentation, as there is a transgenic mouse model for this allele for future vaccine studies. The highest scoring DRB0101 sequence within this peptide was QIRCSSNIT.

HXB2 Location gp160 (446–461)
Author Location gp120 (IIIB)
Epitope SSNITGLLLTRDGGTC
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

HXB2 Location gp160 (452–471)
Author Location gp120 (452–471 IIIB)
Epitope LLLTRDGGNSNNESEIFRPG?
Epitope name I1
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 nonresponders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 2/15 responders recognized this peptide, average SI = 3.5.

HXB2 Location gp160 (456–470)
Author Location gp120 (IIIB)
Epitope RDGGTNVTNDTEVFRC
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

HXB2 Location gp160 (459–473)
Author Location gp120 (459–473 IIIB, B10)
Epitope GNSNNESEIFRPGGG
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location gp160 (466–480)
Author Location Env
Epitope ETFRPGGGDMRNNWR
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.

- A CD4 helper Env epitope, FRPGGGDMRDNWRSEL was found within peptide ETFRPGGGDMRNNWR and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (468–483)
Author Location gp120 (466–481)
Epitope FRPGGGDMRDNWRSEL
Immunogen HIV-1 infection
Species (MHC) human
References Krowka *et al.* 1990

- Conjugation of HIV peptides to liposomes and rIL-2 stimulation may enhance cell-mediated responses.

HXB2 Location gp160 (472–491)
Author Location gp120 (472–491 IIIB)
Epitope GGDMRDNWRSELYKYKVVKI?
Epitope name I3
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 2/15 responders recognized this peptide, average SI = 7.2.

HXB2 Location gp160 (474–488)
Author Location gp120 (474–488 IIIB, B10)
Epitope DMRDNWRSELYKYKV
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location gp160 (476–490)
Author Location gp120 (483–497 IIIB)
Epitope RDNWRSELYKYKVVK
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^{d}, H-2^{t4})
References Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

HXB2 Location gp160 (476–490)
Author Location gp160 (483–497 IIIB)
Epitope RDNWRSELYKYKVVK
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^{k}, H-2^{s})
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in B10.BR mice (H-2A^{k} and B10.S(9R) mice (H-2A^{s}, E^{s})
- RDNWRSELYKYKVVKIEPLGVAPT encompasses several murine Th epitopes including RDNWRSELYKYKVVK and is referred to as a "multideterminant region" or cluster peptide.

HXB2 Location gp160 (476–499)
Author Location gp160 (483–506 IIIB)
Epitope RDNWRSELYKYKVVKIEPLGVAPT
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) human, mouse (H-2^{b}, H-2^{d}, H-2^{k}, H-2^{s})
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- RDNWRSELYKYKVVKIEPLGVAPT encompasses several murine Th epitopes and is referred to as a "multideterminant region" or cluster peptide.
- Six multideterminant region cluster peptides were evaluated Th responses in different MHC/HLA backgrounds after vaccination of mice with gp160, or in infected people.
- This cluster peptide elicited proliferative responses in cells from all H-2 haplotypes tested: B10.BR mice (H-2A^{k}, E^{k}), B10.D2 mice (H-2A^{d}, E^{d}), B10.A(5R) mice (H-2A^{b}, E^{b}), and B10.S(9R) mice (H-2A^{s}, E^{s})
- IL-2 production in response to this peptide was observed in 52% (14/27) of asymptomatic HIV-infected individuals.

HXB2 Location gp160 (479–498)
Author Location gp120 (481–500 MN)
Epitope WRSELYKYKVVTIEPLGVAP
Epitope name 2013
Subtype B
Immunogen vaccine
Vector/Type: DNA, protein *Strain:* B clade MN *HIV component:* gp120 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) guinea pig
Keywords vaccine-specific epitope characteristics, Th1
References Chattergoon *et al.* 2002

- Hartley guinea pigs were intradermally injected with either recombinant protein or plasmid expressed gp120 and monitored for delayed type hypersensitivity (DTH) responses after vaccination, which are related to Th1 T-cell responses. CFA did not augment responses in animals vaccinated with plasmid.
- A total of 7 gp120 peptides elicited a delayed type hypersensitivity (DTH) response after vaccination, out of a set of 60 overlapping peptides that spanned gp120. The vaccine delivery system, DNA versus rec protein, resulted in the recognition of distinct peptides.

T-Helper CD4+

- 0/5 animals vaccinated with rec gp120 responded by DTH to this peptide, while 6/6 vaccinated with plasmid gp120 DNA responded.

HXB2 Location gp160 (481–498)
Author Location gp160 (481–498 clade B consensus)
Epitope SELYLYKVVKIEPLGVAP
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (DRB1*0101, DRB1*0401, DRB1*0405, DRB1*0701, DRB1*1101, DRB1*1302, DRB1*1501, DRB5*0101)
Country Brazil
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 brazilian HIV-1 chronically infected individuals.
- While the reacting peptide was SELYLYKVVKIEPLGVAP, shorter LYLYKVVKIEPLGV was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

HXB2 Location gp160 (482–496)
Author Location Env
Epitope ELYKYKVVEIKPLGV
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.
- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, previously not described was found within peptides ELYKYKVVEIKPLGV and YKVVEIKPLGVAPTT and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (482–501)
Author Location gp120 (482–501 IIIB)
Epitope ELYKYKVVKIEPLGVAPTKA
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* Env
Species (MHC) macaque
References Lekutis *et al.* 1997

- HIV-1 env DNA vaccine induced Th cell response to this epitope in a rhesus monkey.
- Epitope was recognized by both monkeys used in this study.

HXB2 Location gp160 (482–501)
Author Location gp120 (482–501 IIIB)
Epitope ELYKYKVVKIEPLGVAPTKA?
Epitope name I4
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 3/15 responders recognized this peptide, average SI = 6.0.

HXB2 Location gp160 (483–502)
Author Location gp120 (480–499 89.6)
Epitope LYKYKVVRIEPIGVAPTRAK
Epitope name Peptide 46
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse
Donor MHC H-2k, H2-d
Keywords epitope processing, immunodominance
References Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was reactive in 7/10 BALB/c mice tested, and in only 1/10 CBA/J mice.

HXB2 Location gp160 (483–502)
Author Location gp120 (480–499 89.6)
Epitope LYKYKVVRIEPIGVAPTRAK

T-Helper CD4+

Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 3 out 7 individuals responded to this peptide.

HXB2 Location gp160 (484–496)
Author Location gp120 (484–496 HXB2)
Epitope YKYKVVKIEPLGV
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade HXB2 *HIV component:* Env
Species (MHC) macaque (DR*W201)
References Lekutis & Letvin 1998

- Variants of this epitope with substitutions at position 490(K) retained ability to bind to MHC class II, but failed to induce proliferation/cytokine secretion in HIV-1 env-specific CD4+ Th cells.
- The modified peptide antagonized the wildtype peptide-induced proliferative response.

HXB2 Location gp160 (484–498)
Author Location gp120 (484–498 IIIB, B10)
Epitope YKYKVVKIEPLGVAP
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location gp160 (484–499)
Author Location gp120 (492–506 IIIB)
Epitope CKYKVVKIEPLGVAPT
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^{d}, H-2^{i5}, H-2^{k}, H-2^{t4})
References Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

HXB2 Location gp160 (485–499)
Author Location gp160 (492–506 IIIB)
Epitope KYKVVKIEPLGVAPT
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^{b}, H-2^{d}, H-2^{k}, H-2^{s})
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in cells from all H-2 haplotypes tested: B10.BR mice (H-2A^{k}, E^{k}), B10.D2 mice (H-2A^{d}, E^{d}), B10.A(5R) mice (H-2A^{b}, E^{b}), and B10.S(9R) mice (H-2A^{s}, E^{s})
- RDNWRSELYKYKVVKIEPLGVAPT encompasses several murine Th epitopes including KYKVVKIEPLGVAPT and is referred to as a "multideterminant region" or cluster peptide.

HXB2 Location gp160 (485–500)
Author Location gp120 (IIIB)
Epitope KYKVIKIEPLGIAPTC
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

HXB2 Location gp160 (486–494)
Author Location gp120 (486–494 IIIB)
Epitope YKVVKIEPL
Immunogen SHIV infection
Species (MHC) macaque (DRB*W201)
References Lekutis & Letvin 1997

- C5 region minimal epitope determined through fine epitope mapping.

HXB2 Location gp160 (486–500)
Author Location Env
Epitope YKVVEIKPLGVAPTT
Subtype C
Immunogen vaccine
Vector/Type: vaccinia, modified vaccinia Ankara (MVA), poxvirus, DNA prime with poxvirus boost, attenuated poxvirus vector NYVAC *Strain:* C clade 97CN54 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Switzerland
Assay type proliferation, CD8 T-cell Elispot - IFNγ, Other
Keywords vaccine-induced epitopes, vaccine antigen design
References Harari *et al.* 2008

- A poxvirus based vaccine against HIV-1 subtype C was characterized and found to be efficacious. DNA prime, NYVAC boost vaccine containing Env, Gag, Pol, and Nef as a polypeptide immunogen elicited T-cell responses in 90% vaccinees.

- Vaccine induced T-cell response was of a high magnitude and polyfunctional with respect to CD4 and CD8 cell activation. Each responding vaccinee elicited broad responses to multiple epitopes, especially in Env, that persisted.
- A CD4 helper Env epitope, previously not described was found within peptides ELYKYKVVEIKPLGV and YKVVEIKPLGVAPTT and elicited immune response.
- 9 novel Env epitopes, both CTL and helper, were found to be targeted after vaccination in subjects.

HXB2 Location gp160 (487–512)
Author Location gp120 (494–518 IIIB)
Epitope KVVKIEPLGVAPTKAKRRVVQREKRC
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB
Species (MHC) mouse
References Goodman-Snitkoff *et al.* 1990

- Identification of putative Th epitopes that stimulate an antibody response in peptide immunized mice.

HXB2 Location gp160 (492–512)
Author Location gp120 (492–512 IIIB)
Epitope EPLGVAPTKAKRRVVQREKRA?
Epitope name I5
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 4.9.

HXB2 Location gp160 (493–511)
Author Location gp120 (490–508 89.6)
Epitope PIGVAPTRAKRRTVQREKR
Epitope name Peptide 47
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse
Donor MHC H-2k, H2-d
Keywords epitope processing, immunodominance
References Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was reactive in only 2/10 BALB/c mice tested, and in 8/10 CBA/J mice.

HXB2 Location gp160 (493–511)
Author Location gp120 (490–508 89.6)
Epitope PIGVAPTRAKRRTVQREKR
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords immunodominance, structure
References Mirano-Bascos *et al.* 2008

- This study presents helper T-cell epitope mapping data on 7 HIV patients, performed with 47 overlapping 20-mer peptides spanning gp120 sequence, strain 89.6.
- Immunodominance patterns measured as either the number of IFN-γ producing cells or the number of responding individuals, were similar to the immunodominance patterns previously described in mice, and correlated to the structure of the protein antigen.
- Epitopes were found adjacent to flexible protein regions and variable sequences. Immunodominant epitopes were found to be located primarily in the outer domain, an average of 12 residues C-terminal to flexible loops. In the less immunogenic inner domain, epitopes were found an average of five residues N-terminal to conserved regions of the protein, once again placing the epitopes C-terminal to flexible loops.
- 6 out 7 individuals responded to this peptide.

HXB2 Location gp160 (499–511)
Author Location gp120 (IIIB)
Epitope TKAKRRVVEREKR
Immunogen in vitro stimulation or selection
Species (MHC) human (DR)
References Wilson *et al.* 1997b

- Thought to be a mimic of a HLA class II DR β chain variable region.
- Response to this epitope may cause a breakdown of self-tolerance.
- Presentation of epitope induced autoreactive T-cell lines in PBMC from uninfected donors.
- Suppression of proliferation to soluble antigens by the CD8+ fraction of TKAKRRVVEREKR stimulated T-cells was observed.

HXB2 Location gp160 (499–519)
Author Location gp41 (MN)
Epitope TKAKRRVVQREKRAAIGALF
Epitope name TF20
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type Cytokine production, proliferation, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords HAART, ART, acute/early infection
References Malhotra *et al.* 2003

T-Helper CD4+

- 92 acute- or early-HIV infected subjects were tested for Env- and Gag-specific Th responses. There was an overall low probability of detecting HIV-1-specific Th responses, Env responses were rare and (5%) and only detected very early in infection, probably reflecting a low frequency of response and impaired lymophoproliferative capacity, not viral escape. Gag-specific Th responses were observed more frequently (16%), were found throughout the acute and early infection phases, and predominated after ARV therapy.
- This epitope is one of six Env-specific Th responses detected in one patient 11 days post-infection that were studied in detail. These Th reponses were not detected at subsequent time points, despite the Env specific Th cells being maintained as detected by TCR clonal transcripts, and the epitope sequence being maintained in Env.

HXB2 Location gp160 (512–534)
Author Location
Epitope AVGIGAVFLGFLGAAGSTMGAAS
Epitope name HIV-VAX-1060
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 1/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was FLGFLGAAG.

HXB2 Location gp160 (519–543)
Author Location gp41 (519–543)
Epitope FLGFLGAAGSTMGAASLTLTVQARC
Immunogen vaccine
Vector/Type: peptide
Species (MHC) mouse ($H\text{-}2^{bxk}$, $H\text{-}2^{sxd}$)
References Sastry & Arlinghaus 1991

- Peptides induced T-cell proliferative response to immunizing peptide and to gp160.

HXB2 Location gp160 (519–543)
Author Location Env (519–543)
Epitope FLGFLGAAGSTMGAASLTLTVQARC
Immunogen vaccine
Vector/Type: peptide
Species (MHC) macaque
References Nehete *et al.* 1993

- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice, and in rhesus monkeys.
- Proliferative response to this peptide was observed in 3/3 immunized rhesus monkeys.

HXB2 Location gp160 (519–543)
Author Location Env (519–543)
Epitope FLGFLGAAGSTMGAASLTLTVQARQ
Immunogen HIV-1 infection
Species (MHC) human, chimpanzee
References Nehete *et al.* 1998b

- HIV-infected chimpanzees and HIV-positive patients show positive proliferative responses to multiple peptides from five conserved regions of the HIV-1 Env.

HXB2 Location gp160 (547–561)
Author Location gp41 (547–561 IIIB, B10)
Epitope GIVQQQNNLLRAIEA
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location gp160 (562–576)
Author Location gp41 (562–576 IIIB, B10)
Epitope QQHLLQLTVWGIKQL
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location gp160 (562–576)
Author Location
Epitope QQHLLQLTVWGIKQL
Immunogen
Species (MHC)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 25/50 Brazilian sequences; variant QQHmLQLTVWGIKQL has high frequency in subtypes B, C, and BF recombinant sequences.

HXB2 Location gp160 (570–589)
Author Location gp41 (MN)
Epitope VWGIKQLQARVLAVERYLKD
Epitope name VD20
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DR)
Assay type Cytokine production, proliferation, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
References Malhotra *et al.* 2003

- 92 acute- or early-HIV infected subjects were tested for Env- and Gag-specific Th responses. There was an overall low probability of detecting HIV-1-specific Th responses, Env responses were rare and (5%) and only detected very early in infection, probably reflecting a low frequency of response and impaired lymophoproliferative capacity, not viral escape. Gag-specific Th responses were observed more frequently

(16%), were found throughout the acute and early infection phases, and predominated after ARV therapy.
- This epitope is one of six Env-specific Th responses detected in one patient 11 days post-infection that were studied in detail. The CD4+ clones showed MHC-restricted cytotoxicity and secreted high levels of cytokines when stimulated. These Th reponses were not detected at subsequent time points, despite the Env specific Th cells being maintained as detected by TCR clonal transcripts, and the epitope sequence being maintained in Env.
- This peptide showed promiscuous binding to DRB1*0101, DRB1*1101, DRB1*1302, DRB1*0701, DRB1*0801 DRB4*0101 DRB5*01.

HXB2 Location gp160 (572–591)
Author Location gp41 (572–591)
Epitope `GIKQLQARILAVERYLKDQQ`
Immunogen vaccine
Vector/Type: peptide
Species (MHC) mouse (H-2^b, H-2^d)
References Brown *et al.* 1995
- This peptide was a good immunogen in BALB/c and CBA mice, producing a strong proliferative response.
- At least one of the four residues GIKQ enhances stimulation, and in CBA mice these residues influence the ability to prime T-cells *in vivo*.
- QLQARILAVERY stimulated the greatest *in vitro* T-cell response.
- VERYLKDQQ was the minimal reactive sequence recognized by a T-cell line.

HXB2 Location gp160 (576–591)
Author Location gp41 (576–591)
Epitope `LQARILAVERYLKDQQ`
Immunogen vaccine
Vector/Type: peptide
Species (MHC) mouse (H-2^b, H-2^d)
References Brown *et al.* 1995
- This peptide was a poor immunogen in BALB/c and CBA mice used in this experiment, producing a weak proliferative response.

HXB2 Location gp160 (578–608)
Author Location gp41 (585–615 IIIB)
Epitope `ARILAVERYLKDQQLLGIWGCSGKLICTTAV`
Immunogen vaccine
Vector/Type: peptide
Species (MHC) mouse
References Goodman-Snitkoff *et al.* 1990
- Identification of putative Th epitopes that can stimulate an antibody response in peptide immunized mice.

HXB2 Location gp160 (579–601)
Author Location gp41 (579–601)
Epitope `RILAVERYLKDQQLLGGIWGCSGK`
Immunogen vaccine
Vector/Type: peptide
Species (MHC) mouse (H-2^b, H-2^d)
References Brown *et al.* 1995
- This peptide was a good immunogen in BALB/c and CBA.
- This peptide produced a strong Th response in both mice strains which was more responsive towards GIKQLQARILAVERYLKDQQ and LQARILAVERYLKDQQ than to immunizing peptide.

HXB2 Location gp160 (579–604)
Author Location gp41 (584–609 LAI)
Epitope `RILAVERYLKDQQLLGIWGCSGKLIC`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989
- Stimulates T-cell proliferation in HIV-infected donors.

HXB2 Location gp160 (586–597)
Author Location Env (586–598)
Epitope `YLRDQQLLGIWG`
Immunogen HIV-1 infection
Species (MHC) human, chimpanzee
References Nehete *et al.* 1998b
- HIV-infected chimpanzees and HIV-positive patients show positive proliferative responses to multiple peptides from five conserved regions of the HIV-1 Env.

HXB2 Location gp160 (586–598)
Author Location Env (586–598)
Epitope `YLRDQQLLGIWGC`
Immunogen vaccine
Vector/Type: peptide
Species (MHC) macaque, mouse
References Nehete *et al.* 1993
- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice.
- Proliferative response to this peptide was observed in 1/3 immunized rhesus monkeys, with a weak transient response in the other two.

HXB2 Location gp160 (593–604)
Author Location gp41 (598–609 LAV-1)
Epitope `LGLWGCSGKLIC`
Immunogen vaccine
Species (MHC) mouse (H-2^d)
References Schrier *et al.* 1988
- Murine T-dependent B-cell response – 7/29 had a proliferative response to this peptide.

HXB2 Location gp160 (593–604)
Author Location gp41 (593–604 IIIB)
Epitope `LGIWGCSGKLIC`
Immunogen HIV-1 infection
Species (MHC) human
References Bell *et al.* 1992
- Elicits T-cell proliferation and B cell responses, but only during the asymptomatic phase of HIV infection.

HXB2 Location gp160 (593–604)
Author Location
Epitope `LGIWGCSGKLIC`
Immunogen
Species (MHC)

Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007
- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 27/50 Brazilian sequences.

HXB2 Location gp160 (594–603)
Author Location gp41 (594–603 IIIB)
Epitope GIWGCSGKLI
Immunogen HIV-1 infection
Species (MHC) human
References Kelleher *et al.* 1998b
- Epitope documented as a "previously described' epitope Bell *et al.* [1992], but in Bell *et al.* it was described as gp41(594-603 IIIB), LGIWGCSGKLIC.
- Immunization with a p24-VLP virus-like particle did not significantly impact CD4+ lymphocyte count, viral load, or p24 antibody titre.
- Immunization with p24-VLP did not increase the proliferative response to this gp41 epitope, however, there was a modest, short-lived increased proliferative response to p24.

HXB2 Location gp160 (594–603)
Author Location
Epitope GIWGCSGKLI
Immunogen
Species (MHC)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007
- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 27/50 Brazilian sequences.

HXB2 Location gp160 (594–604)
Author Location gp41 (consensus)
Epitope GIWGCSGKLIC
Immunogen HIV-1 infection
Species (MHC) human
References Mutch *et al.* 1994
- Core region of peptides that can stimulate proliferative responses from seronegative and seropositive people.

HXB2 Location gp160 (594–604)
Author Location
Epitope GIWGCSGKLIC
Immunogen
Species (MHC)
Keywords subtype comparisons, viral fitness and reversion
References de Queiroz *et al.* 2007
- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 27/50 Brazilian sequences.

HXB2 Location gp160 (598–609)
Author Location gp41 (603–614 LAI)
Epitope CSGKLICTTAVP
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989
- Stimulates T-cell proliferation in HIV-infected donors.

HXB2 Location gp160 (604–615)
Author Location gp41 (609–620 LAI)
Epitope CTTAVPWNASWS
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989
- Stimulates T-cell proliferation in HIV-infected donors.

HXB2 Location gp160 (606–620)
Author Location gp41 (UG92005)
Epitope TNVPWNASWSNKSLE
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001
- This gp140 epitope of UG92005 (UG, clade D) was recognized by five hybridomas with Vβ usage Vβ 8.1, 14 and not determined – one of the Vβ 8.1 was shown to utilize Vα 8.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be

T-Helper CD4+

influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (606–620)
Author Location gp41 (1035)
Epitope TNVPWNASWSNKSLE
Subtype B
Immunogen vaccine
Vector/Type: vaccinia prime with gp120 boost *Strain:* B clade 1035 *HIV component:* Env *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse
Assay type T-cell Elispot
Keywords epitope processing, vaccine-induced epitopes, escape, TCR usage
References Zhan *et al.* 2003

- A very narrow Th response was stimulated in C57BL/6 mice vaccinated with vaccinia expressed HIV-1 env clone 1035, to the peptide PKVSFEPIPIHYCAP, located in the C2 region of gp120. The only other peptide recognized using Elispot on Env overlapping peptides to test vaccine responses in the mice was this one: TNVPWNASWSNKSLE, located in gp41.

HXB2 Location gp160 (609–616)
Author Location gp41 (consensus)
Epitope PWNASWSN
Immunogen HIV-1 infection
Species (MHC) human
References Mutch *et al.* 1994

- Core region of peptides that can stimulate proliferative responses from seronegative and seropositive people.

HXB2 Location gp160 (611–620)
Author Location gp41 (1007, UG92005)
Epitope NASWSNKSLE
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2 IA^b)
Keywords subtype comparisons, epitope processing, TCR usage
References Surman *et al.* 2001

- This gp41 epitope is conserved in 1007 (US, clade B) and UG92005 (UG, clade D) and was recognized by two hybridomas from two different mice that were vaccinated with different clades – the Vβ usage was Vβ 4 and 14.
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (T[TN]VPWNASWSNKSLE and NASWSNKSLEQIWNN) – the only difference between 1007 and UG92005 for these two proteins is that 1007 has a T and UG92005 has an N in the second position of the first peptide.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA^b transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennesee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA^b restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

HXB2 Location gp160 (614–629)
Author Location gp41 (IIIB)
Epitope WSNKSLEDIWDNMTWC
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

HXB2 Location gp160 (620–634)
Author Location Env (620–634 HXB2)
Epitope EQIWNHTTWMEWDRE
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DP4)
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, epitope processing, computational epitope prediction, dendritic cells
References Cohen *et al.* 2006

- Motif-based quantitative matrices binding predictions, binding assays and cellular assays were used to identify 4 HLA-DP4 epitopes by scanning the whole HIV-1 genome.
- 21 peptides were predicted to bind HLA-DP4, 17 of them did bind in binding assays, 6 of them were good binders. Of the 6 good binders, 4 peptides primed peptide-specific CD4+ T cell lines restricted to HLA-DP4 molecules.

HXB2 Location gp160 (634–649)

T-Helper CD4+

Author Location gp41 (IIIB)
Epitope EIDNYTNTIYTLLEEC
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

HXB2 Location gp160 (647–661)
Author Location gp41 (647–661 IIIB, B10)
Epitope EESQNQQEKNEQELL
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location gp160 (650–662)
Author Location gp41 (655–667 LAI)
Epitope QNQQEKNEQELLE
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

HXB2 Location gp160 (667–681)
Author Location gp41 (667–681 IIIB, B10)
Epitope ASLWNWFNITNWLWY
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location gp160 (682–696)
Author Location gp41 (682–696 IIIB, B10)
Epitope IKLFIMIVGGLVGLR
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

HXB2 Location gp160 (688–710)
Author Location
Epitope IVGGLIGLRIVFAVLSIVNRVRQ
Epitope name HIV-VAX-1058
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 1/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was LRIVFAVLS.

HXB2 Location gp160 (696–718)
Author Location
Epitope RIVFAVLSIVNRVRQGYSPLSFQ
Epitope name HIV-VAX-1061
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 2/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was SIVNRVRQG.

HXB2 Location gp160 (724–745)
Author Location gp41 (731–752)
Epitope PRGPDRPEGIEEEGGERDRDRS
Immunogen vaccine
Vector/Type: peptide in cowpea mosaic virus (CPMV) *HIV component:* gp41 *Adjuvant:* Quillaja saponin (Quil-A)
Species (MHC) mouse (H-2^{k})
Keywords Th1
References McInerney *et al.* 1999

- A gp41 peptide was expressed in a cowpea mosaic virus (CPMV) and mice were vaccinated with a purified chimeric particle – out of five adjuvants tested, only Quil A could stimulate anti-gp41 antibodies and an *in vitro* proliferative response.
- The antibodies were predominantly IgG2a, suggesting a Th1 response.

HXB2 Location gp160 (732–744)
Author Location gp41 (737–749 LAI)
Epitope GIEEEGGERDRDR
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

HXB2 Location gp160 (761–783)
Author Location
Epitope RSLCLFSYHRLRDLLLIVTRIVE
Epitope name HIV-VAX-1059
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States

T-Helper CD4+

Assay type CD4 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 4/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was YHRLRDLLL.

HXB2 Location gp160 (772–787)
Author Location gp41 (261–276 clade B consensus)
Epitope `RDLLLIVTRIVELLGR`
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (DRB1*0101, DRB1*0701, DRB1*1101)
Country Brazil
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 brazilian HIV-1 chronically infected individuals.
- While RDLLLIVTRIVELLGR was the reacting peptide, shorter LLLIVTRIVELL peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

HXB2 Location gp160 (780–794)
Author Location gp41 (787–801 IIIB)
Epitope `RIVELLGRRGWEALK`
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^d, H-2^k, H-2^{t4})
References Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

HXB2 Location gp160 (780–794)
Author Location gp160 (787–801 IIIB)
Epitope `RIVELLGRRGWEALK`
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^d, H-2^k, H-2^s)
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in cells from B10.BR mice (H-$2A^k$, E^k), B10.D2 mice (H-$2A^d$, E^d), and B10.S(9R) mice (H-$2A^s$, E^s)
- RIVELLGRRGWEALKYWWNLLQYWSQELKNSAVS encompasses several murine Th epitopes including RIVELLGRRGWEALK and is referred to as a "multideterminant region" or cluster peptide, but the longer peptide only stimulates cells from H-2^k mice.

HXB2 Location gp160 (780–813)
Author Location gp160 (787–820 IIIB)
Epitope `RIVELLGRRGWEALKYWWNLLQYWSQELKNSAVS`
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^k)
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- RIVELLGRRGWEALKYWWNLLQYWSQELKNSAVS encompasses several murine Th epitopes and is referred to as a "multideterminant region" or cluster peptide.
- Six multideterminant region cluster peptides were evaluated Th responses in different MHC/HLA backgrounds after vaccination of mice with gp160, or in infected people.
- This cluster peptide elicited proliferative responses in cells from only B10.BR mice (H-$2A^k$, E^k), and not from B10.D2 mice (H-$2A^d$, E^d), B10.A(5R) mice (H-$2A^b$, E^b), or B10.S(9R) mice (H-$2A^s$, E^s)
- IL-2 production in response to this peptide was observed in 59% (17/29) of asymptomatic HIV-infected individuals.

HXB2 Location gp160 (794–808)
Author Location gp41 (801–815 IIIB)
Epitope `KYWWNLLQYWSQELK`
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^k)
References Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

HXB2 Location gp160 (794–808)
Author Location gp160 (801–815 IIIB)
Epitope `KYWWNLLQYWSQELK`
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^d, H-2^k, H-2^s)
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in cells from B10.BR mice (H-$2A^k$, E^k), B10.D2 mice (H-$2A^d$, E^d), and B10.S(9R) mice (H-$2A^s$, E^s)
- RIVELLGRRGWEALKYWWNLLQYWSQELKNSAVS encompasses several murine Th epitopes including KYWWNLLQYWSQELK and is referred to as a "multideterminant region" or cluster peptide, but the longer peptide only stimulates cells from H-2^k mice.

T-Helper CD4+

HXB2 Location gp160 (799–813)
Author Location gp160 (806–820 IIIB)
Epitope LLQYWSQELKNSAVS
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^d, H-2^k, H-2^s)
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A^k, E^k), B10.D2 mice (H-2A^d, E^d), and B10.S(9R) mice (H-2A^s, E^s)
- RIVELLGRRGWEALKYWWNLLQYWSQELKNSAVS encompasses several murine Th epitopes including LLQYWSQELKNSAVS and is referred to as a "multideterminant region" or cluster peptide, but the longer peptide only stimulates cells from H-2^k mice.

HXB2 Location gp160 (799–813)
Author Location gp41 (806–820 IIIB)
Epitope LLQYWSQELKNSAVS
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^d, H-2^k, H-2^{t4})
References Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

HXB2 Location gp160 (799–813)
Author Location gp41 (806–820 IIIB)
Epitope LLQYWSQELKNSAVS
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^d, H-2^k, H-2^{t4})
References Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

HXB2 Location gp160 (814–829)
Author Location gp41 (IIIB)
Epitope WLNATAIAVTEGTDRC
Immunogen in vitro stimulation or selection
Species (MHC) human
References Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

HXB2 Location gp160 (821–835)
Author Location gp41 (828–842 IIIB)
Epitope AVAEGTDRVIEVVQG
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^k)
References Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

HXB2 Location gp160 (821–835)
Author Location gp160 (828–842 IIIB)
Epitope AVAEGTDRVIEVVQG
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^b, H-2^k, H-2^s)
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A^k, E^k), B10.A(5R) mice (H-2A^b, E^b), and B10.S(9R) mice (H-2A^s, E^s)
- AVAEGTDRVIEVVQGAYRAIRHIPRRIRQGLER encompasses several murine Th epitopes including AVAEGTDRVIEVVQG and is referred to as a "multideterminant region" or cluster peptide.

HXB2 Location gp160 (821–838)
Author Location gp41 (827–843)
Epitope YVAEGTDRVIEVVQGACR
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression
References Caruso *et al.* 1997

- As HIV-1-infected individuals progress to disease, T-cells show reduced ability to proliferate in response to HIV antigen, but retain the ability to express the activation antigens CD25 and CD71.
- The ability to express activation markers in response to HIV is retained, but the response to tetanus toxoid recall antigen is lost.
- This study investigated CD25 and CD71 expression in PBMC from patients at various stages of progression, measuring the response to *in vitro* stimulation by peptide cocktail containing four antigenic Env peptides, or p17 and p24.

HXB2 Location gp160 (821–853)
Author Location gp160 (828–860 IIIB)
Epitope AVAEGTDRVIEVVQGAYRAIRHIPRRIRQGLER
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) human, mouse (H-2^b, H-2^d, H-2^k, H-2^s)
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- AVAEGTDRVIEVVQGAYRAIRHIPRRIRQGLER encompasses several murine Th epitopes and is referred to as a "multideterminant region" or cluster peptide.
- Six multideterminant region cluster peptides were evaluated for Th responses in different MHC/HLA backgrounds after vaccination of mice with gp160, or in infected people.
- This cluster peptide elicited proliferative responses in cells from all four MHC types tested: B10.BR mice (H-2A^k, E^k), B10.D2 mice (H-2A^d, E^d), B10.A(5R) mice (H-2A^b, E^b), and B10.S(9R) mice (H-2A^s, E^s)

- IL-2 production in response to this peptide was observed in only 8% (1/12) of asymptomatic HIV-infected individuals.

HXB2 Location gp160 (827–835)
Author Location gp41 (834–842 IIIB)
Epitope DRVIEVVQG
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^k)
References Hale *et al.* 1989

- Suggested H-2^k epitope based on region of overlap.

HXB2 Location gp160 (827–841)
Author Location gp41 (827–841)
Epitope DRVIEVVQGAYRAIR
Epitope name N15
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) mouse (H-2^b, H-2^k)
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- Peptide N15, DRVIEVVQGAYRAIR, was used as a specific antigen for ELISpot positive control. N15 was previously known to induce T-helper responses not only in mice but also in humans and monkeys. It is a previously known epitope that is a part of TCI fragment SLLNATDIAVAEGTDRVIEVVQ-GAYRAIRHIPRRIRQGLERILL in this vaccine construct.

HXB2 Location gp160 (827–841)
Author Location gp160 (834–848 IIIB)
Epitope DRVIEVVQGAYRAIR
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^b, H-2^k)
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A^k, E^k) and B10.A(5R) mice (H-2A^b, E^b)

HXB2 Location gp160 (827–841)
Author Location gp41 (834–848 IIIB)
Epitope DRVIEVVQGAYRAIR
Epitope name TH4
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^{i5}, H-2^k)
References Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.
- Called Th4.1 and TH4.

HXB2 Location gp160 (827–841)
Author Location gp41 (834–848 IIIB)
Epitope DRVIEVVQGAYRAIR
Epitope name TH4
Immunogen vaccine
Vector/Type: peptide prime with protein boost *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) macaque
References Hosmalin *et al.* 1991

- Peptide priming to induce T-cell help enhances antibody response to gp160 immunization.
- Called Th4.1 and TH4.

HXB2 Location gp160 (827–841)
Author Location gp41 (834–848 IIIB)
Epitope DRVIEVVQGAYRAIR
Epitope name TH4
Immunogen HIV-1 infection
Species (MHC) human
References Clerici *et al.* 1997

- used in a study of the influence of pentoxifylline on HIV specific T-cells.

HXB2 Location gp160 (827–841)
Author Location gp41 (834–848 IIIB)
Epitope DRVIEVVQGAYRAIR
Epitope name TH4
Immunogen
Species (MHC) human
References Pinto *et al.* 1995

- CTL activity analyzed in parallel with Th reactivity in exposed but uninfected health care workers.
- Called Th4.1 and TH4.

HXB2 Location gp160 (827–841)
Author Location gp41 (834–848 IIIB)
Epitope DRVIEVVQGAYRAIR
Epitope name TH4
Immunogen HIV-1 infection
Species (MHC) human
References Clerici *et al.* 1991a

- Peptides stimulate Th cell function and CTL activity in similar patient populations.
- Called Th4.1 and TH4.

HXB2 Location gp160 (827–841)
Author Location gp41 (834–848 IIIB)

T-Helper CD4+

Epitope DRVIEVVQGAYRAIR
Epitope name TH4
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) human
References Clerici *et al.* 1991b

- Immunizing uninfected individuals with rgp160 results in stronger Th response than does natural infection.
- Called Th4.1 and TH4.

HXB2 Location gp160 (827–841)
Author Location gp41 (834–848 IIIB)
Epitope DRVIEVVQGAYRAIR
Epitope name TH4
Immunogen
Species (MHC) human
References Clerici *et al.* 1992

- Cell-mediated immune response to HIV-1 peptides in HIV-1 exposed seronegative men.
- Called Th4.1 and TH4.

HXB2 Location gp160 (827–841)
Author Location gp41 (834–848 IIIB)
Epitope DRVIEVVQGAYRAIR
Epitope name TH4
Immunogen HIV-1 infection
Species (MHC) human
References Clerici *et al.* 1989

- IL-2 production detection of Th lymphocytes from asymptomatic HIV-positive individuals.
- Called Th4.1 and TH4.

HXB2 Location gp160 (827–841)
Author Location gp41 (834–848 IIIB)
Epitope DRVIEVVQGAYRAIR
Epitope name TH4
Immunogen HIV-1 infection
Species (MHC) human
References Kaul *et al.* 1999

- Kenyan sex workers that remained seronegative were found to frequently have HIV-env peptide specific Th responses detected by an IL-2 assay (11/20 cases) and mucosal genital tract anti-HIV IgA (16/21 cases)
- Helper epitopes used in this study were noted to be previously described Clerici *et al.* [1989], and were not explicitly described in Kaul *et al.* [1999]

HXB2 Location gp160 (827–841)
Author Location gp41
Epitope DRVIEVVQGAYRAIR
Epitope name TH4, Th4.1
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC) human
Keywords subtype comparisons, responses in children, mother-to-infant transmission
References Kuhn *et al.* 2001a

- In a S. African perinatal transmission study, 33% (33/86) of cord blood samples from infants with seropositive mothers produced T-helper responses (measured by a bioassay measuring IL2 production in a murine cell line and confirmed with a proliferation assay) against a peptide cocktail containing Th epitopes P18 MN, P18 IIIB, T1, T2, and TH4.
- The mothers were predominantly infected with subtype C, but the T help response was detectable in a number of cord blood samples despite using peptides based on B subtype reagents.
- 3/33 infants with cord blood T help responses to Env were infected *in utero*, 2/33 were lost to follow up, and 28/33 were not infected. 6/53 of the infants with cord blood that was unresponsive to Env peptide stimulation were infected before delivery, and 8/47 contracted HIV intrapartum or via breast-feeding.
- Measurable HIV specific T help responses elicited in the immunologically immature newborn, possibly in response to *in utero* exposure, are associated with a protective natural immunity that helps block mother-infant transmission of HIV-1.

HXB2 Location gp160 (827–841)
Author Location Env (834–848 IIIB)
Epitope DRVIEVVQGAYRAIR
Epitope name TH4.1
Immunogen HIV-1 infection, HIV-1 exposed seronegative
Species (MHC)
Assay type Cytokine production
Keywords mother-to-infant transmission
References Clerici *et al.* 1993a

- Cord blood samples in 8/23 infants with HIV+ mothers showed IL-2 production in response to peptides from HIV-1 gp1260, demonstrating that Th cell priming to HIV env determinants can occur in utero. HIV-specific Th immunity in utero may be protective, as none of the 8 with HIV-1 specific Th activity became infected, while 3/15 infants with no detectable Th activited were infected.
- PBL from 10/21 of the mother showed HIV-1 specific Th activity through IL-2 production in response to Env peptides.

HXB2 Location gp160 (827–841)
Author Location Env (IIIB)
Epitope DRVIEVVQGAYRAIR
Epitope name TH4.1
Subtype B
Immunogen HIV-1 exposed seronegative
Species (MHC)
Assay type Cytokine production
References Clerici *et al.* 1994a

- Six of eight HIV-exposed health care workers had transient HIV-specific T-helper responses after percutaneous exposure to HIV, responding to two or more Env peptides among the set T1, T2, Th4.1, P18IIIB and P18MN. Responses were lost after 12-56 weeks. The HIV-specific Th responses occurred without seroconversion or PCR evidence for infection.
- Six of the eight HIV-exposed individuals responded to two or more peptides, whereas, only one individual exposed to HIV-negative blood responded to one peptide.

HXB2 Location gp160 (827–841)
Author Location HIV-1 (IIIB)

T-Helper CD4+

Epitope DRVIEVVQGAYRAIR
Epitope name TH4.1
Subtype B
Immunogen HIV-1 infection
Species (MHC)
Assay type Cytokine production
References Clerici *et al.* 1994b

- IL-10-specific mRNA was upregulated in PBMC from asymptomatic, HIV-infected (HIV+) patients, and was particularly high in those with severely compromised Th cells function. Th response to HIV peptides *in vitro* could be restored by IL-10 Ab.

HXB2 Location gp160 (827–841)
Author Location Env (834–848)
Epitope DRVIEVVQGAYRAIR
Epitope name TH4-1
Immunogen HIV-1 infection
Species (MHC) human
Assay type proliferation
Keywords responses in children, mother-to-infant transmission
References Kuhn *et al.* 2001b

- Th proliferative responses in cord blood at delivery to a cocktail of HIV envelope peptides were infrequent (1/41) among infants whose HIV-positive mothers received antiretroviral prophylaxis at delivery to prevent transmission. Responses were 10 times more frequent among infants of HIV-seropositive women who had no antiretroviral treatment (7/29). Reductions of HIV-specific responses occurred despite persistance of detectable HIV RNA in the mothers at delivery.
- The reduction of Th responses in newborns raises the possibility that anti-retrovial exposure during pregnancy may block subsequent immune protection. The authors point two relevant citations that showed ARV exposed infants had a more rapid course of progression (Kuhn *et al.*, JID 182:104 (2000)), but were at no greater risk of infection due to subsequent breast feeding (Ditrame *et al.*, Lancet 354:2050 (1999)).

HXB2 Location gp160 (827–841)
Author Location Env (gp160) (421–436)
Epitope DRVIEVVGQAYRAIR
Epitope name TH4.1
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type proliferation
Keywords responses in children, variant cross-recognition or cross-neutralization
References Meddows-Taylor *et al.* 2004

- Viral isolates (gp160) from 16 vertically HIV-1 infected children (8 T-helper cell Env responders and 8 non-responders) were analyzed for variation after comparison with Env peptide sequences (conserved regions T1, T2 and TH4.1, hypervariable regions P18 MN and P181 IIIB) used for in vitro stimulation.
- No correlation between the age, clinical category (mild or severe), HIV-1 viral load and the degree of epitope variation was established.

HXB2 Location gp160 (827–853)
Author Location Env (HIV-1 IIIB)
Epitope DRVIEVVQGAYRAIRHIPRRIRQGLER
Subtype B
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB, SIV *HIV component:* Env, Gag, Pol *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72), Montanide (ISA 51)
Species (MHC) macaque
Assay type proliferation
Keywords mucosal immunity
References Belyakov *et al.* 2001

- Different HIV strains were used for different regions: env HIV-1 IIIB, gag SIV, pol SIV
- Intrarectal vaccination with a Th and CTL peptide vaccine provided better protection against intrarectal challenge with pathogenic SHIV-Ku1 than subcutaneous administered vaccine. In some animals after the initial viremia, viral loads were diminished to undetectable levels in the blood and intestine, and CD4+ T cells were better preserved.
- The CD4 T-cell proliferative response correlated with the level of the CTL response.

HXB2 Location gp160 (829–843)
Author Location gp160 (836–850 IIIB)
Epitope VIEVVQGAYRAIRHI
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^b, H-2^k)
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in cells from B10.BR mice (H-$2A^k$, E^k) and B10.A(5R) mice (H-$2A^b$, E^b)

HXB2 Location gp160 (834–841)
Author Location gp41 (841–848 IIIB)
Epitope QGAYRAIR
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^{i5})
References Hale *et al.* 1989

- Suggested H-2^k epitope based on region of overlap.

HXB2 Location gp160 (834–848)
Author Location gp41 (834–848)
Epitope QGAYRAIRHIPRRIR
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) mouse (H-2^b, H-2^d, H-2^k, H-2^s)
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

T-Helper CD4+

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- QGAYRAIRHIPRRIR is a previously known epitope that is a part of TCI fragment SLLNATDIAVAEGTDRVIEVVQ-GAYRAIRHIPRRIRQGLERILL in this vaccine construct.

HXB2 Location gp160 (834–848)
Author Location gp41 (841–855 IIIB)
Epitope `QGAYRAIRHIPRRIR`
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^{d}, H-2^{i5}, H-2^{t4})
References Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

HXB2 Location gp160 (834–848)
Author Location gp160 (841–855 IIIB)
Epitope `QGAYRAIRHIPRRIR`
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (H-2^{b}, H-2^{d}, H-2^{k}, H-2^{s})
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A^{k}, E^{k}), B10.A(5R) mice (H-2A^{b}, E^{b}), B10.D2(H-2A^{d}, E^{d}), and B10.S(9R) mice (H-2A^{s}, E^{s})

HXB2 Location gp160 (834–853)
Author Location Env
Epitope `QGAYRAIRHIPRRIRQGLER`
Immunogen vaccine
Vector/Type: ISCOM *Strain:* multiple epitope immunogen *HIV component:* Env, Gag, Tat
Species (MHC) macaque
Assay type Other
Keywords vaccine antigen design
References Pahar *et al.* 2006

- Rhesus macaques were immunized intrarectally with an ISCOM vaccine containing a single SIV-Gag CTL epitope, a single human HIV-Env Th epitope, plus a negative control mouse H-2d Tat epitope. Following challenge with SHIV-SF162p4, immunized macaques became infected, but had significantly lower viral loads than non-immunized animals.

HXB2 Location gp160 (839–848)
Author Location gp41 (846–855 IIIB)
Epitope `AIRHIPRRIR`
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^{d}, H-2^{t4})
References Hale *et al.* 1989

- Suggested H-2^{d,t4} epitope based on region of overlap.

HXB2 Location gp160 (839–848)
Author Location gp41 (839–848)
Epitope `AIRHIPRRIR`
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) mouse (H-2^{d}, H-2^{t4})
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- AIRHIPRRIR is a previously known epitope that is a part of TCI fragment SLLNATDIAVAEGTDRVIEVVQ-GAYRAIRHIPRRIRQGLERILL in this vaccine construct.

HXB2 Location gp160 (839–853)
Author Location gp41 (846–860 IIIB)
Epitope `AIRHIPRRIRQGLER`
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^{d}, H-2^{t4})
References Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

HXB2 Location gp160 (839–853)
Author Location gp41 (839–853)
Epitope `AIRHIPRRIRQGLER`
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) mouse (H-2^{d}, H-2^{t4})
Country Russia
Assay type T-cell Elispot

T-Helper CD4+

Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- AIRHIPRRIRQGLER is a previously known epitope that is a part of TCI fragment SLLNATDIAVAEGTDRVIEVVQ-GAYRAIRHIPRRIRQGLERILL in this vaccine construct.

HXB2 Location gp160 (839–853)
Author Location gp160 (828–842 IIIB)
Epitope `AIRHIPRRIRQGLER`
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) human, mouse (H-2^b, H-2^k, H-2^s)
References Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in cells from B10.BR mice (H-$2A^k$, E^k), B10.A(5R) mice (H-$2A^b$, E^b), and B10.S(9R) mice (H-$2A^s$, E^s)

HXB2 Location gp160 (842–856)
Author Location gp41 (842–856 IIIB, B10)
Epitope `HIPRRIRQGLERILL`
Immunogen HIV-1 infection
Species (MHC) human
References Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

III-B-17 Env Helper/CD4+ T-cell epitopes

HXB2 Location Env
Author Location gp160 (IIIB)
Epitope
Immunogen vaccine
Vector/Type: peptide, protein *Strain:* B clade IIIB *HIV component:* gp160, V3 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (MHC) mouse (H-2^d)
Keywords Th1, Th2
References Morris *et al.* 2000

- Mice were intranasally immunized with 20 ug of HIV-gp160 and 5 ug of peptide E7 (RIHIGPGRAFYAARK) with the adjuvant LT(R192G), a heat-labile enterotoxin produced by E. coli.
- Adjuvant LT(R192G) was required for stimulation of antigen-specific IgG1, IgG2 antibodies, and Th1 and Th2 cytokines responses to gp160, and peptide-specific CTL responses.
- Increased IFN-γ, IL-10 and IL-6 cytokine production specific to gp160 was measured with co-immunization of gp160 with LT(R192G)

HXB2 Location Env
Author Location gp160 (IIIB)
Epitope
Immunogen vaccine
Vector/Type: DNA with CMV promotor *Strain:* B clade IIIB *HIV component:* gp160, Rev *Adjuvant:* Br-cAMP
Species (MHC) mouse (H-2^d)
Keywords Th1
References Arai *et al.* 2000

- The CMV promotor responds to the intracellular level of cAMP, and 8 Br-cAMP can increase transgene expression so it was co-administered with a CMV-based DNA vaccine both intranasally and intramuscularly.
- 8 Br-cAMP increased serum IgG responses, HIV-specific CTL, DTH and Th1 responses, and IgA in the intranasal vaccination.
- A CAT assay study showed adjuvant effect was due to CMV promotor activation.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Env, Gag, Pol *Adjuvant:* IFNγ, IL-2, IL-4
Species (MHC) mouse (H-2^d)
Keywords Th1
References Kim *et al.* 2000

- Co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine used to enhance the immune response – co-expression of Th1 cytokine IFN-γ drove Th1 immune responses and enhanced CTL responses.

HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (MHC) mouse (H-2^d)
Keywords Th1, Th2
References Shirai *et al.* 2001

- Helicobacter pylori induces Th1 responses early, but predominantly Th2 responses later in infection (at 6 weeks) – differentiation of HIV-1 gp160 CD4+ help and CD8+ CTL effector cells in response to HIV gp160-vaccinia vaccination is impaired in BALB/c mice infected with H. pylori.

T-Helper CD4+

HXB2 Location Env
Author Location gp120 (V3) and p24 (IIIB, MN, BH10)
Epitope
Subtype A, B
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *Strain:* A clade UG5.94UG018, B clade IIIB *HIV component:* Gag, gp120
Species (MHC) mouse (H-2^d)
Keywords subtype comparisons
References Buonaguro *et al.* 2002

- Different HIV strains were used for different regions: gp120 A clade UG5.94UG018; Gag HIV-1 IIIB
- BALB/c mice were given intraperitoneal immunization in the absence of adjuvants with virus-like particles (VLPs) expressing recombinant subtype A gp120 and Pr55gag.
- High dose-independent humoral responses were elicited against both gp120 and p24 peptides, and CTL responses were observed against target cells carrying vaccinia expressed gp120 and Gag.
- Recombinant rgp120 (clade B, MN) induced T cell proliferative responses *in vitro* from vaccinated animals.

HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* gp120, gp160
Species (MHC) mouse
Keywords Th1
References Shiver *et al.* 1997

- DNA vaccinations of BALBc mice with a gp120 or gp160 DNA vaccine elicited a strong T-cell proliferative response with Th1-like secretion of γ interferon and IL-2, with little or no IL-4, as well as antigen specific gp120 Abs.
- An intramuscular route of inoculation gave a stronger proliferative response than intradermal.
- A proliferative response could be detected in all lymph tissues tested: spleen, PBMC, and mesenteric, iliac, and inguinal lymph nodes.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Gag, gp160, Pol *Adjuvant:* CD86
Species (MHC) mouse
References Kim *et al.* 1997d

- A gp160 DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecule CD86, gives an increase in the proliferative responses to gp120 in mice.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen
Species (MHC) human
References De Berardinis *et al.* 1997

- Sequences flanking helper T-cell immunogenic domains can be important for immunogenicity.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Rosenberg *et al.* 1997

- A strong proliferative response to p24 and gp160 was found in a healthy long term survivor.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen HIV-1 infection
Species (MHC) macaque
Keywords Th1, Th2
References Kent *et al.* 1997b

- Macaca nemestrina can be infected with HIV, and clear the infection within 6 months, so it is of interest to examine their initial immune response.
- A strong proliferative response against gp160 with IL-4 production, indicating a Th2 response, was found with 4 weeks of infection.
- The gp160 proliferative response by 8 weeks produces both IL-4 and γ interferon, indicating both Th1 and Th2 responses.

HXB2 Location Env
Author Location gp120 (HXBc2)
Epitope
Immunogen vaccine
Vector/Type: DNA prime with gp160 boost *Strain:* B clade HXBc2 *HIV component:* gp160
Species (MHC) macaque
References Letvin *et al.* 1997

- Vaccination of Macaca mulatta (rhesus monkeys) with a HXBc2 env DNA prime and a protein boost elicited a T-cell proliferative response, a CTL response, and type-specific neutralizing antibodies.
- Vaccinated animals challenged with SHIV-HXB2 were protected from infection.

HXB2 Location Env
Author Location gp120 (MN)
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade MN *HIV component:* Env, Rev
Species (MHC) human
References MacGregor *et al.* 1998

- An HIV DNA env and rev vaccine given to 15 asymptomatic HIV+ individuals at three different dosages, 30, 100 or 300 μg, was safe.
- All three groups showed an increased proliferative response after vaccination.

HXB2 Location Env

T-Helper CD4+

Author Location Env
Epitope
Immunogen
Species (MHC) human
References Mazzoli *et al.* 1997

- Study of HIV-specific immunity in seronegative partners of HIV-positive individuals – Env peptides could stimulate IL-2 production in 9/16 HIV-exposed seronegative individuals, and only 1/50 low-risk controls.
- Exposed-uninfected produced more IL-2 and less IL-10 then HIV-infected individuals.
- 8/9 of those whose PBMC produce IL-2 in response to Env peptides had concomitantly detected urinary or vaginal tract anti-HIV IgA.

HXB2 Location Env
Author Location Env
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Plana *et al.* 1998

- Patients from later stages of infection given HAART do not show restoration of HIV-1 specific Th proliferative responses.

HXB2 Location Env
Author Location Env
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Kelleher *et al.* 1998a

- Env and gag Th epitopes were pooled and used to test Th proliferative responses after IL2 therapy – while IL2 therapy causes an increase in CD4+ lymphocyte count, it does not increase HIV-1 specific proliferative responses.

HXB2 Location Env
Author Location gp160
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *HIV component:* gp160
Species (MHC) human
References Ratto-Kim *et al.* 1999

- Vaccinations with rgp160 did not enhance Th immunoproliferative responses in individuals who were immunized every 2 months for 5 years starting early in infection.

HXB2 Location Env
Author Location gp160
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *HIV component:* gp160
Species (MHC) human
Keywords subtype comparisons
References Leandersson *et al.* 2000

- 27 HIV subtype B, 4 subtype C, 2 D and one of each subtype E, F, G infected individuals were either given rgp160 B clade immunizations or placebo. All rgp160 immunized individuals showed increased proliferation responses to the B clade immunizing antigen rgp160.
- gp120 was prepared from A, B, C, D, and E subtype virions and used as antigenic stimulus – 7 of 10 tested individuals responded to native gp120 from at least one additional subtype in addition to B subtype, while a placebo recipient did not respond to any gp120.
- This study shows that cross-subtype HIV-specific T-cell proliferative responses can be stimulated in patients already infected with another HIV-1 subtype – all immunized subjects could respond to the subtype B immunogen, but many developed responses to at least one more subtype.

HXB2 Location Env
Author Location gp160 (MN)
Epitope
Immunogen vaccine
Vector/Type: gp160 prime with gp120 boost *Strain:* B clade MN *HIV component:* gp120, gp160
Species (MHC) human
Keywords Th1, Th2
References Gorse *et al.* 1999a

- Helper T-cell memory responses were induced by MN rgp160 as measured by proliferation and Th1 and Th2 cytokine release – this response could be boosted by MN rgp120.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen vaccine
Vector/Type: fowlpoxvirus, ISCOM *Strain:* B clade SF2 *HIV component:* gp120
Species (MHC) macaque
Keywords Th1, Th2
References Heeney *et al.* 1998b

- Vaccinated monkeys with the highest level of Th1 and Th2 responses and the highest levels of NAbs were protected against a SHIV SF13 challenge – the ISCOM strategy gave more potent anti -gp120 responses than the Fowl pox strategy.
- When animals were challenged 4 months after boost, those that maintained high levels of HIV-1 specific IFN-γ responses, indicative of a Th 1 response, were still protected.

HXB2 Location Env
Author Location (IIIB)
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* Env, Rev
Species (MHC) human
References Boyer *et al.* 1999

- A DNA vaccine containing env and rev was tested for safety and immune response in 15 HIV+ asymptomatic individuals.
- Enhanced proliferative activity and higher levels of MIP-1 alpha were detected in multiple study subjects.

HXB2 Location Env
Author Location Env
Epitope
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* GM-CSF/ENV chimera
Species (MHC) mouse
References Rodríguez *et al.* 1999

- A chimeric GM-CSF-env antigen expressed in a vaccinia vector elicits a higher HIV-specific env cellular immune response than when native env is used.

HXB2 Location Env
Author Location Env (LAI)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost *Strain:* B clade LAI *HIV component:* Env, Gag
Species (MHC) macaque
Keywords Th1, Th2
References Kent *et al.* 1998

- Priming with an HIV-DNA vaccine and boosting with a vaccinia construct induced greater levels of HIV T-cell immunity than either vaccine alone.
- The proliferative response to Env and Gag after the DNA vaccination had a mean SI of 1.5-4, but after boosting with rHIV-fowlpox virus, there was a 6-17 fold increase in the mean SI for HIV Gag and Env. The T help response happened despite a fall in antibody titers, suggesting that the Th response was primarily Th1, not Th2. The CTL response was also enhanced.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen vaccine
Vector/Type: DNA, protein, virus-like particle (VLP), ISCOM
Species (MHC) macaque
Keywords Th1, Th2
References Heeney *et al.* 1999

- Ten different vaccine strategies were evaluated for their ability to protect from infection in a rhesus macaque model using a non-pathogenic SHIV challenge. Protection correlated with the magnitude of NAb responses, beta-chemokines, and a balanced Th response. DNA, protein+adjuvant, VLP and ISCOM vaccines were tested.
- HIV-1/ISCOMS gave the highest NAb titers, Th1 and Th2 responses, was the only vaccine formulation tested with a detectable CTL response, and gave enhanced beta-chemokine production.

HXB2 Location Env
Author Location gp160 (MN)
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade MN *HIV component:* gp160
Species (MHC) human
References Kundu *et al.* 1998a

- This study followed 10 HLA-A2 asymptomatic HIV+ individuals as they received MN gp160 vaccinations over a two year period.
- There was an increased lymphoproliferative response but this did not impact viral load or CTL response.

HXB2 Location Env
Author Location gp120 (SF2)
Epitope
Immunogen vaccine
Vector/Type: DNA, protein, ISCOM *Strain:* B clade SF2 *HIV component:* gp120 *Adjuvant:* MF59
Species (MHC) macaque
References Verschoor *et al.* 1999

- 16 rhesus Macaques were vaccinated with either an epidermal SF2 gp120 DNA vaccine, rgp120 with a MF59 adjuvant, or rgp120 incorporated into ISCOMs.
- DNA vaccination elicited a weak Th type 1 response and low antibody response, rgp120/MF59 triggered a strong antibody response, and rgp120/ISCOM induced both kinds of Th cells, and a strong humoral response.
- Animals were challenged with SF13 SHIV. Early induction of Th type 1 and type 2 responses with the rgp120/ISCOM vaccine provided the most effective immunity, protecting from infection.

HXB2 Location Env
Author Location Env (MN)
Epitope
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade MN *HIV component:* Env, Gag, Pol *Adjuvant:* CD80, CD86
Species (MHC) mouse
References Kim *et al.* 1998

- Co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine used to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses.

HXB2 Location Env
Author Location Env (LAI, MN)
Epitope
Immunogen vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Protease
Species (MHC) human
References Salmon-Ceron *et al.* 1999

- A live attenuated canarypox vector expressing MN gp120 and LAI gp41/gag/protease could induce CTL and a lymphoproliferative response in healthy uninfected volunteers.

HXB2 Location Env
Author Location Env
Epitope

Immunogen vaccine
Vector/Type: DNA *Strain:* ZF1 *HIV component:* complete genome
Species (MHC) macaque
References Akahata *et al.* 2000

- Rhesus macaques were vaccinated by i.m. injection with naked plasmid DNA carrying an HIV-1 complete genome vaccine, strain ZF1, with a mutated zinc finger in the nucleocapsid to prevent packaging.
- Env and Gag specific CTL but no antibody responses were induced in 2/4 vaccinated monkeys (MM145 and MM153)
- 2/4 monkeys (MM146 and MM143) produced antibodies against p24 and/or gp160, but no CTL response was detected.
- PBMC from all vaccinated monkeys produced IFN-γ, in response to HIV-1 gp160, indicating a Th response – this response was 5 times higher in MM145, the animal with the strongest CTL response.
- 4 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM145 and MM153 (with a homologous Env) decreased to near or below the detection limit.
- 6-8 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM146 and MM143 decreased near or below the detection limit.

HXB2 Location Env
Author Location gp120 (W6.ID)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Zhang *et al.* 2001b

- T-helper cell proliferative responses to HIV p24, p55 and gp120 were tested in 27 patients with HIV infection – vigorous responses directed at Gag were detected in ten patients, but an Env specific response was detected in only one patient.

HXB2 Location Env
Author Location gp160
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Blazevic *et al.* 2000

- Prolonged viral suppression resulting from potent antiretroviral therapy did not allow an HIV T helper response to p24 or gp160, but Th proliferative responses to influenza, alloantigen, and PHA did develop in many HIV+ patients, and asymptomatic patients had stronger and more frequent Th response recovery than AIDS patients.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost *HIV component:* gp120
Species (MHC) human
Keywords Th1, Th2
References Sabbaj *et al.* 2000

- Proliferative responses in PBMC of uninfected individuals that were vaccinated with canarypox vector expressing HIV-1 antigens (ALVAC-HIV) and boosted with a recombinant gp120 subunit vaccine gave a Th1 and Th2 proliferative response upon stimulation with HIV-1 Env.
- All vaccinees produced IFN-γ and IL10, most also produced IL-2, IL-6, IL-4 and IL-5.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade MN *HIV component:* gp120
Species (MHC) human
Keywords Th1
References Hladik *et al.* 2001

- 16/29 HIV-1 infected and 24/30 vaccinated individuals had DTH reactions within 48 hours after an intradermal rec gp120 injection. Of nine DTH positive individuals, none had detectable proliferative responses. Thus skin testing may be a sensitive way to identify people with Th recall responses to vaccines, or in the absence of lymphoproliferaion.
- No 48 hour DTH responses were detected among uninfected volunteers, although 10/35 (40%) of the high risk and 11/32 (34%) of the low risk individuals developed an induration resembling DTH after 7-12 days, that may be indicative of primary induction of HIV-1 specific Th1-immunity.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression, Th1, Th2
References Wilson *et al.* 2000b

- Dysfunction of HIV-1 specific proliferative responses, but not responses to other antigens, is evident in HIV-1 progressive disease.

- Vigorous HIV-1 specific responses to p24, Nef and gp120 with SI between 8-99 were seen in 6/7 long term non-progressors (LTNP), the seventh had a borderline responses. IL-2 production was seen in all cases, and IL-4 production was also evident many responses.
- None of the progressors (0/5) had HIV-1 specific proliferative responses, or IL-2 or IL-4 induction.
- Non-HIV antigens (cytomegalovirus, PPD, Staphylococcus enterotoxin B, tetanus toxoid) gave similar responses in HIV-1 + LTNP, progressors, and HIV-1 controls.

HXB2 Location Env
Author Location gp160
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression, Th1
References Kalams *et al.* 1999a

- The strength of p24 specific Gag proliferative responses (SIs) were inversely correlated with viral load in 21 ARV naive patients. The responses were Th1, IFNgamma producing.
- Proliferative responses against gp160 were rarely observed (only 4 cases).

HXB2 Location Env
Author Location Env
Epitope
Immunogen vaccine
Vector/Type: DNA with CMV promotor *Strain:* B clade MN *HIV component:* Env, Rev *Adjuvant:* Bupivacaine
Species (MHC) human
Keywords early-expressed proteins
References MacGregor *et al.* 2002

- A phase I clinical trial of a HIV-1 Env and Rev DNA vaccine with a CMV promoter was conducted and Th proliferative, CTL and Elispot responses monitored. The construct was modified for safety and included no LTRs or packaging signals. The vaccine strategy was safe, and elicited strong CD4-T cell responses, but not CD8 T-cell responses. Rev elicited strong Th responses, and is a early produced protein so may confer advantages.
- With a 300 ug dose, 4/6 individuals had a lymphocyte proliferation (LP) responses to gp120, 3/6 to Rev.
- With a 1000 ug dose, 4/6 individuals had a LP and 2/6 had IFNgamma Elispot responses to gp160; 3/6 had LP, and 4/6 had IFNgamma Elispot responses to Rev.
- No responses to three specific CTL epitopes were observed by Elispot in individuals with appropriate HLA. Some cytotoxic activity against whole protein was observed that was CD4+ T-cell mediated.

HXB2 Location Env
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Clerici *et al.* 2002b

- Specific immunity was compared in a two-year study of chronically HIV-1 infected i) HAART-naive patients who were not progressing and had strong immune responses, ii) newly treated patients followed for 24 months after initiation of HAART, iii) and long-term HAART patients who had been on HAART at least 12 months prior to the study.
- HAART naïve patients had strongest proliferative responses at time zero, but long-term HAART patients the most significant increase in specific responses over the two year study period against HIV-1 gp160, influenza, and Candida. Similarly, IL-2 and IFN-γ production in responses to gp160 was highest in the naïve group at time zero, but increased the most in the long-term HAART treated patients.
- Short-term HAART patients showed a significant improvement in their CD4+ T cell count and a reduction of plasma viremia, and had augmented IL-7 production, which was slightly reduced in long-term HAART patients.

HXB2 Location Env
Author Location gp160
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Palmer *et al.* 2002

- CD4+ T cell proliferative responses from 33 HIV-1 infected patients with HAART suppression were compared to 19 patients with active viral replication (HAART failures and HAART naive). Patients with HAART suppression showed stronger p24- and p66-specific proliferative responses compared to patient groups with active HIV-1 replication, suggesting active viral replication *in vivo* specifically reduces proliferation responses.
- gp160 proliferation responses were apparent in 7/32 donors tested, but weaker overall, with a median value for the suppressed group not above that found for HIV seronegative controls.
- No differences in the frequency of HIV-specific CD4+ T-cells that were positive for cytokine secretion in a flow cytometry assay were found in the HAART suppressed group versus the group with active viral replication.

HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 4/15 responders recognized this peptide, average SI = 4.4.

T-Helper CD4+

HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Immunogen HIV-1 infection
Species (MHC) human
References Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 4/15 responders recognized this peptide, average SI = 4.4.

HXB2 Location Env
Author Location gp120 (SF2)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons, rate of progression
References Imami *et al.* 2002b

- 70 patients with chronic disease progression, 10 clinical non-progressors, and 3 immunologically discordant progressors (individuals who controlled viremia but had progressive CD4+ T-cell decline) were analyzed for their T-helper cell responses to p24 and cytokine profile.
- In a comparison of responses to HIV-1 proteins based on 10 non-progressors, 3 immunologically discordant, and 70 progressors, SIs were always much higher for non-progressors and immunologically discordant than progressors. Among the non-progressors, the responses to different antigens were greater using p24 peptides than native p24. Native p24, Nef, gp120 proteins, and Remune (gp120 depleted HIV-1, p24 is subtype G), had roughly comparable distributions of SI values from the non-progressors, Nef and gp120 responses were somewhat diminished in immunologically discordant patients.

HXB2 Location Env
Author Location (BRU)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade BRU *HIV component:* virus *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse
References Haas *et al.* 1991

- Of 5 mouse inbred lines tested: DBA/2 (H-2d, Ad, Ed), B10.A(4R) (H-2h4, Ak) and B10.A(5R) (H-2i5) showed particularly good CD4+ T cell proliferative responses to HIV proteins (gp160, gp120, p17, p24, Nef and RT), after vaccination with inactivated virus.
- B10.BR (H-2k, Ak, Ek) and C57BL/6 (H-2b and Ab) had weaker responses.

HXB2 Location Env
Author Location gp120 (HIV-1,IIIB)
Epitope
Immunogen HIV-1 exposed seronegative
Species (MHC) human
Assay type Cytokine production
Keywords HIV exposed persistently seronegative (HEPS)
References Fowke *et al.* 2000

- A cohort of Nairobi sex-worders were defined to be resistant to infection by virtue of remaining seronegative despite repeated high risk exposure. 24 were tested for HIV specific T-helper responses detemined by IL-2 production *in vitro* in response to gp120 peptides or soluble gp120 protein.
- In 7/17 resistant women showed IL-2 stimulation >= 2.0, and specific CTL responses were detected in 15/22 resistant women. 0/12 of the control low-risk subjects had detecatble T-cell responses.

HXB2 Location Env
Author Location gp160
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *HIV component:* gp160 *Adjuvant:* aluminum phosphate
Species (MHC) human
Assay type proliferation
Keywords HAART, ART, immunotherapy
References Hejdeman *et al.* 2003

- Groups of ten asymptomatic HAART-treated HIV-1 + patients with undetected viral loads were monitored for two years after i) no immunization, ii) immunization with rgp160, or iii) immunization with tetanus. Ten HIV-1- volunteers were immunized with tetanus as a control. Results were compared with an rgp160 group tested before HAART was available. The HAART-treated group had increased magnitude and duration of proliferative response to rgp160, maintaining the response for the two year study period. CD4 T-cell responses to tetenus were also improved in the HAART group.
- The recall response to tetanus toxoid and tuberculin were boosted by the rgp160 immunization, particularly in the HAART-treated group.

HXB2 Location Env
Author Location
Epitope
Immunogen HIV-1 exposed seronegative
Species (MHC)
Assay type Cytokine production
Keywords HIV exposed persistently seronegative (HEPS), acute/early infection, early treatment
References Puro *et al.* 2000

- This was a case report of a health care worker who had an percutaneous injury and exposure to HIV, and was immediatedly given combination therapy. The individual remained HIV Ab negative, but had tranisiently detectable viral RNA 2-3 weeks after the exposure. 58 weeks after exposure a Th response was detected by IL-2 production in response to HIV Env peptides.

T-Helper CD4+

HXB2 Location Env
Author Location
Epitope
Immunogen vaccine
Vector/Type: fowlpoxvirus, DNA prime with virus-like particle (VLP) boost *Strain:* B clade 89.6 *HIV component:* Env, Gag-Pol
Species (MHC) rabbit
Assay type Cytokine production
Keywords Th1, Th2
References Radaelli *et al.* 2003

- Rabbits were immunized with fowlpox recombinant vectors or expression plasmids, which express either SIVmac239 gag/pol or HIV-1 env 89.6P genes, and then boosted with virus-like particles (VLPs)(gag/pol SIV with HIV env 89.6).
- A lymphoproliferative Th0 profile response and homologous neutralizing Ab were seen in all three groups. The pcDNA3gag/pol SIV construct was more efficient at producing Abs than the fowlpox construct, although the fowlpox env89.6 construct elicited good humoral and cellular responses. VLP boosting was shown to be efficacious; the pseudoviral structure of the VLP providing a more natural protein conformational was considered helpful for eliciting long term memory cells.

HXB2 Location Env
Author Location gp160
Epitope
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: canarypox prime with gp160 boost *Strain:* B clade MN/LAI-2 *HIV component:* gp160
Species (MHC) human
Assay type proliferation
Keywords vaccine-specific epitope characteristics, vaccine-induced epitopes
References Ratto-Kim *et al.* 2003

- The CD4+ T-helper response to vaccinees given ALVAC-HIV(vCP205) alone, rgp160 MN/LAI-2 alone, or the two combined in a prime-boost was investigated by establishing T cell lines and comparing proliferative responses to a series of peptides (15 mers overlapping by 10) spanning autologous gp160 MN/LAI-2. Th responses against Env during natural HIV-1 infection were also studied.
- Broad, strong T-helper responses scattered across the Env were obtained from volunteers who received a prime boost vCP205 + rgp160MN/LAI-2, while those receiving rgp160 responded to fewer peptides, and vCP205 to very few peptides.
- HIV-1 + volunteers had less breadth and amplitude of Th responses than vaccinees that got the prime-boost vaccine, although T-cell lines were readily generated from HIV+ individuals. Some vaccinees targeted C1 and C5, while infected individuals did not, and some infected individuals targeted V3, while vaccinees did not.
- The authors note that the differences in response may be contributed to by the fact the peptides used to screen the responses were the same as the vaccine strain, and different than the strains in the natural infection, but that there also may be real immunological differences in the two scenarios of vaccine verses natural infection.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen HIV-1 infection
Species (MHC)
Assay type proliferation
Keywords HAART, ART
References Sullivan *et al.* 2003

- Lymphoproliferative responses to HIV antigens p24, gp120 and Nef were enhanced in eight patients who were switched from protease inhibitors to non-nucleoside reverse transcriptase inhibitors.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Assay type Cytokine production, proliferation
Keywords HAART, ART
References Hardy *et al.* 2003

- Upon initiating HAART, CD4+ T cell proliferative responses in 36 patients were restored to specific antigens, mitogens, and IL-2. Restored recall responses were largely to persistent antigens, and not to HIV-1 or new antigens, and recall responses were associated with IL-2, not IL-4 production.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords review, Th1, Th2, immune dysfunction
References Becker 2004b

- The review suggests HIV-1 shed gp120 virions can act as an allergen, inducing Th2 cytokine production, in particular IL-4, by Fc epsilon RI+ hematopoietic cells. This could inhibit IgG production and CTL responses, and inactivate Th1 cells. New vaccination strategies employing IL-4 inhibitors and anti-allergen drugs are discussed.

HXB2 Location Env
Author Location gp120
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords review, Th1, Th2, immune dysfunction
References Becker 2004a

- Review raises the possiblity that the switch from Th1 to Th2 activity along with an increase in IL-4 and IgE production in HIV-1 infected patients are an allergic response to HIV-1 protein gp120. Alternative treatments to block Th2 cytokine production, e.g with Il-4 receptor inhibitors, are discussed.

HXB2 Location Env
Author Location gp120 (IIIB)
Epitope

Subtype B
Immunogen vaccine
Vector/Type: peptide, heat-shock protein (HSP70) *Strain:* B clade IIIB *HIV component:* gp120
Species (MHC) macaque
Assay type Cytokine production, proliferation, CD4 T-cell Elispot - IFNγ, T-cell Elispot
Keywords genital and mucosal immunity, vaccine antigen design
References Bogers *et al.* 2004

- Macaques were given vaginal or iliac lymph node immunizations with a novel peptide vaccine composed of SIV p27, CCR5, and N-terminal gp120 fragment, and hsp70 as a carrier.
- 5/8 SHIV 89.6P challenged macaques were protected from infection and vaccinated animals had higher CD4+ T cell numbers than non-vaccinated controls. T-cell proliferation in responses to gp120, vaginal IgG and IgA Abs, and cells producing IL-2, IL-4, and IFNgamma were increased in vaccinated animals.

HXB2 Location Env
Author Location gp160 (IIIB)
Epitope
Subtype B
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA, protein, baculovirus *Strain:* B clade IIIB *HIV component:* gp160, Nef, Rev, Tat *Adjuvant:* aluminum phosphate
Species (MHC) human
Country Sweden
Assay type proliferation, CD8 T-cell Elispot - IFNγ
Keywords HAART, ART, subtype comparisons, supervised treatment interruptions (STI), immunotherapy
References Boström *et al.* 2004

- In this study, HIV-infected patients who had previously been immunized with DNA plasmid (nef, tat and ref) or recombinant gp160 were followed longitudinally to determine the impact of HAART on specific T-cell responses. While therapeutic immunizations had transient effects on CD4 cell counts, there was increased survival at 2 years.
- After gp160 vaccination, gp160-specific proliferative CD4+ T cell responses to both baculovirus (MGS HIV-1 rgp 160) and to IMMUNO AG derived gp160 were increased, as well as to p24. Long term HAART treatment was associated with increased IFN-γ producing T-cells.
- T-cell proliferative responses to gp160 vaccination were maintained for up to 7 years.

HXB2 Location Env
Author Location Env (HXB2. BaL)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade 1007 *HIV component:* Env, Gag-Pol, Nef
Species (MHC) macaque
Assay type CD4 T-cell Elispot - IFNγ, T-cell Elispot
Keywords variant cross-recognition or cross-neutralization, co-receptor
References Letvin *et al.* 2004

- SIVmac239 gag-pol-nef vaccination of macaques confers better protective responses against a SHIV 89.6 challenge if Env is included even when the vaccine and challenge strain were heterologous in Env. This protection, realized by decreased viral replication and higher levels of CD4+ T cells over time, was associated with T-cell responses early in infection, but not neutralizing Abs.
- The 24 Indian-origin rhesus macaques included in this study did not express Mamu-A*01.

HXB2 Location Env
Author Location
Epitope
Subtype CRF02_AG
Immunogen HIV-1 or HIV-2 infection
Species (MHC) human
Country Senegal
Assay type CD4 T-cell Elispot - IFNγ
Keywords rate of progression, variant cross-recognition or cross-neutralization
References Zheng *et al.* 2004

- Gag, Env, Tat, and Nef-specific T-cell responses were evaluated in 68 HIV-1 and 55 HIV-2 infected drug naive, generally asymptomatic, infected Senegalese patients.
- HIV-1 peptides were derived from HIV-1 CRF-02 (HIV-1 A/G, AJ251056)and HIV-2 peptides spanning HIV-2 ROD (M15390).
- Gag specific responses dominated in both groups, but overall magnitude and frequencies did not correlate with viral load or CD4 counts. More Nef responses were found in HIV-1 infected people than HIV-2, and Nef in HIV-2 is more diverse.

HXB2 Location Env
Author Location
Epitope
Immunogen vaccine
Vector/Type: DNA with CMV promotor *Strain:* B clade HXB2, B clade NL43, A clade 92RW020, C clade 97ZA012 *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country United States
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords therapeutic vaccine
References Catanzaro *et al.* 2006

- 14 volunteers uninfected with HIV completed a set of injections with a 6-plasmid DNA vaccine encoding EnvA, EnvB, EnvC, and subtype B Gag, Pol, and Nef. CD4 and CD8 T cell responses to Env and Gag were most frequently detected.
- For EnvA, 11/14 subjects showed a positive CD4+ T cell response by ICS.

HXB2 Location Env
Author Location

T-Helper CD4+

Epitope
Immunogen vaccine
Vector/Type: adenovirus type 5 (Ad5) *HIV component:* Env, Gag *Adjuvant:* Cholera toxin (CT)
Species (MHC) macaque
Assay type proliferation, CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, Other
Keywords vaccine antigen design
References Mercier *et al.* 2007

- 3 rhesus macaques were given oral immunizations with an enteric-coated mixture of adenoviral vectors expressing HIV-1 gag and a string of conserved env peptides representing broadly cross-reactive CD4+ and CD8+ epitopes. The macaques were boosted intranasally with a mixture of 6 HIV-1 envelope peptides plus cholera toxin adjuvant.
- The immunizations increased cellular immune responses, including antigen-specific IFNgamma-producing CD4+ and CD8+ effector memory T cells in the intestine. After only the oral immunization, there were no EliSpot responses to env peptides or to gag. After the intranasal boost, EliSpot responses against env peptides and against inactivated HIV were markedly increased, but gag responses were not.

HXB2 Location Env
Author Location Env
Epitope
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost *Strain:* B clade JRFL, A clade 92RW020, M group Consensus, C clade 96ZM651 *HIV component:* Env
Species (MHC) mouse
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ
Keywords variant cross-recognition or cross-neutralization, vaccine antigen design
References Weaver *et al.* 2006

- 3 different mouse strains were immunized with subtype A, B, C, and M-group consensus env DNA immunogens. CTL and Helper T-cell epitopes were mapped using peptide sets from heterologous A, B, and C viruses. The consensus immunogen induced a greater number and magnitude of T-cell responses than any single wild-type env.

HXB2 Location Env
Author Location
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade
Species (MHC) macaque
Assay type Intracellular cytokine staining
Keywords subtype comparisons, vaccine antigen design
References Smith *et al.* 2005

- Macaques were immunized with a clade B HIV vaccine and tested for responses to pools of clade B and A/G Env and Gag peptides. While CD4 responses were more frequent than CD8 responses, higher cross-clade responses were found for CD8 responses. The authors suggest that the better cross-clade reactivity of the CD8 responses reflects the size difference between CD8 and CD4 epitopes; the smaller CD8 epitopes provide a smaller target for mutation.
- All 5 pools of B Env and Gag peptides stimulated CD4 responses, while only 2 pools of A/G peptides stimulated responses, suggesting that 1 or 2 out of 5 CD4 epitopes were cross-reactive.

HXB2 Location Env
Author Location
Epitope
Subtype B
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* Other *HIV component:* Env, Gag, Pol, Rev, Tat, Vif, Vpr
Species (MHC) macaque
Assay type CD8 T-cell Elispot - IFNγ, Tetramer binding, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords vaccine-induced epitopes, vaccine antigen design
References Sadagopal *et al.* 2005

- 22/23 macaques that were immunized with a DNA prime SHIV-89.6 and boosted with rMVA showed successful control of viremia, with low or undetectable viral loads and normal CD4 counts 200 weeks postchallenge. IFN-gamma producing T cells were found in unexpectedly low breadths and frequencies. T-cell responses were stable over time and maintained their production of IFN-gamma and IL-2. Long-term control was found in macaques of diverse histocompability types. The CD8 T cells seemed to have the most impact on well-contained chronic infections in the vaccinated and challenged animals.
- After challenge, vaccinated animals maintained normal levels of CD4 cells, while unvaccinated animals quickly lost CD4 cells. Both CD4 and CD8 responses were found to the SIV Gag and HIV Env proteins; 60% of CD8+ epitopes and 80% of CD4+ epitopes were in p27.

III-B-18 Nef Helper/CD4+ T-cell epitopes

HXB2 Location Nef (1–20)
Author Location Nef (1–20 LAI)
Epitope MGGKWSKSSVVGWPTVRERM
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^d)
References Hinkula *et al.* 1997

T-Helper CD4+

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Nef (1–20)
Author Location Nef (1–20 HXB2)
Epitope MGGKWSKSSVIGWPTVRERM
Subtype B
Immunogen HIV-1 infection
Species (MHC) (H-2^d)
Keywords class I down-regulation by Nef
References Peng & Robert-Guroff 2001

- Deletion of the 19 N-terminal amino acids from Nef including the myristolation signal eliminates Nef-induced downregulation of MHC class I and CD4 molecules. Such a construct has the potential to serve as a more potent immunogen. The known T-cell epitopes that that would be disputed by this deletion are minimal, a murine H-2d Th epitope in the peptide MGGKWSKSSVIGWPTVRERM, and a HLA-B8 CTL epitope, WPTVRERM.

HXB2 Location Nef (8–23)
Author Location (clade B consensus)
Epitope RSVVGWPAVRERMRRA
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101, A*0201, B*0801, B*1302, Cw*0602, Cw*0701, DRB1*0301
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords escape
References Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- ckmsGWsnVRERMRRt variant coincided with a positive response. ckmsGWsnVREkMRRt variant 5 weeks later coincided with no response.

HXB2 Location Nef (14–22)
Author Location Nef (14–22 SF2)
Epitope SAIRERMRR
Epitope name 95.12, 33.6
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DRw6)
Donor MHC DP4, DQw1, DQw6, DRw15(2), DRw52, DRw6
Assay type proliferation
Keywords epitope processing
References Wentworth & Steimer 1994

- Seven CD4+ T-cell clones that proliferated in responses to SF2 Nef were generated *in vitro* by stimulation of PBMC from uninfected donors. These CD4+ clones also had cytotoxic activity.
- These seven clones were capable as of presenting their epitopes to themselves, if Nef peptides were provided.
- The two clones that recognized the epitope SAIRERMRR could also auto-present Nef protein, suggesting that they recognized this epitope in the context of the intact, unprocessed protein.

HXB2 Location Nef (14–30)
Author Location (clade B consensus)
Epitope PAVRERMRRAEPAADGV
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101, A*0201, B*0801, B*1302, Cw*0602, Cw*0701, DRB1*0301; A*0101, A*0201, B*4001, C*0304, DRB1*0801, DRB1*1301
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords escape
References Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- In one patient, snVRERMRRtEPAADGV variant coincided with a positive response. snVREkMRRtEPAADGV variant 5 weeks later coincided with no response. In another patient, PkVRERMkqAEPAADGV variant coincided with a positive response. PkVRERMkqAEPAAnGV variant 4 weeks later coincided with very diminished response.

HXB2 Location Nef (16–35)
Author Location Nef (16–35 LAI)
Epitope VRERMRRAEPAADGVGAASR
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^d)
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Nef (21–37)
Author Location (clade B consensus)
Epitope RRAEPAADGVGAVSRDL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0101, A*0201, B*4001, C*0304, DRB1*0801, DRB1*1301
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords escape
References Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.

T-Helper CD4+

- kqAEPAADGVGAVSqDL variant coincided with low response. kqAEPAAnGVGAVSqDL variant 4 weeks later coincided with an increased response.

HXB2 Location Nef (31–50)
Author Location Nef (31–50 LAI)
Epitope GAASRDLEKHGAITSSNTAA
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^{d})
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Nef (37–51)
Author Location
Epitope LEKHGAITSSNTAAT
Epitope name N010
Immunogen HIV-1 infection
Species (MHC) human
Country Canada
Assay type proliferation, Flow cytometric T-cell cytokine assay
Keywords memory cells
References Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN-γ, but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN-γ only-producing cells are short lived.

HXB2 Location Nef (37–51)
Author Location
Epitope LEKHGAITSSNTAAT
Epitope name N010
Immunogen HIV-1 infection
Species (MHC) human
Country Canada
Assay type proliferation, Flow cytometric T-cell cytokine assay
Keywords memory cells
References Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN-γ, but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN-γ only-producing cells are short lived.

HXB2 Location Nef (43–49)
Author Location Nef (47–53 SF2)
Epitope ITSSNTA
Epitope name 1.13
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DQw7)
Donor MHC DP4, DQw1, DQw7, DR1, DR8, DRw52
Assay type proliferation
Keywords epitope processing
References Wentworth & Steimer 1994

- Seven CD4+ T-cell clones that proliferated in responses to SF2 Nef were generated *in vitro* by stimulation of PBMC from uninfected donors. These CD4+ clones also had cytotoxic activity.
- These seven clones were capable as of presenting their epitopes to themselves, if Nef peptides were provided.

HXB2 Location Nef (45–59)
Author Location
Epitope SSNTAATNAACAWLE
Epitope name N012
Immunogen HIV-1 infection
Species (MHC) human
Country Canada
Assay type proliferation, Flow cytometric T-cell cytokine assay
Keywords memory cells
References Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN-γ, but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN-γ only-producing cells are short lived.

HXB2 Location Nef (45–69)
Author Location Nef (45–69 BRU)
Epitope SSNTAATNAACAWLEAQEEEEVGFP
Immunogen vaccine
Vector/Type: peptide prime with protein boost *Strain:* B clade BRU *HIV component:* Nef
Species (MHC) chimpanzee, rat
References Estaquier *et al.* 1992

- Antigenic domain: ATNAACAWL, priming with peptide enhanced subsequent Ab response to Nef protein immunization.

HXB2 Location Nef (45–69)
Author Location Nef (45–69)
Epitope SSNTAATNAACAWLEAQEEEEVGFP
Immunogen vaccine
Vector/Type: peptide *Adjuvant:* aluminum hydroxide
Species (MHC) rat
Keywords vaccine-specific epitope characteristics
References Rouaix *et al.* 1994

- Covalently linking the potent Th epitope Nef 45-69, which can induce Th proliferative responses at low doses with no adjuvant in Lou/M rats, to a weaker epitope from Schistosoma mansoni allows the induction of detectable Th responses to the Schistosoma epitope.

HXB2 Location Nef (46–65)
Author Location Nef (46–65 LAI)
Epitope SNTAATNAACAWLEAQEEEE
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^d)
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Nef (56–68)
Author Location Nef (56–68)
Epitope AWLEAQEEEEVGF
Epitope name Nef-4
Immunogen HIV-1 infection
Species (MHC) human (DQ)
Country France
Assay type proliferation
Keywords computational epitope prediction, cross-presentation by different HLA
References Pancré *et al.* 2007

- Responses to 4 Nef epitopes (3 HLA-DR epitopes selected with TEPITOPE software and 1 HLA-DQ epitope) were evaluated in treatment naive asymptomatic patients and long term non-progressors. 2 years later, more than half medium- and non-responders followed bi-therapy, while high responders to Nef peptides still were without antiretroviral treatment and conserved stable CD4 counts, indicating that Nef specific CD4+ response is associated with non-progression.
- Proliferative response to Nef epitopes was always associated with high IFN-γ secretion.
- AWLEAQEEEEVGF was described as promiscuous HLA-DQ epitope in Pancre2002.

HXB2 Location Nef (56–68)
Author Location Nef (56–68 HXB2)
Epitope AWLEAQEEEEVGF
Immunogen vaccine
Vector/Type: peptide *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse (DQ2, DQ3, DQ5, DQ6, DQ7, DQ8)
Keywords binding affinity, cross-presentation by different HLA, Th1, TCR usage
References Pancré *et al.* 2002

- This highly conserved Nef epitope has promiscuous HLA-DQ class II binding potential. It has a can bind to 6 different HLA-DQ alleles, but did not bind to any HLA-DR alleles tested. It bound to DQ2 and DQ8 with particularly high affinity, and with DQ7 with low affinity.
- DQ transgenic mice (in particular DQ8) mounted strong cellular and humoral responses after immunization with this peptide.
- Ex vivo stimulation of CD4+ T-cells from 14 healthy donors (with diverse HLAs) with this peptide presented on autologous DCs resulted in Th1-associated cytokine production. IFNgamma production was stimulated in 7/14 cases, both IFNgamma and IL-2 in 6/14, and just IL-2 in 1/14. No IL-4 or IL-5 production was observed.
- Peptide-specific CD4+ T-cell clones with different HLA presenting molecules demonstrated a preference for TCR Vβ6.1.

HXB2 Location Nef (56–68)
Author Location Nef (56–68)
Epitope AWLEAQEEEEVGF
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade *HIV component:* Nef
Species (MHC) transgenic mouse (DQ6, DQ8)
Assay type proliferation, HLA binding
Keywords binding affinity, computational epitope prediction
References Depil *et al.* 2006

- A combination of peptide-binding assays and HLA II transgenic mice experiments was sugggested for selecting T helper epitopes. HIV Nef peptide AWLEAQEEEEVGF and Sm28GST peptide ENLLASSPRLAKYLSNRPATPF were used as models.

HXB2 Location Nef (61–80)
Author Location Nef (61–80 LAI)
Epitope QEEEEVGFPVTPQVPLRPMT
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^b)
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Nef (64–73)
Author Location Nef (68–77 SF2)
Epitope EEVGFPVRPQ

Epitope name 59.25
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DRw15(2))
Donor MHC DP4, DQw1, DR1, DRw15(2)
Assay type proliferation
Keywords epitope processing
References Wentworth & Steimer 1994

- Seven CD4+ T-cell clones that proliferated in responses to SF2 Nef were generated *in vitro* by stimulation of PBMC from uninfected donors. These CD4+ clones also had cytotoxic activity.
- These seven clones were capable as of presenting their epitopes to themselves, if Nef peptides were provided.

HXB2 Location Nef (65–79)
Author Location
Epitope EVGFPVIPQVPLRPM
Epitope name N017
Immunogen HIV-1 infection
Species (MHC) human
Country Canada
Assay type proliferation, Flow cytometric T-cell cytokine assay
Keywords memory cells
References Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN-γ, but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN-γ only-producing cells are short lived.

HXB2 Location Nef (66–73)
Author Location Nef (70–77 SF2)
Epitope VGFPVRPQ
Epitope name 29.16
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DR1, DRw15(2))
Donor MHC DP4, DQw1, DR1, DRw15(2)
Assay type proliferation
Keywords epitope processing
References Wentworth & Steimer 1994

- Seven CD4+ T-cell clones that proliferated in responses to SF2 Nef were generated *in vitro* by stimulation of PBMC from uninfected donors. These CD4+ clones also had cytotoxic activity.
- These seven clones were capable as of presenting their epitopes to themselves, if Nef peptides were provided.

HXB2 Location Nef (66–88)
Author Location
Epitope VGFPVRPQVPLRPMTYKAAVDLS
Epitope name HIV-VAX-1062
Immunogen HIV-1 infection
Species (MHC) human (DRB*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords subtype comparisons, computational epitope prediction, vaccine antigen design
References De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 5/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was QVPLRPMTY.

HXB2 Location Nef (66–97)
Author Location Nef (66–97)
Epitope VGFPVTPQVPLRPMTYKAAVDLSHFLKEKGGL
Epitope name Nef-2
Immunogen HIV-1 infection
Species (MHC) human (DQ)
Country France
Assay type proliferation
Keywords computational epitope prediction, cross-presentation by different HLA
References Pancré *et al.* 2007

- Responses to 4 Nef epitopes (3 HLA-DR epitopes selected with TEPITOPE software and 1 HLA-DQ epitope) were evaluated in treatment naive asymptomatic patients and long term non-progressors. 2 years later, more than half medium- and non-responders followed bi-therapy, while high responders to Nef peptides still were without antiretroviral treatment and conserved stable CD4 counts, indicating that Nef specific CD4+ response is associated with non-progression.
- Proliferative response to Nef epitopes was always associated with high IFN-γ secretion.
- VGFPVTPQVPLRPMTYKAAVDLSHFLKEKGGL was predicted by TEPITOPE to bind HLA DR1, DR3, DR4, DR7, DR11, DR15, DRB5.

HXB2 Location Nef (66–97)
Author Location Nef (66–97 LAI)
Epitope VGFPVTPQVPLRPMTYKAAVDLSHFLKEKGGL
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide
Species (MHC) human
References Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 5/10 reacted to this Nef peptide.
- 9/12 tested mounted a CTL responses to at least one of the six peptides, each of the six peptides elicited a CTL response in at least one individual.
- 5/12 tested had an IgG response to this peptide.

HXB2 Location Nef (73–90)

T-Helper CD4+

Author Location (clade B consensus)
Epitope QVPLRPMTYKAAVDLSHF
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0201, A*0205, B*3501, B*4901, Cw*040, Cw*0701, DRB1*0101, DRB1*100101; A*0201, A*290201, B*1501, B*4403, Cw*0304, Cw*1601, DRB1*0401, DRB1*0701
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords escape
References Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- In one patient, QVPLRPMTYKAAlDLSHF mutation was coincident with a gain of response. In another patient, QVPLRPMTYKgAlDLtHF variant coincided with no response. QVPLRPMTYKgAlDLSHF variant 4 weeks later coincided with a positive response.

HXB2 Location Nef (76–95)
Author Location Nef (76–95 LAI)
Epitope LRPMTYKAAVDLSHFLKEKG
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^{b})
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Nef (81–97)
Author Location Nef (81–97 B Consensus)
Epitope YKAAVDLSHFLKEKGGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location Nef (81–97)
Author Location (clade B consensus)
Epitope YKAAVDLSHFLKEKGGL
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Donor MHC A*0201, A*290201, B*1501, B*4403, Cw*0304, Cw*1601, DRB1*0401, DRB1*0701
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords escape
References Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- YKgAlDLtHFLKEKGGL coincided with no response. YKgAlDLSHFLKEKGGL variant 4 weeks later coincided with a positive response.

HXB2 Location Nef (81–97)
Author Location Nef (81–97)
Epitope YKAAVDLSHFLKEKGGL
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- YKAAVDLSHFLKEKGGL is a previously known epitope that is a part of TCI fragment FPVRPQVPLRPMTYKAAVDLSHFLKEKGGLEGL in this vaccine construct.

T-Helper CD4+

HXB2 Location Nef (91–110)
Author Location Nef (91–110 LAI)
Epitope `LKEKGGLEGLIHSQRRQDIL`
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^b)
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Nef (98–112)
Author Location Nef (98–112 BRU)
Epitope `EGLIHSQRRQDILDL`
Immunogen vaccine
Vector/Type: peptide prime with protein boost *Strain:* B clade BRU *HIV component:* Nef
Species (MHC) chimpanzee
References Estaquier *et al.* 1992

- Peptide alone could stimulate monkey T-cells in the absence of carrier protein – required carrier protein in rat.

HXB2 Location Nef (104–121)
Author Location Nef (104–121 B Consensus)
Epitope `QKRQDILDLWVYHTQGYF`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location Nef (104–121)
Author Location Nef (104–121)
Epitope `QKRQDILDLWVYHTQGYF`
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- QKRQDILDLWVYHTQGYF is a previously known epitope that is a part of TCI fragment IHSQKRQDILDLWVYHTQGYFPDWQNYTPGPGIRYPLTFGWCYKLVP in this vaccine construct.

HXB2 Location Nef (104–123)
Author Location Nef (106–125 HXB3)
Epitope `QRRQDILDLWIYHTQGYFPD?`
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade HXB3 *HIV component:* Nef
Species (MHC) mouse (H-2^b)
References Sandberg *et al.* 2000

- A strong T helper proliferative response against a rec Nef protein was observed 2 weeks after immunization of HLA-A201 transgenic mice in a C57Bl/6 background – the response was weak by 4 weeks post immunization.
- Mice were immunized with nef DNA under the control of a CMV promotor, coated on gold particles delivered to abdominal skin by a gene gun.
- Primary responses were directed at peptides 106-125, 166-185, and 181-205, indicating a response to multiple epitopes.

HXB2 Location Nef (106–125)
Author Location Nef (106–125 LAI)
Epitope `RQDILDLWIYHTQGYFPDWQ`
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^b)
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

T-Helper CD4+

HXB2 Location Nef (112–127)
Author Location Nef (112–127 B Consensus)
Epitope LWVYHTQGYFPDWQNY
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 14% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location Nef (112–127)
Author Location Nef (112–127)
Epitope LWVYHTQGYFPDWQNY
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (MHC) human
Country Russia
Assay type T-cell Elispot
Keywords vaccine antigen design
References Bazhan *et al.* 2008

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef.
- Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation.
- LWVYHTQGYFPDWQNY is a previously known epitope that is a part of TCI fragment IHSQKRQDILDLWVYHTQGYFPDWQNYTPGPGIRYPLTFGWCYKLVP in this vaccine construct.

HXB2 Location Nef (112–128)
Author Location Nef (111–128)
Epitope LWVYHTGQGYFPDWQNYT
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Netherlands
Assay type Cytokine production
References Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. LWVYHTGQGYFPDWQNYT had fixation of 1 mutation (LWVYHTGQGYFPDW[q/d]NYT) in 1 of the patients.

HXB2 Location Nef (117–147)
Author Location Nef (117–147 LAI)
Epitope TQGYFPDWQNYTPGPGVRYPLTFGWCYKLVP
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide
Species (MHC) human
References Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 1/10 reacted to this Nef peptide.
- 9/12 tested mounted a CTL responses to at least one of the six peptides, each of the six peptides elicited a CTL response in at least one individual.
- 10/12 tested had an IgG response to this peptide.

HXB2 Location Nef (121–140)
Author Location Nef (121–140 LAI)
Epitope FPDWQNYTPGPGVRYPLTFG
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^{b})
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Nef (133–159)
Author Location Nef (133–159)
Epitope VRYPLTFGWCYKLVPVEPDKVEEANKG
Epitope name Nef-3
Immunogen HIV-1 infection
Species (MHC) human (DR)

T-Helper CD4+

Country France
Assay type proliferation
Keywords computational epitope prediction, cross-presentation by different HLA
References Pancré *et al.* 2007

- Responses to 4 Nef epitopes (3 HLA-DR epitopes selected with TEPITOPE software and 1 HLA-DQ epitope) were evaluated in treatment naive asymptomatic patients and long term non-progressors. 2 years later, more than half medium- and non-responders followed bi-therapy, while high responders to Nef peptides still were without antiretroviral treatment and conserved stable CD4 counts, indicating that Nef specific CD4+ response is associated with non-progression.
- Proliferative response to Nef epitopes was always associated with high IFN-γ secretion.
- VRYPLTFGWCYKLVPVEPDKVEEANKG was predicted by TEPITOPE to bind HLA DR1, DR3, DR4, DR7, DR11, DR15, DRB5.

HXB2 Location Nef (136–155)
Author Location Nef (136–155 LAI)
Epitope `PLTFGWCYKLVPVEPDKVEE`
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^d)
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Nef (151–170)
Author Location Nef (151–170 LAI)
Epitope `DKVEEANKGENTSLLHPVSL`
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^d)
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Nef (162–178)
Author Location Nef (162–178 B Consensus)
Epitope `NSLLHPMSLHGMDDPEK`
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location Nef (164–183)
Author Location Nef (166–185 HXB3)
Epitope `LLHPVSLHGMDDPEREVLEW?`
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade HXB3 *HIV component:* Nef
Species (MHC) mouse (H-2^b)
References Sandberg *et al.* 2000

- A strong T helper proliferative response against a rec Nef protein was observed 2 weeks after immunization of HLA-A201 transgenic mice in a C57Bl/6 background – the response was weak by 4 weeks post immunization.
- Mice were immunized with nef DNA under the control of a CMV promotor, coated on gold particles delivered to abdominal skin by a gene gun.
- Primary responses were directed at peptides 106-125, 166-185, and 181-205, indicating a response to multiple epitopes.

HXB2 Location Nef (166–185)
Author Location Nef (166–185 LAI)
Epitope `HPVSLHGMDDPEREVLEWRF`
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^b, H-2^d)
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Nef (176–193)
Author Location Nef (176–193 B consensus)
Epitope `PEKEVLVWKFDSRLAFHH`
Subtype B
Immunogen HIV-1 infection

T-Helper CD4+

Species (MHC) human (DRB1*0101, DRB1*0401, DRB1*0701, DRB1*1101, DRB1*1302, DRB1*1501, DRB5*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 36% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The peptides that were recognized by the most people were able to bind broadly to multiple HLA-DR molecules. This peptide showed high cross-reactive binding capacity and bound to 7/8 tested HLA-DR molecules.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location Nef (179–198)
Author Location Nef (181–205 HXB3)
Epitope `EVLEWRFDSRLAFHHVAREL?`
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade HXB3 *HIV component:* Nef
Species (MHC) mouse (H-2^b)
References Sandberg *et al.* 2000

- A strong T helper proliferative response against a rec Nef protein was observed 2 weeks after immunization of HLA-A201 transgenic mice in a C57Bl/6 background – the response was weak by 4 weeks post immunization.
- Mice were immunized with nef DNA under the control of a CMV promotor, coated on gold particles delivered to abdominal skin by a gene gun.
- Primary responses were directed at peptides 106-125, 166-185, and 181-205, indicating a response to multiple epitopes.

HXB2 Location Nef (180–194)
Author Location Nef (180–194 clade B consensus)
Epitope `VLEWRFDSRLAFHHV`
Subtype B
Immunogen HIV-1 infection, computer prediction
Species (MHC) human (DRB1*0101, DRB1*0701, DRB1*1101, DRB1*1501, DRB5*0101)
Country Brazil
Assay type CD4 T-cell Elispot - IFNγ, HLA binding
Keywords binding affinity, computational epitope prediction, cross-presentation by different HLA
References Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 brazilian HIV-1 chronically infected individuals.
- While VLEWRFDSRLAFHHV is the reacting peptide, shorter WRFDSRLAF peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

HXB2 Location Nef (180–202)
Author Location Nef (180–202)
Epitope `VLEWRFDSRLAFHHVARELHPEY`
Epitope name Nef-1
Immunogen HIV-1 infection
Species (MHC) human (DR)
Country France
Assay type proliferation
Keywords computational epitope prediction, cross-presentation by different HLA
References Pancré *et al.* 2007

- Responses to 4 Nef epitopes (3 HLA-DR epitopes selected with TEPITOPE software and 1 HLA-DQ epitope) were evaluated in treatment naive asymptomatic patients and long term non-progressors. 2 years later, more than half medium- and non-responders followed bi-therapy, while high responders to Nef peptides still were without antiretroviral treatment and conserved stable CD4 counts, indicating that Nef specific CD4+ response is associated with non-progression.
- Proliferative response to Nef epitopes was always associated with high IFN-γ secretion.
- VLEWRFDSRLAFHHVARELHPEY was predicted by TEPITOPE to bind HLA DR1, DR3, DR4, DR7, DR11, DR15, DRB5.

HXB2 Location Nef (181–188)
Author Location Nef (185–192 SF2)
Epitope `LVWRFDSK`
Epitope name 6.38
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DP5)
Donor MHC DP5, DQw7, DRw11, DRw52
Assay type proliferation
Keywords epitope processing
References Wentworth & Steimer 1994

- Seven CD4+ T-cell clones that proliferated in responses to SF2 Nef were generated *in vitro* by stimulation of PBMC from uninfected donors. These CD4+ clones also had cytotoxic activity.
- These seven clones were capable as of presenting their epitopes to themselves, if Nef peptides were provided.

HXB2 Location Nef (181–205)
Author Location Nef (181–205 LAI)

T-Helper CD4+

Epitope LEWRFDSRLAFHHVARELHPEYFKN
Subtype B
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade LAI *HIV component:* Nef, Rev, Tat
Species (MHC) mouse (H-2^d)
References Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

HXB2 Location Nef (182–205)
Author Location Nef (182–205 LAI)
Epitope EWRFDSRLAFHHVARELHPEYFKN
Subtype B
Immunogen vaccine
Vector/Type: lipopeptide
Species (MHC) human
References Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 4/10 reacted to this Nef peptide.
- 9/12 tested mounted a CTL responses to at least one of the six peptides, each of the six peptides elicited a CTL response in at least one individual.
- None of the 12 tested had an IgG response to this peptide.

HXB2 Location Nef (184–199)
Author Location Nef (184–199 B consensus)
Epitope KFDSRLAFHHMARELH
Subtype B
Immunogen HIV-1 infection
Species (MHC) human (DRB1*0101, DRB1*0701, DRB1*1101, DRB1*1501, DRB5*0101)
Country United States
Assay type CD4 T-cell Elispot - IFNγ
Keywords supervised treatment interruptions (STI), immunodominance
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 25% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The peptides that were recognized by the most people were able to bind broadly to multiple HLA-DR molecules. This peptide showed high cross-reactive binding capacity and bound to 5/8 tested HLA-DR molecules.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location Nef (184–199)
Author Location Nef (184–199)
Epitope KFDSRLAFHHMARELH
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Netherlands
Assay type Cytokine production
References Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. KFDSRLAFHHMARELH had fixation of 2 mutations (KFDS[r/h]LAF[h/r]HMARELH) in 1 of the patients.

HXB2 Location Nef (185–200)
Author Location Nef (183–198)
Epitope FDSRLAFHHVARELHP
Immunogen HIV-1 infection
Species (MHC) human
References Ranki *et al.* 1997

- T-cell response to this epitope persisted after seroreversion.

HXB2 Location Nef (186–206)
Author Location Nef (p27) (185–205 BRU)
Epitope DSRLAFHHVARELHPEYFKNC
Epitope name PF63
Subtype B
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU *HIV component:* gp160, Nef, p17/p24 Gag, p25 Gag *Adjuvant:* muramyl-dipeptide base adjuvant (Syntex)
Species (MHC) chimpanzee
Keywords immunodominance
References Bahraoui *et al.* 1990

- Six chimpanzees were immunized with rec vaccinia viruses (VV) expressing HIV-1 gp160, Gag, and Nef.
- 2/6 chimpanzees showed persistent T-helper proliferative responses against a putative immunodominant epitope located at the C-term end of Nef.

HXB2 Location Nef (189–203)
Author Location
Epitope LAFHHVARELHPEYF
Epitope name N048
Immunogen HIV-1 infection

T-Helper CD4+

Species (MHC) human
Country Canada
Assay type proliferation, Flow cytometric T-cell cytokine assay
Keywords memory cells
References Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN-γ, but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN-γ only-producing cells are short lived.

HXB2 Location Nef (190–206)
Author Location Nef (190–206 B Consensus)
Epitope AFHHMARELHPEYYKDC
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country United States
Assay type CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining, HLA binding
Keywords supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection
References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN-γ EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 14% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

HXB2 Location Nef (191–199)
Author Location Nef (195–203 SF2)
Epitope FHHMARELH
Epitope name 3.2
Subtype B
Immunogen in vitro stimulation or selection
Species (MHC) human (DR1)
Donor MHC DP4, DQw1, DQw7, DR1, DR8, DRw52
Assay type proliferation
Keywords epitope processing
References Wentworth & Steimer 1994

- Seven CD4+ T-cell clones that proliferated in responses to SF2 Nef were generated *in vitro* by stimulation of PBMC from uninfected donors. These CD4+ clones also had cytotoxic activity.
- These seven clones were capable as of presenting their epitopes to themselves, if Nef peptides were provided.

HXB2 Location Nef
Author Location Nef
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Nef, Vif, Vpu
Species (MHC) mouse (H-2^d)
Keywords subtype comparisons, Th1
References Ayyavoo *et al.* 2000

- Splenocytes from BALB/c mice immunized with pVVN-P DNA were incubated with Vif, Vpu or Nef antigens for 3 days and assayed for IL-4 and IFN-γ levels.
- Antigen stimulation increased IFN-γ production in pVVN-P immunized mice, indicating a Th1 response.
- IL-4 production was not significantly changed after antigen stimulation compared to control levels.
- Cross-clade CTL activity was also observed: A, B clade, CRF01(AE) clade antigens could serve as targets for the B clade immunization stimulated CTL – an HIV-1 AC recombinant, however, did not stimulate a CTL response, but was expressed at lower levels on the target cell.

HXB2 Location Nef
Author Location Nef (LAI)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
References da Silva & Hughes 1998

- This study compares the level of variation in Nef CTL epitopes to helper and MAb epitopes from the same region.
- CTL epitopes tend to be more conserved than either helper or MAb epitopes and there are stronger functional constraints in the regions where CTL epitopes cluster.

HXB2 Location Nef
Author Location Nef
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Nef, Rev, Tat
Species (MHC) human
Keywords HAART, ART
References Calarota *et al.* 1999

- 9/9 HIV-1 + subjects were given one of three DNA vaccinations for nef, rev or tat, and novel proliferative and CTL responses were generated.
- The nef DNA immunization induced the highest and most consistent CTLp activity, IFN-γ production, and IL-6 and IgG responses.

T-Helper CD4+

- Highly active antiretroviral treatment (HAART) did not induce new HIV-specific CTL responses but reduced viral load, while DNA vaccination induced new immune responses but did not reduce viral load – thus this is a potentially complementary and promising combination.

HXB2 Location Nef
Author Location Nef
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA *HIV component:* Nef, Rev, Tat *Adjuvant:* CpG immunostimulatory sequence (ISS)
Species (MHC) human
Keywords review, Th1
References Calarota & Wahren 2001

- This review discusses the cellular immune response, and comments on CpG induction of Th1 cytokines and enhanced immune responses, and HIV-1 DNA vaccine boosting of CTL and Th proliferative responses in asymptomatic HIV+ individuals.

HXB2 Location Nef
Author Location Nef
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART
References Oxenius *et al.* 2000

- Patients who started therapy at acute HIV infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.

HXB2 Location Nef
Author Location Nef
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords rate of progression, Th1, Th2
References Wilson *et al.* 2000b

- Dysfunction of HIV-1 specific proliferative responses, but not responses to other antigens, is evident in HIV-1 progressive disease.
- Vigorous HIV-1 specific responses to p24, Nef and gp120 with SI between 8-99 were seen in 6/7 long term non-progressors (LTNP), the seventh had a borderline responses. IL-2 production was seen in all cases, and IL-4 production was also evident many responses.
- None of the progressors (0/5) had HIV-1 specific proliferative responses, or IL-2 or IL-4 induction.
- Non-HIV antigens (cytomegalovirus, PPD, Staphylococcus enterotoxin B, tetanus toxoid) gave similar responses in HIV-1 + LTNP, progressors, and HIV-1 controls.

HXB2 Location Nef
Author Location Nef (BRU)
Epitope
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA), PLG
Species (MHC) mouse
Keywords Th2
References Moureau *et al.* 2002

- BALB/c mice were immunized with Nef alone, Nef with Freund's adjuvant, or Nef encapsulated in poly(DL-lactide-co-glycolide) PLG microparticles.
- High Ab titers (predominantly IgG1) against Nef were retained for seven months in the mice infected with Nef-PLG, 3-fold higher than Nef in Freund's, 5-fold higher than Nef alone.
- CD4+ T-cell lymphoproliferative were observed, and cytokine profiles indicated this was primarily a Th2 response.

HXB2 Location Nef
Author Location Nef (SF2)
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Keywords subtype comparisons, rate of progression
References Imami *et al.* 2002b

- 70 patients with chronic disease progression, 10 clinical non-progressors, and 3 immunologically discordant progressors (individuals who controlled viremia but had progressive CD4+ T-cell decline) were analyzed for their T-helper cell responses to p24 and cytokine profile.
- In a comparison of responses to HIV-1 proteins based on 10 non-progressors, 3 immunologically discordant, and 70 progressors, SIs were always much higher for non-progressors and immunologically discordant than progressors. Among the non-progressors, the responses to different antigens were greater using p24 peptides than native p24. Native p24, Nef, gp120 proteins, and Remune (gp120 depleted HIV-1, p24 is subtype G), had roughly comparable distributions of SI values from the non-progressors, Nef and gp120 responses were somewhat diminished in immunologically discordant patients.

HXB2 Location Nef
Author Location (BRU)
Epitope
Subtype B
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade BRU *HIV component:* RT, virus *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (MHC) mouse
References Haas *et al.* 1991

- Of 5 mouse inbred lines tested: DBA/2 (H-2d, Ad, Ed), B10.A(4R) (H-2h4, Ak) and B10.A(5R) (H-2i5) showed particularly good CD4+ T cell proliferative responses to HIV proteins (gp160, gp120, p17, p24, Nef and RT), after vaccination with inactivated virus.

- B10.BR (H-2k, Ak, Ek) and C57BL/6 (H-2b and Ab) had weaker responses.

HXB2 Location Nef
Author Location Nef
Epitope
Immunogen
Species (MHC)
References

HXB2 Location Nef
Author Location Nef
Epitope
Immunogen HIV-1 infection
Species (MHC)
Assay type proliferation
Keywords HAART, ART
References Sullivan *et al.* 2003

- Lymphoproliferative responses to HIV antigens p24, gp120 and Nef were enhanced in eight patients who were switched from protease inhibitors to non-nucleoside reverse transcriptase inhibitors.

HXB2 Location Nef
Author Location Nef
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Assay type Cytokine production, proliferation
Keywords HAART, ART
References Hardy *et al.* 2003

- Upon initiating HAART, CD4+ T cell proliferative responses in 36 patients were restored to specific antigens, mitogens, and IL-2. Restored recall responses were largely to persistent antigens, and not to HIV-1 or new antigens, and recall responses were associated with IL-2, not IL-4 production.

HXB2 Location Nef
Author Location Nef
Epitope
Subtype B
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords immunotherapy
References Kavanagh *et al.* 2006

- Transfection of antigen-presenting cells with a clade B consensus nef construct bearing lysosomal targeting signals produced rapid and prolonged antigen presentation to CD4+ and CD8+ T cells. Lysosome-targeted antigen drove a significantly greater expansion of Nef-specific CD4+ T cells, compared with cytoplasm-targeted antigen.

III-B-19 HIV-1 Helper/CD4+ T-cell epitopes

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords review, HIV exposed persistently seronegative (HEPS), mother-to-infant transmission
References Kuhn *et al.* 2002

- Intrauterine exposure of infants to HIV from their mothers results in HIV-1 specific T-helper cell proliferative responses in 1/3 of exposed uninfected babies, and HIV-1 specific CTL in some. It is unknown whether these responses are associated with lack of infection, but there is some evidence that HIV-1 T-cell responses may reduce transmission in breastfeeding mothers. Summary tables are provided of CD4 and CD8 T-cell responses detected in earlier studies.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: gp120 depleted virus HZ321 (REMUNE(TM)) *Strain:* AG recombinant HZ321 *HIV component:* gp120 depleted virus *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human
Keywords HAART, ART, rate of progression
References Kahn *et al.* 2000

- No benefit was observed in terms of progression free survival for HIV-1 patients on ART given vaccinations with HIV-1 antigen (N=1,262) versus those vaccinated with placebo (N=1,265). There was no statistically different outcome in HIV RNA, CD4 percentage, or body weight. HIV-1 ART patients that were vaccinated did have higher absolute CD4 counts.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: gp120 depleted virus HZ321 (REMUNE(TM)) *Strain:* AG recombinant HZ321 *HIV component:* gp120 depleted virus *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human
Keywords HAART, ART
References Moss *et al.* 1999

- 15 HIV-1 + patients on ARV given vaccinations with HIV-1 antigen versus vaccinated with placebo. Lymphocyte proliferation of CD4+, CD8+ memory cells and NK cells to p24 and Remune HIV-1 antigen increased in HAART treated patients after vaccination.

HXB2 Location HIV-1
Author Location

T-Helper CD4+

Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: gp120 depleted virus HZ321 (REMUNE(TM)) *Strain:* AG recombinant HZ321 *HIV component:* gp120 depleted virus *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human
Keywords Th1
References Moss *et al.* 1997

- HIV-1 specific stimulation of T-cell proliferation, and beta-chemokines (RANTES) and Th1-type cytokine (IFNgamma) production are found after immunization of HIV-1 + individuals with HIV-1 immunogen.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: gp120 depleted virus HZ321 (REMUNE(TM)) *Strain:* AG recombinant HZ321 *HIV component:* gp120 depleted virus *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human
References Levine *et al.* 1996

- Long-term follow up of HIV-1 + individuals given HIV-1 immunogen, suggesting those patients who became HIV-DTH-responsive in response to the HIV-1 immunogen had a better clinical outcome. Of twelve who developed DTH-responsiveness, one got an opportunistic infection and died, and one developed KS. Of the 13 patients who remained HIV-DTH-nonresponsive, 9 (69%) progressed to AIDS and 7 of these had died.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen vaccine
Vector/Type: HIV-1 immunogen *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (MHC) human
References Turner *et al.* 1994

- A dose response study of HIV immunogen in IFA was conducted. Doses of 50, 100, 200, or 400 micrograms (total protein) were tested by DTH skin testing to the inactivated HIV-1 antigen. The HIV-1 immunogen was well tolerated, and the minimum dose required to induce HIV-1 DTH was 100 micrograms.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human, macaque
Keywords dynamics, HAART, ART
References Wodarz 2002

- Mathematical modeling is used to support the idea that T-helper cell dysfunction results in a compromised ability to maintain an anti-HIV CTL memory response. Models suggest strategies to restore CTL memory through therapy and improve long-term immunological control of the virus.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA, canarypox, gp120 depleted virus HZ321 (REMUNE(TM)), protein, virus-like particle (VLP), adenovirus *Adjuvant:* GM-CSF, Growth Hormone, IL-12, IL-2, IL-7, CpG immunostimulatory sequence (ISS), Thymosin α-1
Species (MHC) human
Keywords HAART, ART, review, rate of progression, immunotherapy
References Imami *et al.* 2002a

- This review addresses the use of immunotherapy and therapeutic immunization to help chronically infected patients maintain a strong anti-HIV-1 T-cell response. The loss of anti HIV-1 proliferative responses early after infection is reviewed, as are therapeutic vaccinations, with or without HAART, and strategies for immunomodulation that can be given with or without vaccination.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords review, rate of progression, Th1, Th2
References Heeney 2002

- Review of the importance of balanced Th1 and Th2 HIV-specific CD4 T-cell responses in control of infection and for vaccination strategies.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC)
Keywords dynamics, rate of progression, escape
References Bernaschi & Castiglione 2002

- A cellular automata model was used to model the dynamics of HIV-1 infection and progression to disease. The model suggests the long aymptomatic period is due to immune escape mutants with lower viral fitness, and with AIDS resulting from a drastic reduction of the T-helper cell reservoire.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen vaccine
Species (MHC)
Keywords dynamics, kinetics
References Altes *et al.* 2002

- This study employs a mathematical model to study the consequences of increasing the T-helper response through a vaccine, which would have counter-balancing effects in a new infection: a more intense response provides more help but also more target cells. The model indicates that if the infecting virus had a low replication rate, then CTLp and CD4 helper cells could control an infection. Only a vaccine that could increase CTL responsiveness could reduce viral set point with observed replication rates.
- A CD4+ T-cell response without maintained CTL response was deleterious in this model.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC)
Keywords dynamics, HAART, ART, rate of progression
References Bajaria *et al.* 2002

- This paper presents a dynamical model of HIV infection and progression that includes CD4 T-cell naive and memory populations distributed between the peripheral blood and the lymph nodes, as well as the effects of HAART. Increasing viral replication and infectivity and decreasing T-cell immunity had impact on the rate of disease progression in this model.

HXB2 Location HIV-1
Author Location (HZ321)
Epitope
Subtype AG
Immunogen vaccine
Vector/Type: gp120 depleted virus HZ321 (REMUNE(TM)) *Strain:* AG recombinant HZ321 *Adjuvant:* Incomplete Freund's Adjuvant (IFA), CpG immunostimulatory sequence (ISS)
Species (MHC) mouse
Keywords Th1, Th2
References Ayash-Rashkovsky *et al.* 2002

- Parasitic helminthic infections in humans, common in parts of Africa and Asia, can shift immune responses to Th2 responses. To model this, BALB/c mice were infected with the parasite Schistosoma mansoni, and the infected mice showed a dominant Th2 immune response. Vaccination with gp120-depleted HIV-1 viral particles and incomplete Freund's adjuvant induced Th2 responses in these mice, but this could be shifted towards a Th1 profile when CpG oligodeoxynucleotide was added to the vaccine as an immunostimulatory agent.

HXB2 Location HIV-1
Author Location HIV-1 except gp120
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, rate of progression
References Ghanekar *et al.* 2001

- 12 long term non-progressors (>10 years) went on HAART, while 14 elected not to go on HAART. After a year on HAART, higher frequencies and absolute numbers of HIV-specific memory CD4+ T-cells were observed in untreated patients than patients receiving HAART therapy, tested by stimulation an proliferation responses to HIV Remune antigen (gp120 depleted vaccine).
- These results indicate a control of viral replication in therapy-naive patients may be mediated by their ability to respond to recall viral antigen, and that the diminished response in treated patients may contribute to viral rebound.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords HAART, ART, Th2
References Pido-Lopez *et al.* 2002

- The thymic output in HAART-treated HIV-1 infected patients with progressive disease was studied. One patient also receiving steroid treatment therapy had a weak response in a sjTREC assay indicating a dysfunctional thymus, while four patients not on steroids had clear positive sjTREC readings after HAART. Stimulation of PBMC with multiple recall antigens including gp120, p24 and Nef and mitogens, and revealed that in the patient treated with steroids there was and induction of a Th2 type response indicated by increased levels of IL-4 secretion in response to antigen.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen vaccine
Vector/Type: peptide *Adjuvant:* GM-CSF, IL-12, IL-2, IL-4, Tumor Necrosis Factor α (TNFα)
Species (MHC)
Assay type Th support of CTL response
Keywords binding affinity, review, Th1, Th2, mucosal immunity
References Berzofsky 2001

- Vaccine clusters were constructed containing T helper, CTL aand neutralizing antibody epitopes, and used to immunize mice. Four things were found to enhance the vaccine immune response: i) increasing the affinity of the peptide for the presenting MHC molecule, called epitope enhancement; ii) increasing the avidity of MHC/peptide complex for the T-cell receptor; iii) incorporating cytokines IL-2, GM-CSF, TFN-α, or IL-12 and IL-4 which steer responses towards Th1 or Th2 responses; iv) inducing mucosal immunity specifically, with intrarectal being most effective.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen vaccine
Vector/Type: DNA *HIV component:* Env, Gag *Adjuvant:* B7, GM-CSF, IL-12, IL-15
Species (MHC) human
Keywords review, Th1, Th2
References Boyer *et al.* 2002

T-Helper CD4+

- The first generation of HIV-1 plasmid vaccines in 167 individuals induced T-helper responses in most vaccine recipients, however CTL responses were below a 20% response rate. REV-independent RNA optimized constructs (pGag and pEnv) as well as B7 costimulatory molecules could significantly enhance CD8 effector cell responses. Co-administered GM-CSF enhanced antibody repsonses, IL-12 CTL production. IL-15 increased T cell expansion without increasing T cell help.

HXB2 Location HIV-1
Author Location HIV-1
Epitope
Immunogen HIV-1 infection
Species (MHC)
Assay type Cytokine production
Keywords review
References Breen 2002

- HIV-1 triggers immunological dysfunction in multiple ways, including the loss of CD4-positive T helper cells in quantity and function and hyperactivity and changes in the production and activity of cytokines. The role of pro- and anti-inflamatory cytokines are discussed, including IL-10, which can suppress HIV-1, and IL-1, IL-6, TNFα which up-regulate HIV-1.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Assay type Cytokine production, proliferation
References Clerici *et al.* 1993b

- rCD4-IgG treatment was associated with improved Th cell function measured by IL-2 production in response to alloantigen or PHA, but not to influenza (a recall antigen response), in 9/10 patients. No clinical benefit was evident. rCD40IgG was also shown to block gp120 induced suppression of Th cells *in vitro*. Proposed mechanisms include: inhibiting HIV-cell fusion by blocking the binding of gp120 to CD4, competing with free gp120 for binding to the CD4 receptor and reducing gp120 induced immunosupression, and gp120-induced direct killing of Th cells.

HXB2 Location HIV-1
Author Location Nef
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords assay standardization/improvement
References Draenert *et al.* 2003

- Six different HIV-1 Nef peptide sets ranging in length from 15-20 amino acids with overlap from 10-11 amino acids derived from either the B clade consensus sequences or the B clade sequence B.AU.AF064676 were used to study the impact of using different peptide design strategies to detect CD4 and CD8 T-cell responses. 20 individuals were tested using the six sets of peptides. 17/20 had CD8 T-cell responses to all peptides sets, and 15 of these 17 had CD4 T-cell responses.

HXB2 Location HIV-1
Author Location Nef
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords assay standardization/improvement
References Draenert *et al.* 2003

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- Although there was a trend in detecting more CD8 T cell responses using the shorter 15-mer peptides, longer 20-mers were best for detecting more CD4 T-cell responses, but neither result was statistically significant. Similar results were seen in the 15 to 20 amino acid range for both IFN gamma Elispot and ICS assays.
- Use of the consensus versus the natural strain identified slightly increased numbers of reactive peptides. Seven reactive peptides were observed with the B consensus peptides but not the B.AU.AF064676 peptides, but on the other hand four reactivites were observed using the B.AU.AF064676 peptides but not the consensus.
- Using an overlap of 10 or 11 amino acids did not make a difference.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC)
Assay type Cytokine production
Keywords HAART, ART
References Galli *et al.* 2003

- HIV-1-infected women who developed Adepose tissue alterations (ATA) while recieving antiretroviral treatment (ART) had a favorable immunological profile with efficient IL-2 production and T-helper function. The authors suggest that ATA may be related to the ART-driven restoration of immune function.
- The most prominant feature of women with ATA that were recieving ART was increased IL-12 production with a lower TNF alpha and IL-10 synthesis.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC)
Keywords review

T-Helper CD4+

References Norris & Rosenberg 2002

- This paper reviews the role of Th cells in controlling HIV-1 infection, and in other viral infections. It describes CD4+ T-cell support of Ab production, CTL responses, as well as antiviral cytokine production and infected-cell killing. HIV+ patients with a low viral load and rare vigorous HIV-specific CD4+ proliferative responses, and the benefit of early treatment in preserving Th HIV-specific responses allowing immune control when therapy is subsequently stopped, are described.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords review, rate of progression, acute/early infection
References Norris & Rosenberg 2001

- This review goes over the evidence for HIV-1 specific Th and CTL responses being critical for inhibiting viral replication. LTNPs and those treated during acute HIV-1 infection generate specific Th responses, but most chronically infected individuals do not.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 and GBV-C co-infection
Species (MHC) human
Assay type Cytokine production
Keywords HAART, ART, rate of progression, Th1, Th2
References Nunnari *et al.* 2003

- HIV-1 positive patients co-infected the GBV-C, the hepatitis G virus, have a longer survival time to AIDs and higher CD4+ T cell counts than patients that were not infected with GBV-C. GBV-C co-infected patients showed an intact Th-1 profile over time, with high serum levels of IL-2 and IL-12, and diminishing Th-2 responses reflected by lower levels of IL-4 and IL-10. The opposite was true for HIV-1 + patients that were not co-infected with GBV-C.
- AIDs progression is slower in patients infected with both HIV-1 and hepatitis G virus. It is unclear whether Th-2 and Th-1 cytokines in co-infected patients show cause or consequence of slower AIDs progression. CD4+ cells may support hepatitis G replication.

HXB2 Location HIV-1
Author Location HIV-1
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Keywords dynamics, acute/early infection
References Korthals Altes *et al.* 2003

- A model of progression was developed that explicitly assumes CD4+ T-cells are both targets of infection and mediators of the immune response. In this model, high viral inoculum with few initial CD4+ T-cells resulted in target-cell-limited infection and high viral load, but with many CD4+ clones and low initial inoculum, infection was controlled by CD4+ clones.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen vaccine
Vector/Type: DNA *Adjuvant:* GM-CSF, IFNγ, IL-12, IL-15, IL-18, IL-1α, IL-2, IL-2/Ig, MIP-1α, Tumor Necrosis Factor α (TNFα), Tumor Necrosis Factor β (TNFβ), M-CSF, G-CSF, IL-8, SDF-1α, RANTES, MCP1
Species (MHC)
Keywords review, Th1, Th2, adjuvant comparison
References Calarota & Weiner 2004

- Review summarizes the developments of DNA vaccine enhancement/modulation by 1) improving Th1 cytokine-encoding plasmids 2) by prime-boost vaccine regimens and 3) by chemokine- or T -cell costimulatroy molecule encoding plasmids. Studies involving many approaches for stimulating Th1 responses upon vaccination are compared, and given the initial promise of these strategies, future studies of coadministration or prime boosting with different combinations are advocated.

HXB2 Location HIV-1
Author Location p24 (HIV-2 ROD, HIV-1 IIIB)
Epitope
Immunogen HIV-1 or HIV-2 infection
Species (MHC) human
Country Gambia
Assay type Cytokine production, proliferation, CD8 T-cell Elispot - IFNγ, Chromium-release assay
Keywords rate of progression
References Jaye *et al.* 2004

- A comparison of T cell responses in HIV-1 and HIV-2 infected asymptomatic patients with CD4+ cell counts of 20% showed no significant difference between both groups. Viral loads were roughly 20 times greater in HIV-1 positive patients than HIV-2 positive patients.
- 10/20 (50%) of HIV-1 infected patients demonstrated proliferative responses with SI greater than 1.4 to gp120, and 11/20 to p24. 8/29 (29%) of HIV-2 infected patients recognized gp105, and 8/29 (29%) p26. Cytokine responses in both groups did not differ.
- 9/21 (43%) of HIV-1 + and 15/30 (50%) of HIV-2 + patients had cyotoxic T cell responses to Gag, and 3/21 (14%) HIV-1 + and 8/30 (27%) HIV-2 + responded to Pol.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country Spain
Assay type proliferation, Intracellular cytokine staining
Keywords HAART, ART
References López *et al.* 2004

- A clinical trial compared chronically HIV-1 infected patients who had replaced HAART with didanosine (ddI) and hyroxyurea (HU) were followed for 12 months to an untreated HIV+ group and a group that continued on HAART.

- Approximately 20% of the patients treated with ddI-HU had detectable CD4+ T-cell proliferative responses to Gag and Env in contrast to drug-naive and HAART treated HIV-infected patients, who had few or no responses.
- HIV-specific CD8+ T-cell responses were higher in ddI-HU treated patients than HAART treated patients, even in individuals that maintained undetectable viral loads.

HXB2 Location HIV-1
Author Location Tat (89.6)
Epitope
Immunogen vaccine
Vector/Type: DNA prime with protein boost, ISCOM *Strain:* B clade IIIB, SIV *HIV component:* Env, Gag, Tat *Adjuvant:* Immune stimulating complexes (ISCOM)
Species (MHC) macaque
Assay type Cytokine production, proliferation, CD8 T-cell Elispot - IFNγ
Keywords vaccine-specific epitope characteristics, Th1, Th2, vaccine antigen design
References Mooij *et al.* 2004

- This study compared vaccinating with Tat alone to vaccinating with Tat+Gag+Env. Rhesus macaques (Macaca mulatta) were intramuscularly immunized with a combination of DNA plasmids (HIV-1 IIIB expressing Tat, SHIV-1 89.6P expressing gp120 and SIV mac239 expressing Gag, followed by three boosts with HIV-1 Tat (IIIB) and Env (89.6, gp140) SIV Gag protein. Animals with multi-antigen vaccination had reduced viremia increased CD4+ T-cell counts.
- Tat-Env-Gag immunized animals had weaker Tat-specific Th responses in comparison to animals immunized with Tat alone; but the response to Tat alone was a Th2 response that did not protect from challenge.
- Immunization with Tat-Env-Gag boosted proliferation of Gag-specific IFN-γ and IL-2 producing cells in 3/4 animals (Th1 and Th2 responses) and induced a Th2-immune response (IL-2, IL-4) to Env.
- CD4+ T helper responses to Tat-Env-Gag immunization were correlated with control and reduction of viremia, suggesting a combination of Th1 and Th2 vaccine responses to multiple HIV antigens is advantageous.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen vaccine
Species (MHC) macaque
Keywords review
References Heeney 2004

- Review discusses the status, design and selection of novel HIV vaccines which elicit strong T-helper responses which can in turn can elicit CTL and Ab responses.
- Review discusses the status, design and selection of novel HIV vaccines which elicit strong T-helper responses which can in turn can elicit CTL and Ab responses.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection, vaccine
Species (MHC) human
Keywords review, immunotherapy, adjuvant comparison
References Wahren & Liu 2004

- This review covers immunotherapeutic vaccines use in combination with antiretrovial therapy and use of vaccination in combination with adjuvants and immunomodulators.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen
Species (MHC)
Keywords review, adjuvant comparison
References Mitchison & Sattentau 2005

- Review summarizes mechanisms of immunoregulation relevant for new vaccine development, with a brief summary of adjuvant triggering innate immunity through Toll-like receptors (TLRs), Nod molecules, and other activators. DNA encoded adjuvants that have been tested in DNA vaccines are summarized. The balance between Th1 (CTL activating) and Th2 (B cell activating) responses is discussed, and it is noted that BALB/c mice are predominately Th2 responders, C57BL Th1.

HXB2 Location HIV-1
Author Location
Epitope
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type Flow cytometric T-cell cytokine assay
References Ramduth *et al.* 2005

- The magnitude of HIV-specific CD8+ T cell responses in HIV-1 infected individuals from South Africa correlated with the CD4+ T cell responses. CD4 responses were narrowly focused, with Gag as dominant target, while CD8 responses were equally distributed among Gag, Pol and the regulatory and accessory proteins. The preferential targeting of Gag by CD8+ T-cells was associated with enhanced control of viral load.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type Intracellular cytokine staining
Keywords assay standardization/improvement
References Meddows-Taylor *et al.* 2007

- A whole blood peptide mapping intracellular cytokine staining assay was developed, that allows the direct comparison, at individual peptide level, of CD4+ and CD8+ T cell responses. This assay also allows monitoring of the responding cell type in the same reaction and requires considerably less blood than would be necessary if PBMC were first isolated prior to peptide stimulation.

T-Helper CD4+

- 396 overlapping peptides across Gag, Pol, Nef, Env, Tat, Rev, Vif, Vpu, Vpr were tested. CD8+ responses were higher in magnitude and in frequency than CD4+ responses in HIV patients screened by this method.

HXB2 Location HIV-1
Author Location Env (MN)
Epitope
Subtype B
Immunogen HIV-1 infection, SHIV infection
Species (MHC) macaque
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords assay standardization/improvement
References Chea *et al.* 2005

- The study describes a novel in vivo killing (IVK) assay using overlapping peptide pools pulsed onto autologous fluorescently labeled PBMC. Analysis of SIV/HIV spesific immnunity in several weeks following JVK assays showed a marked enhancement of virus-specific CD8 and CD4 T-cell immunity.

HXB2 Location HIV-1
Author Location Tat (B clade consensus)
Epitope
Subtype B
Immunogen HIV-1 infection, SHIV infection
Species (MHC) macaque
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords assay standardization/improvement
References Chea *et al.* 2005

- The study describes a novel in vivo killing (IVK) assay using overlapping peptide pools pulsed onto autologous fluorescently labeled PBMC. Analysis of SIV/HIV spesific immnunity in several weeks following JVK assays showed a marked enhancement of virus-specific CD8 and CD4 T-cell immunity.

HXB2 Location HIV-1
Author Location Vpu (B clade consensus)
Epitope
Subtype B
Immunogen HIV-1 infection, SHIV infection
Species (MHC) macaque
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Intracellular cytokine staining
Keywords assay standardization/improvement
References Chea *et al.* 2005

- The study describes a novel in vivo killing (IVK) assay using overlapping peptide pools pulsed onto autologous fluorescently labeled PBMC. Analysis of SIV/HIV spesific immnunity in several weeks following JVK assays showed a marked enhancement of virus-specific CD8 and CD4 T-cell immunity.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Assay type CD4 T-cell Elispot - IFNγ
Keywords HAART, ART, early treatment
References Fox *et al.* 2008

- This is a 3-year longitudinal study assessing the long-term impact of a short-course of ART.
- Neither the presence or the magnitude of T helper responses either at baseline or 3 years following ART cessation correlated with clinical outcome.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
References Shalekoff *et al.* 2008

- Correlations between CD4+, CD8+ responses, copy numbers of CCL3L1 and viral load were studied in a cohort of 71 HIV-infected South African women.
- Magnitudes of Gag CD4+, CD8+ and host CCL3L1 copy number correlated negatively with viral load. CCL3L1 copy number greater or equal to the population median of 5 was significantly associated with increased magnitude of Gag CD4+ responses.
- Comparison of women with Gag-specific CD8+ responses only and Gag-specific CD8+ and CD4+ responses showed that viral load was significantly reduced only when CD8+ Gag responses were combined with CD4+ responses, indicating that the presence of detectable Gag CD4+ responses would mark more effective Gag CD8+ responses.
- Gag CD4+ responses were associated with virus control, but ENV CD4+ responses, which occurred in as many individuals and were higher in magnitude than Gag CD4+ responses, did not.

HXB2 Location HIV-1
Author Location
Epitope
Immunogen HIV-1 infection
Species (MHC) human
Assay type T-cell Elispot
Keywords assay standardization/improvement
References Precopio *et al.* 2008

- This study describes and tests an optimized method for configuration of peptide pool matrices encompassing hundreds of overlapping peptides and a method of epitope deconvolution.
- 4 matrices of pools of peptides (15-mers overlapping by 11) were constructed and tested in 3 HIV-positive individuals.
- It was found that the peptide configuration requiring the least amount of blood sample depends on the predicted number of positive peptides in the set.
- In the 3 patients tested, 74 reactive peptides were identified altogether, with minimum 53 potential epitopes taking overlaps into account. Many of the peptides have been previously identified as CTL or helper epitopes.

HXB2 Location HIV-1

Author Location
Epitope
Subtype B
Immunogen HIV-1 infection
Species (MHC) human
Country Jamaica
Assay type CD8 T-cell Elispot - IFNγ, CD4 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay
Keywords responses in children
References Huang *et al.* 2008a

- CD8+ and CD4+ T cell responses were studied in 76 pediatric patients using overlapping peptides spanning B clade consensus.
- T cell responses were present in the majority of infected infants, but there was a qualitative difference in responses in young infants and older children.
- Targeting of Gag was associated with significantly lower plasma HIV-1 RNA levels, but Gag-specific responses were less commonly detected in infants than in children older than 12 months. CD8 T cells exhibiting multiple effector functions (IFN-γ, TNF-α and degranulation) were detected less frequently in younger infants. CD4 T cell responses were of very low magnitude in nearly all pediatric patients and absent in the youngest infants.

HXB2 Location HIV-1
Author Location
Epitope
Subtype C
Immunogen HIV-1 infection
Species (MHC) human
Country South Africa
Assay type Flow cytometric T-cell cytokine assay
Keywords responses in children, mother-to-infant transmission
References Ramduth *et al.* 2008

- CD4 T cell responses to all HIV-1 proteins were studied in 34 clade C acutely infected infants (2-102 days old). 12 infants were further studied longitudinally.
- The earliest detected IFN-γ response was to Gag, in a 6-day-old in utero infected infant, the earliest detected IL-2; response was also to Gag, in a 12-day-old in utero infected infant, and earliest detected TNF-α response was to Env, in a 40-day-old in utero infected infant.

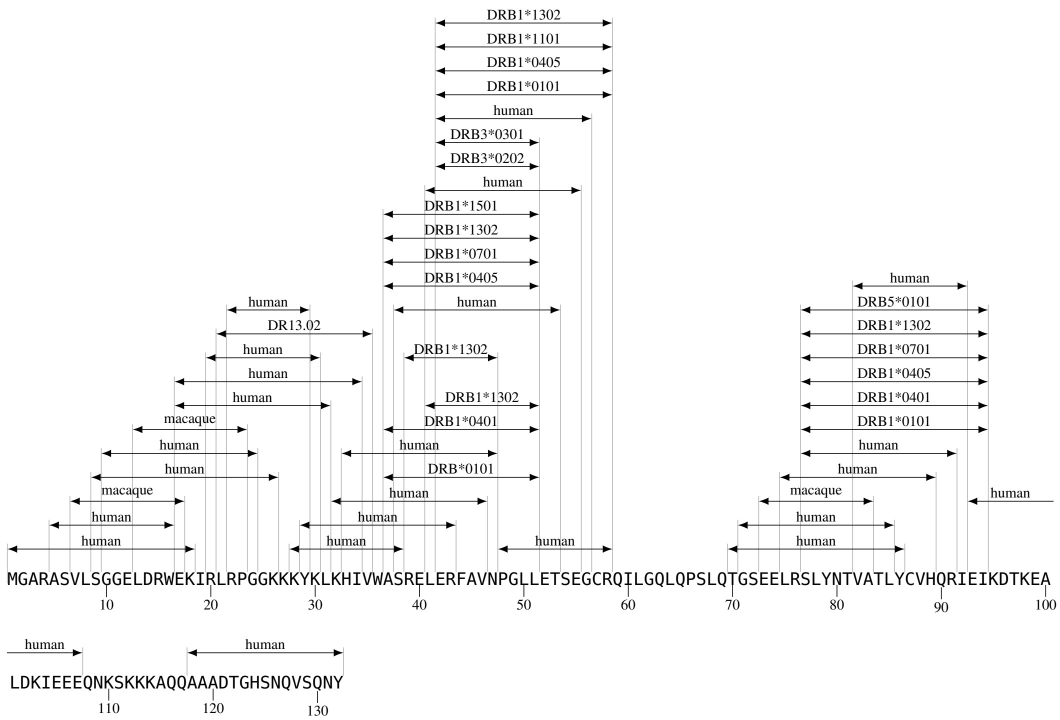
T-Helper CD4+

III-C

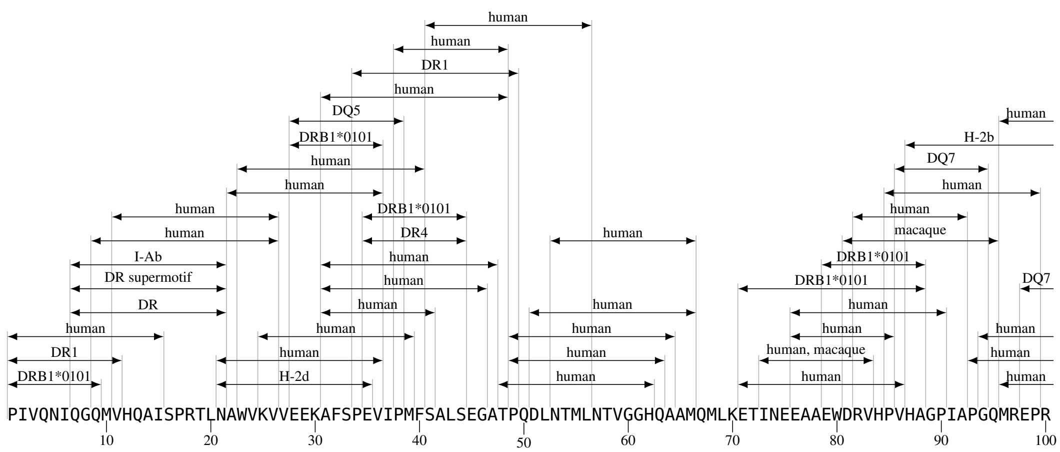
Maps of T-Helper/CD4+ Epitope Locations Plotted by Protein

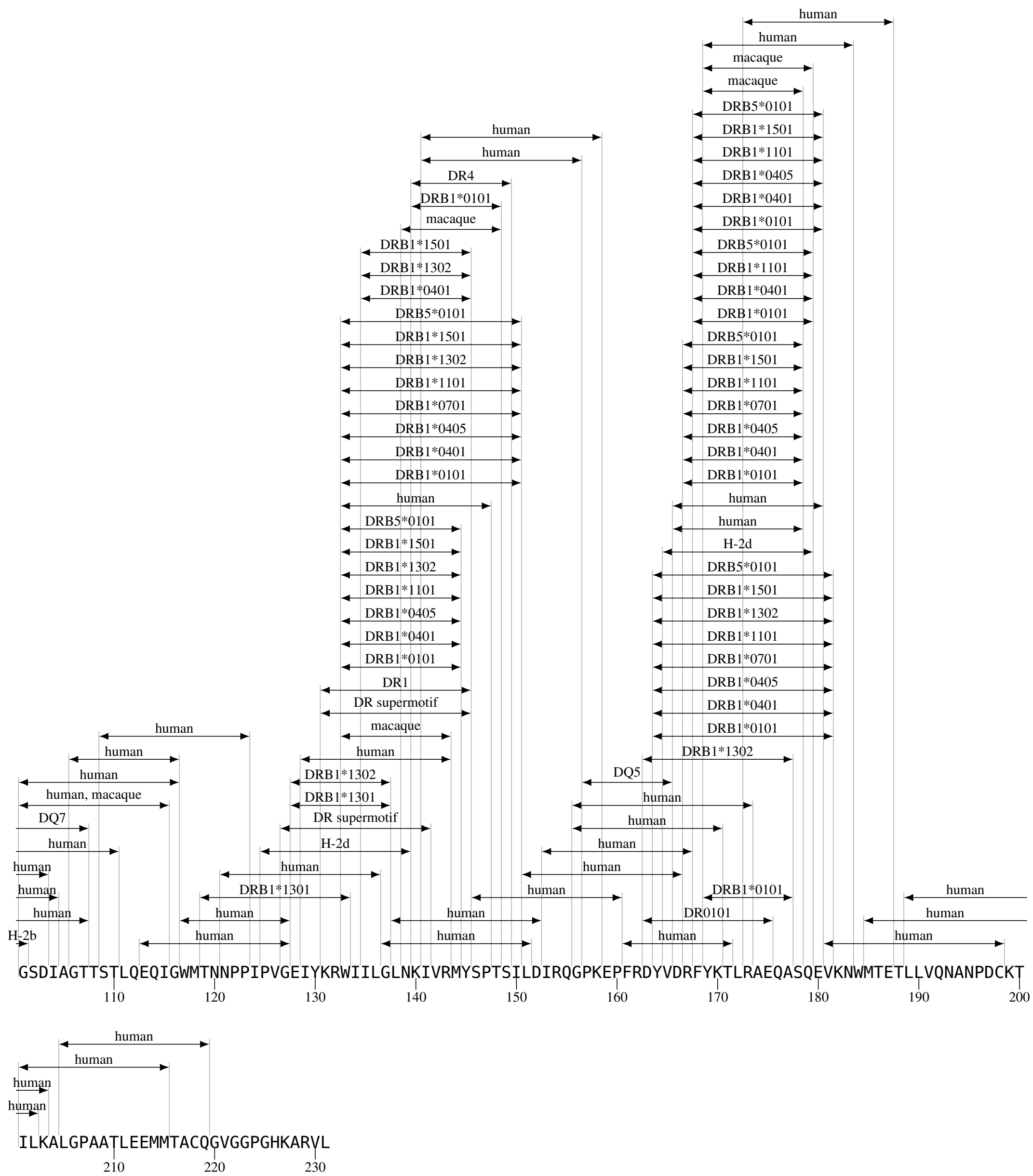
Linear helper T cell (CD4+) epitopes mapped to within a region of 18 amino acids or less are shown.

III-C-1 p17 T-Helper/CD4+ Epitope Map

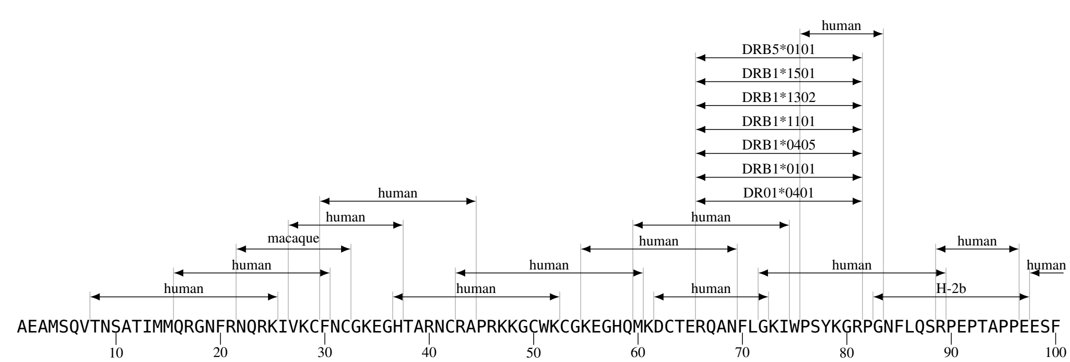


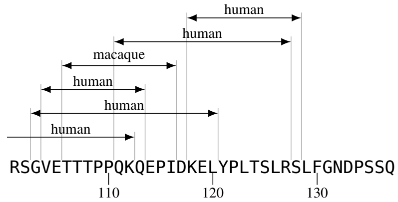
III-C-2 p24 T-Helper/CD4+ Epitope Map



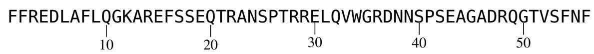


III-C-3 p2p7p1p6 T-Helper/CD4+ Epitope Map

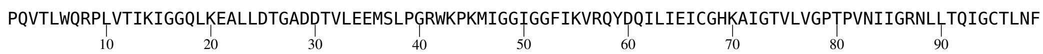




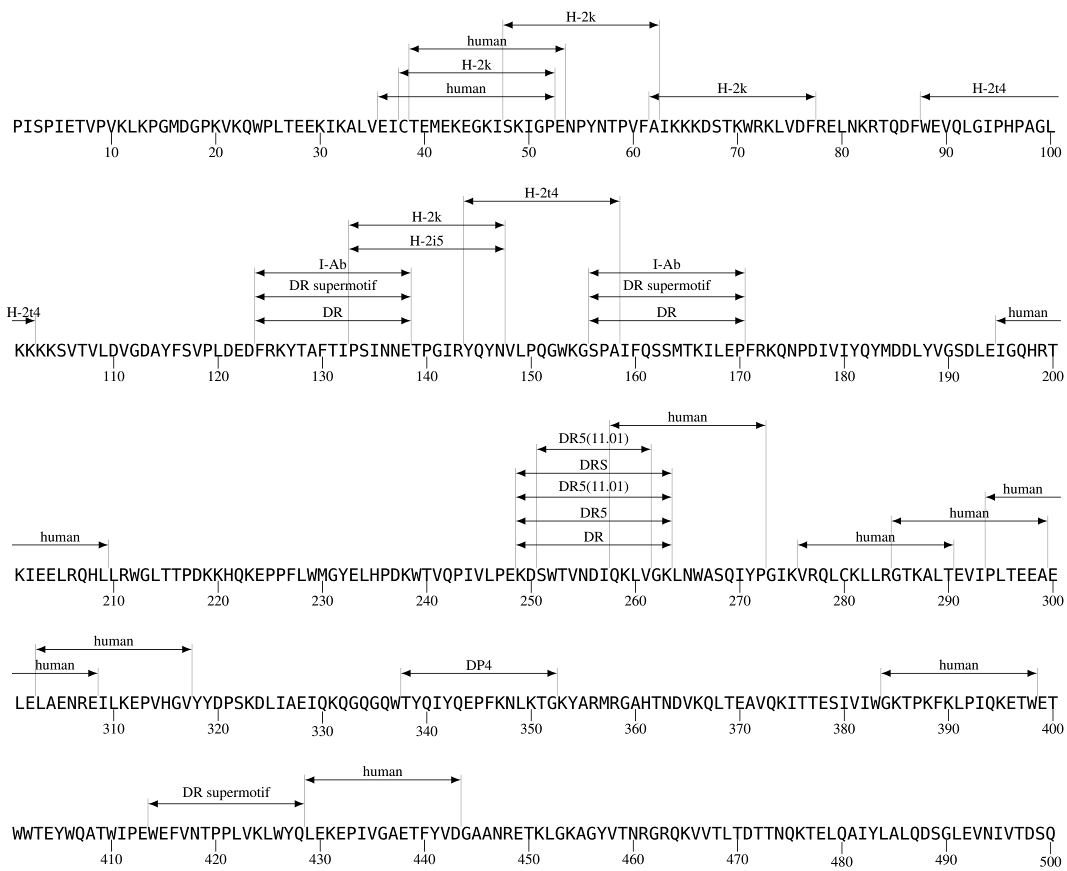
III-C-4 Gag/Pol TF T-Helper/CD4+ Epitope Map



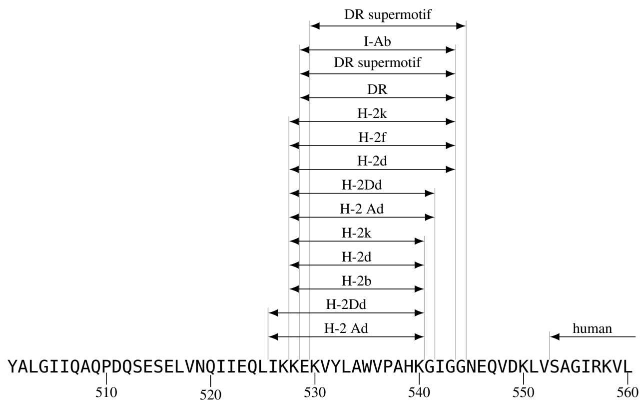
III-C-5 Protease T-Helper/CD4+ Epitope Map



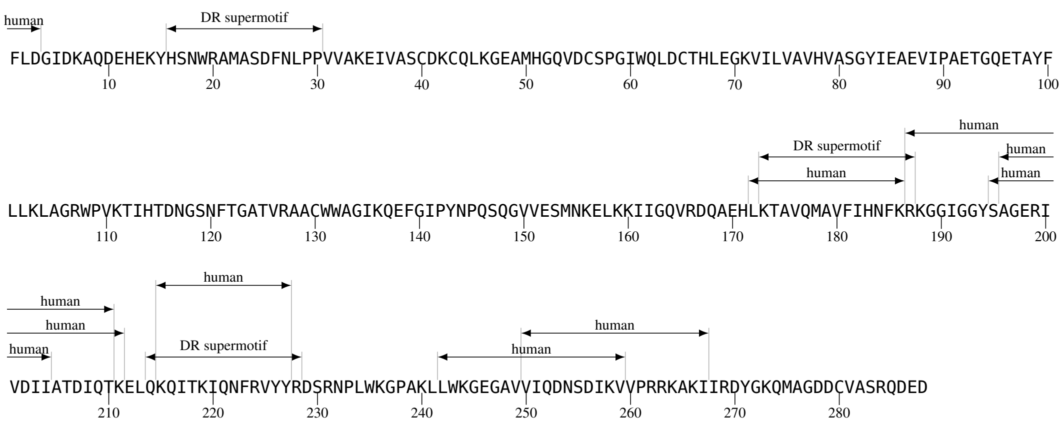
III-C-6 RT T-Helper/CD4+ Epitope Map



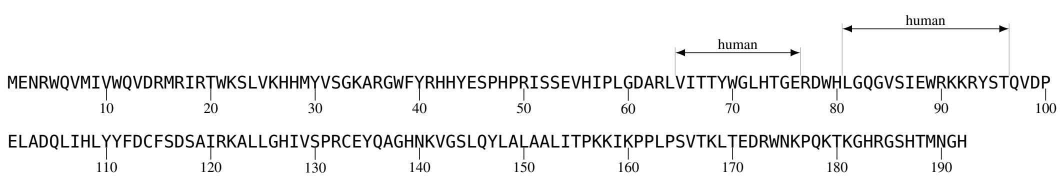
T-Helper CD4+



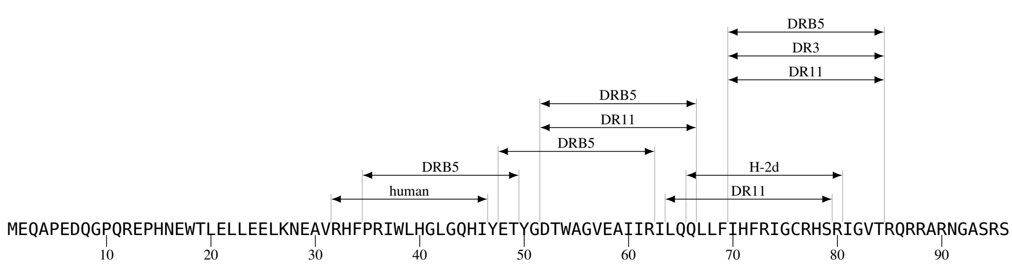
III-C-7 Integrase T-Helper/CD4+ Epitope Map



III-C-8 Vif T-Helper/CD4+ Epitope Map

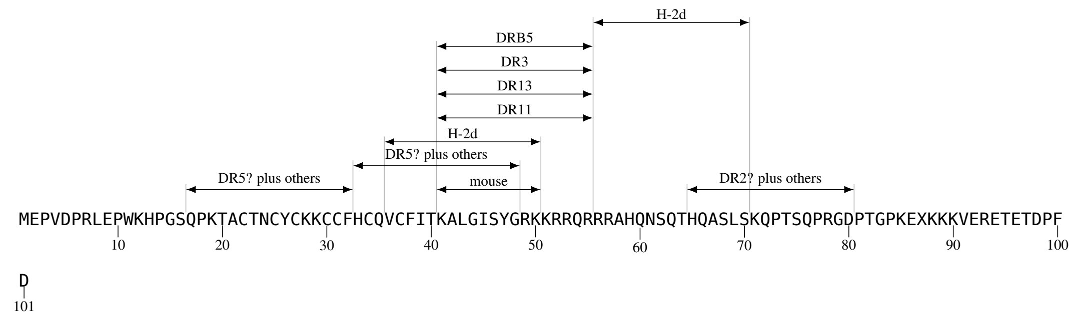


III-C-9 Vpr T-Helper/CD4+ Epitope Map

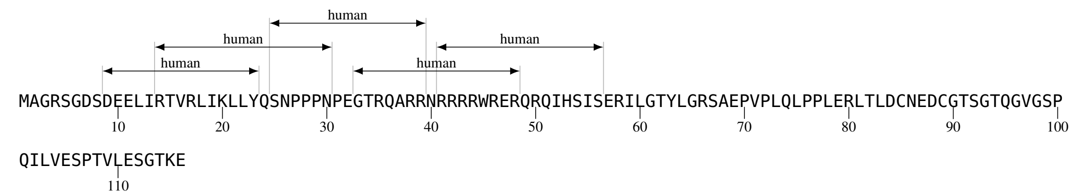


T-Helper CD4+

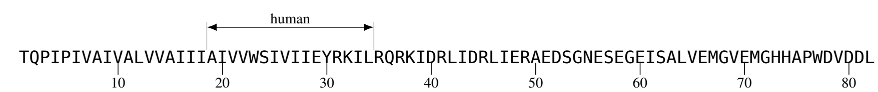
III-C-10 Tat T-Helper/CD4+ Epitope Map



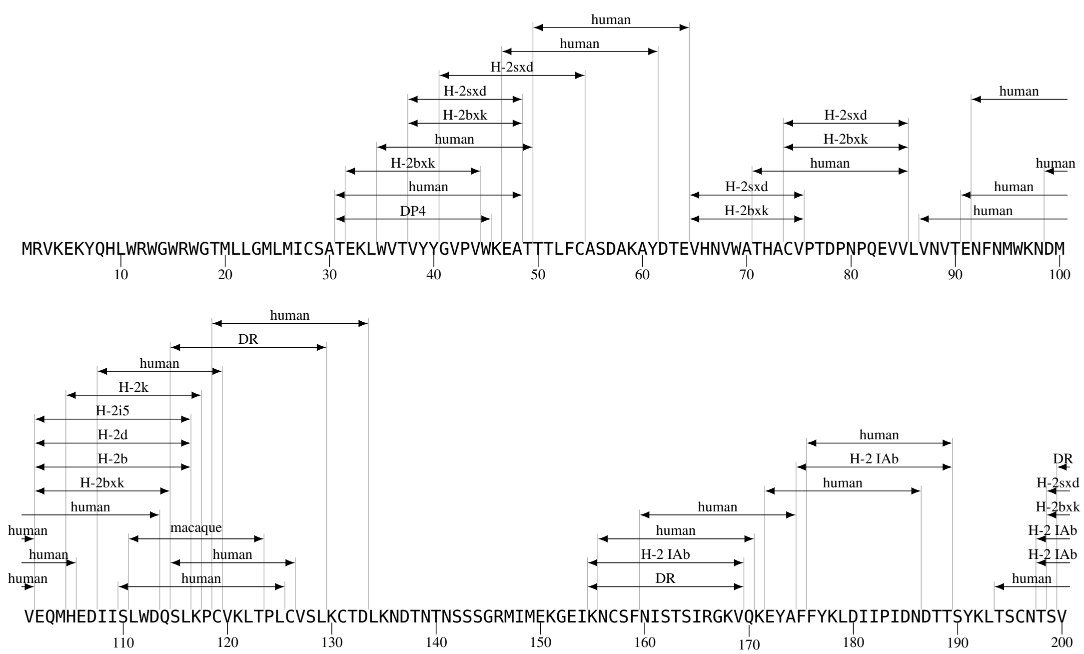
III-C-11 Rev T-Helper/CD4+ Epitope Map



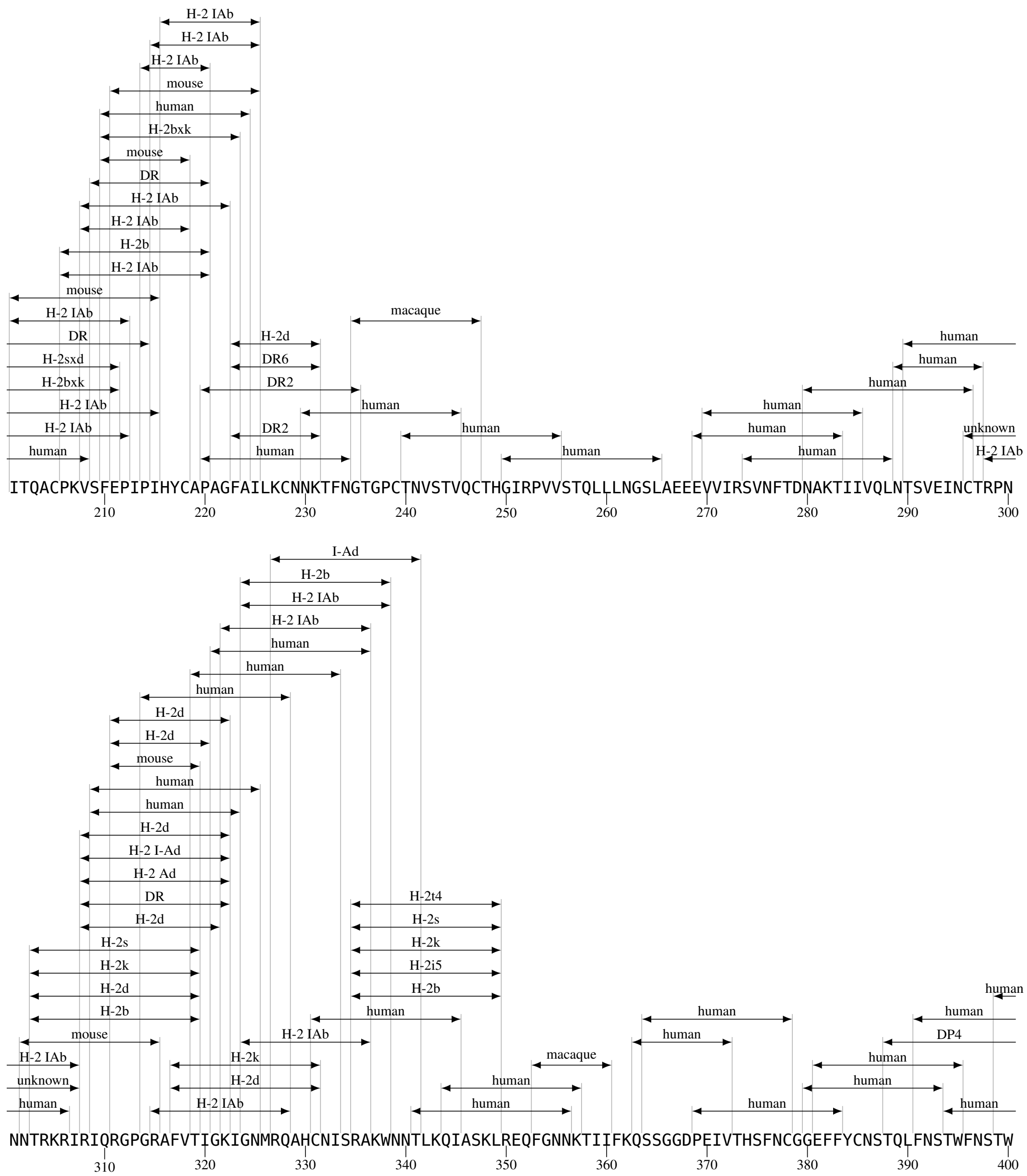
III-C-12 Vpu T-Helper/CD4+ Epitope Map



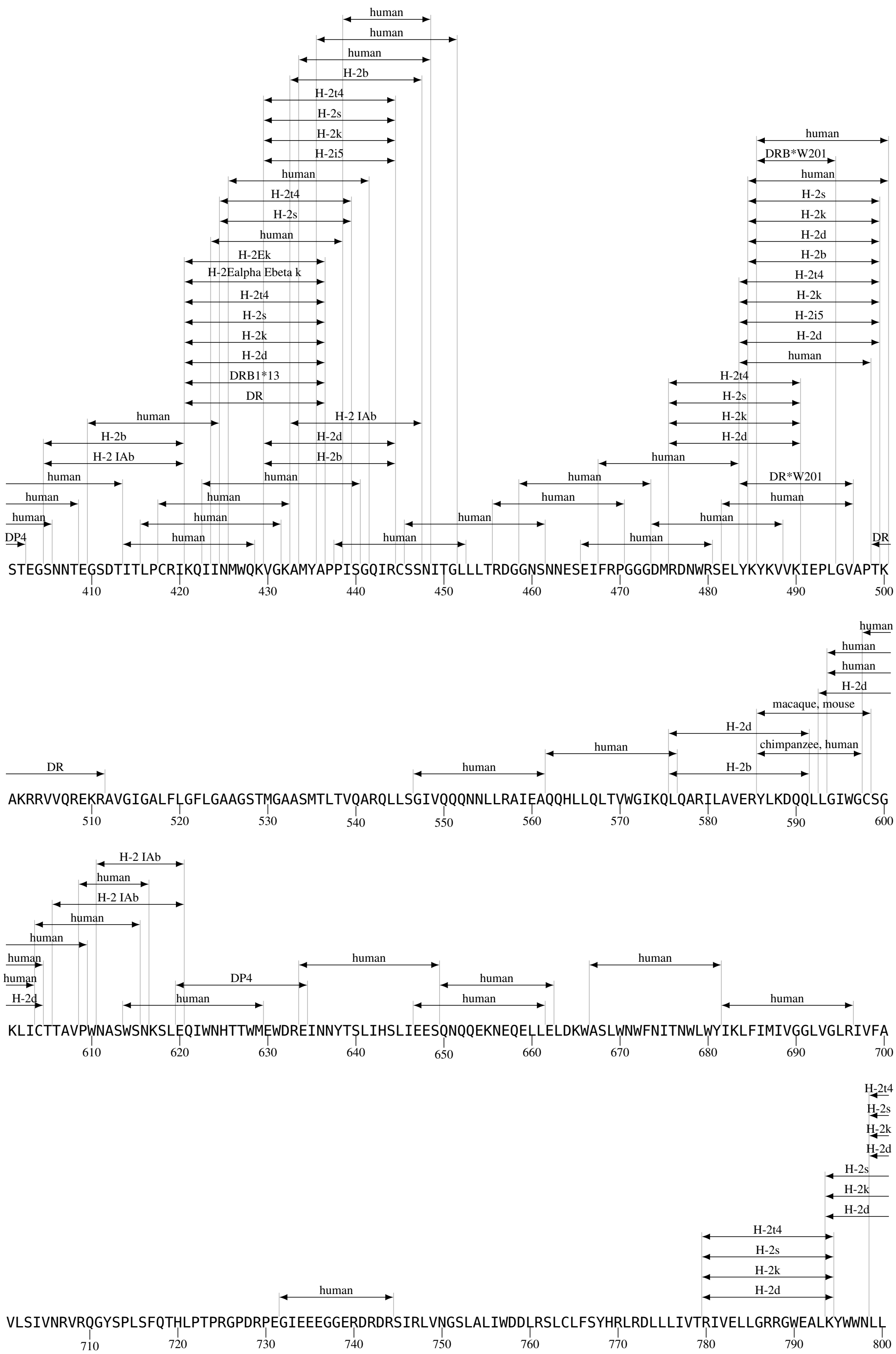
III-C-13 gp160 T-Helper/CD4+ Epitope Map



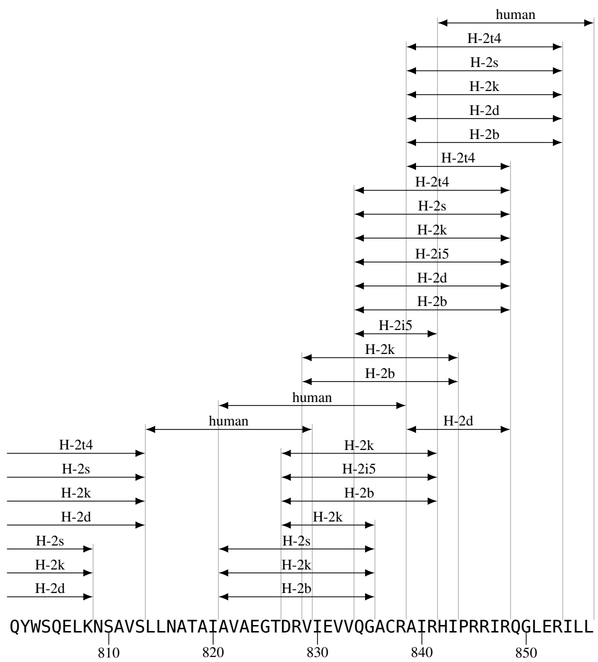
T-Helper CD4+


H-2 IAb
H-2 IAb
H-2 IAb
mouse
human
H-2bxk
mouse
DR
H-2 IAb
H-2 IAb
H-2b
H-2 IAb
mouse
H-2 IAb
macaque
DR
H-2d
human
H-2sxd
DR6
human
H-2bxk
DR2
human
H-2 IAb
human
human
H-2 IAb
DR2
human
human
human
unknown
human
human
human
human
human
H-2 IAb
ITQACPKVSFEPIPIHYCAPAGFAILKCNNKTFNGTGPCTNVSTVQCTHGIRPVVSTQLLLNGSLAEEEVVIRSVNFTDNAKTIIVQLNTSVEINCTRPN
210 220 230 240 250 260 270 280 290 300
I-Ad
H-2b
H-2 IAb
H-2 IAb
human
human
human
H-2d
H-2d
mouse
human
human
H-2d
H-2 I-Ad
H-2 Ad
DR
H-2d
H-2t4
H-2s
H-2s
H-2k
H-2k
H-2i5
H-2d
H-2b
human
H-2b
human
human
human
mouse
H-2 IAb
human
DP4
macaque
H-2 IAb
H-2k
human
unknown
H-2d
human
human
human
H-2 IAb
human
human
human
human
NNTRKRIRIQRGPGRAFVTIGKIGNMRQAHCNISRAKWNNTLKQIASKLREQFGNNKTIIFKQSSGGDPEIVTHSFNCGGEFFYCNSTQLFNSTWFNSTW
310 320 330 340 350 360 370 380 390 400

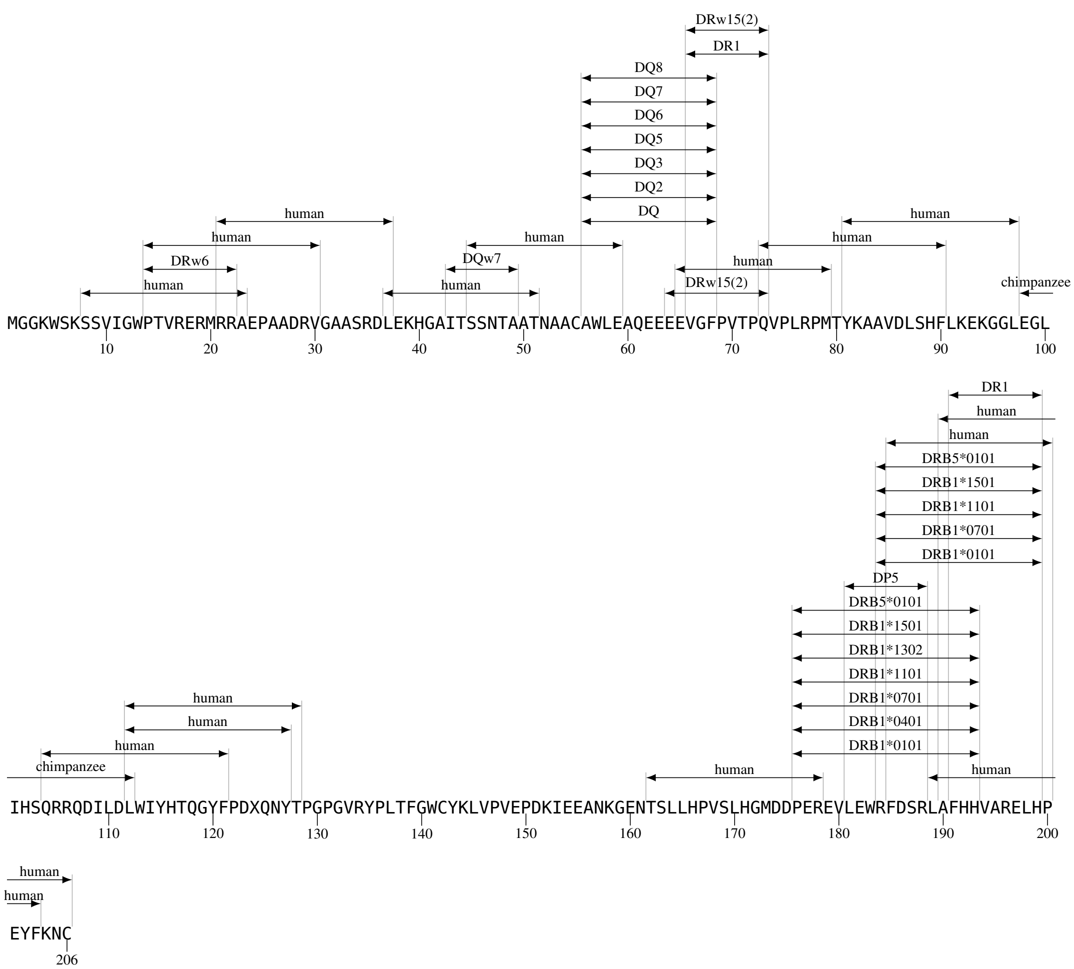
T-Helper CD4+


STEGSNNTEGSDTITLPCRIKQIINMWQKVGKAMYAPPISGQIRCSSNITGLLLTRDGGNSNNESEIFRPGGGDMRDNWRSELYKYKVVKIEPLGVAPTK
410 420 430 440 450 460 470 480 490 500
AKRRVVQREKRAVGIGALFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQLLGIWGCSG
510 520 530 540 550 560 570 580 590 600
KLICTTAVPWNASWSNKSLEQIWNHTTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWFNITNWLWYIKLFIMIVGGLVGLRIVFA
610 620 630 640 650 660 670 680 690 700
VLSIVNRVRQGYSPLSFQTHLPTPRGPDRPEGIEEEGGERDRDRSIRLVNGSLALIWDDLRSLCLFSYHRLRDLLLIVTRIVELLGRRGWEALKYWWNLL
710 720 730 740 750 760 770 780 790 800

T-Helper CD4+



III-C-14 Nef T-Helper/CD4+ Epitope Map



Part IV

HIV Antibody Binding Sites

IV-A

Summary

This part summarizes HIV-specific antibodies (Abs) from the literature arranged sequentially according to the location of their binding domain, organized by protein. We attempted to make this part as comprehensive as possible. For the monoclonal antibodies (MAbs) capable of binding to linear peptides, we require that the binding site be contained within a region of 30 or so amino acids to define the epitope, but not that the precise boundaries be defined. MAbs that do not bind to defined linear peptides are grouped by category at the end of each protein. Antibody categories, for example CD4 binding site (CD4BS) antibodies, are also noted in the index at the beginning of this part. Studies of polyclonal Ab responses are also included. Responses that are just characterized by binding to a protein, with no known specific binding site, are listed at the end of each protein. For more recent updates, epitope sequence alignments, and search capabilities, please see our web site: `http://www.hiv.lanl.gov/content/immunology`.

IV-A-1 Indices

Three indices are provided. The first provides a concise list of anti-HIV-1 MAbs by cross-competition category, with both discontinuous epitopes (for example, CD4BS) and some well known linear epitopes (for example, cluster I) summarized. The second lists the MAbs' IDs in alphabetical order so one can find their location in the table. The third is a listing by order of appearance in the tables.

IV-A-2 Tables

Each MAb has a twelve-part basic entry:

Number: Order of appearance in this table.

MAb ID: The name of the monoclonal antibody with synonyms in parentheses. MAbs often have several names. For example, punctuation can be lost and names are often shortened (M-70 in one paper can be M70 in another). Polyclonal responses are listed as "polyclonal" in this field.

HXB2 location: Position of the antibody binding site relative to the viral strain HXB2 (GenBank Accession Number K03455), which is used as a reference strain throughout this publication. The numbering in this table corresponds to the protein maps. Because of HIV-1 variation, the epitope may not actually be present in HXB2; rather, the position in HXB2 indicates the position aligned to the epitope. HXB2 was selected as the reference strain because so many studies use HXB2, and because crystal structures for HXB2-related proteins are available. The precise positions of an epitope on the HXB2 reference strain can be readily obtained using the interactive position locator at our web site: `http://www.hiv.lanl.gov/content/sequence/LOCATE/locate.html`.

Author location: The amino acid positions of the epitope boundaries and the reference sequence used to define the epitope are listed as given in the primary publication. Frequently, these positions as published are imprecise, and do not truly correspond to the numbering of the sequence, but they provide a reasonable guide to the peptide's approximate location in the protein. Also, in many cases, position numbers were provided but the reference sequence identification was not. Because of HIV-1's variability, position numbers require a reference strain to be meaningful. Binding sites that cannot be defined through peptide binding or interference studies are labeled as discontinuous. The approximate location on the protein, sequence number, and reference sequence are listed.

Sequence: The amino acid sequence of the binding region of interest, based on the reference strain used in the study defining the binding site. On occasions when only the position numbers and not the actual peptide sequence were specified in the original publication, we tried to fill in the peptide sequence based on the position numbers and reference strain. If the sequences were numbered inaccurately by the primary authors, or if we made a mistake in this process, we may have misrepresented the binding site's amino acid sequence. Because of this uncertainty, epitopes that were not explicitly written in the primary publication, that we determined by looking up the reference strain and the numbered location, are followed by a question mark in the table.

Subtype: The subtype under study, generally not specified for B subtype.

Neutralizing: **L**: neutralizes lab strains. **P**: neutralizes at least some primary isolates. **no**: does not neutralize. No information in this field means that neutralization was either not discussed or unresolved in the primary publications referring to the MAb.

Immunogen: The antigenic stimulus of the original B cell response. Often this is an HIV-1 infection. If a vaccine was used as the original antigenic stimulation, not a natural infection, this is noted, and additional information about the vaccine antigen is provided as available.

Species (Isotype): The host in which the antibody was generated, and the isotype of the antibody.

Research Contact: Information about who produced an antibody, how to obtain it, or who should receive credit.

Country: The country where the samples were obtained; this is generally not specified if the study was conducted in the United States.

References: All publications that we could find that refer to the use of a specific monoclonal antibody. First is a list of all references. Additional details for some of the older references can be found in Part V, although we have tried to keep the entries self-contained since 1997.

Keywords: Keywords for antibody entries were initiated in 2004. The keywords are listed when available as part of the main entry, and also follow the note in bold type so references pertaining to particular types of studies can be found quickly.

Notes: Describe the context of each study, and what was learned about the antibody in the study.

IV-A-3 HIV protein binding site maps

The names of MAbs and the location of well characterized linear binding sites of 21 amino acids or less are indicated relative to the protein sequences of the HXB2 clone. This map is meant to provide the relative location of epitopes on a given protein, but the HXB2 sequence may not actually bind to the MAb of interest, as it may vary relative to the sequence for which the epitope was defined. Above each linear binding site, the MAb name is given followed by the species in parentheses. Human is represented by 'h', non-human primate by 'p', mouse by 'm', and others by 'o'. More precise species designations for any given MAb can be found using the web search interface or in the tables in this part.

IV-A-4 Alignments

To conserve space, no epitope alignments are provided in this book, but they can be generated using the Ab search tool at `http://www.hiv.lanl.gov/content/immunology`. The master alignment files from which the epitope alignments were created are available at our web site at `http://www.hiv.lanl.gov/content/sequence/NEWALIGN/align.html`.

IV-B

Cross Reference Listing of MAbs

IV-B-1 MAbs by binding type

Cross reference by protein and binding type of MAb names and their order of appearance in the tables.

Binding type	MAb ID (No.)
p17	
C-term	sc-FV p17 (35)
p24	
C-term	13B5 (117)
Protease	
N-term	1696 (186)
flap region	F11.2.32 (188)
Integrase	
Integrase DNA binding domain	5D9 (227), 2-19 (230), 8-22 (231), 4-20 (232), 6-19 (233)
Integrase catalytic core	7-16 (224), 4F6 (225)
N-term	1C4 (211), 2C11 (212), 2E3 (213), 3E11 (214), 3F9 (215), 5F8 (216), 6G5 (217), 7B6 (218), 7C6 (219), 6C5 (220), 4D6 (223)
Pol	
C-term	33 (263), F-6 (264)
RT palm domain	6B9 (265)
RT thumb domain	5F (266), 5G (267), 7C4 (268)
gp120 V3	polyclonal (262)
Vif	
C-term	TG001 (270)
Tat	
C-term	polyclonal (274), polyclonal (286), polyclonal (287), 1D2F11 (289), 2D9E7 (290), 4B4C4 (291), 5G7D8 (292), NT2/4D5.24 (295), polyclonal (296), 2D9D5 (323), polyclonal (324), polyclonal (325), polyclonal (326)
N-term	polyclonal (274), TA9 (276), TD84 (277), TE135 (278), polyclonal (279), NT3/2D1.1 (280), 1D9D5 (282), polyclonal (286), polyclonal (287), polyclonal (296), polyclonal (324), polyclonal (325), polyclonal (326), G1 (327), G2 (328), J1 (329), TC15 (330), polyclonal (331), polyclonal (332)
Tat Cys-rich domain	polyclonal (283)
Tat basic region	polyclonal (274), TB12 (284), polyclonal (286), polyclonal (287), polyclonal (288), polyclonal (293), polyclonal (296), polyclonal (313), polyclonal (324), polyclonal (325), polyclonal (326), B1E3 (333), J3B2 (334)
Env (gp160)	
C-HR	126-7 (869), m44 (1061), polyclonal (1310)
C-domain	polyclonal (699), 5B2 (781), 9G11 (782), TH-Ab1 (783), polyclonal (784), polyclonal (785), polyclonal (786), polyclonal (787)
C-term	105-306 (669), 750-D (671), 158F3 (674), 161D7 (675), 722-D (677), polyclonal (678), 1131-A (680), 858-D (681), 989-D (682), 14D9 (788), 2F5 (789), 4E10 (791), Z13 (792), C8 (796), 1575 (812), polyclonal (816), polyclonal (817), SAR1 (819), 1577 (820), polyclonal (821), 101-342 (1311), 101-451 (1312), 120-1 (1313), T26 (1314), D33 (1315), polyclonal (1316)

B Cell

Binding type	MAb ID (No.)
Env oligomer	T22 (1442)
Leucine zipper motif	(691), (692)
N-term	polyclonal (700), D33 (1315), 2A2 (1443), AC4 (1444), AD3 (1445), AD3 (1446), ID6 (1447), ID6 (1448)
RT thumb domain	polyclonal (1182)
gp120 C1	M85 (348), 7E2/4 (349), 4D4#85 (350), M92 (351), M86 (352), polyclonal (353), 133/237 (354), 133/290 (355), 133/11 (356), D/3G5 (357), D/6A11 (358), D/5E12 (359), L5.1 (360), 4A7C6 (361), 1D10 (362), B242 (363), 133/192 (364), 489.1(961) (365), 5B3 (366), B10 (367), B2 (368), C6 (369), MF49.1 (370), T1.1 (371), T7.1 (372), T9 (373), GV4D3 (374), B27 (375), B9 (376), B35 (377), D/4B5 (378), D/5A11 (379), D/6B2 (380), B18 (381), B20 (382), MF39.1 (383), 187.2.1 (384), 37.1.1(ARP 327) (385), 6D8 (386), M96 (387), MF119.1 (388), MF4.1 (389), MF53.1 (390), MF58.1 (391), MF77.1 (392), T2.1 (393), 11/65 (394), W1 (395), T11 (396), GV1A8 (397), CA13 (398), 11 (399), 12G10 (400), 135/9 (401), 7C10 (402), C4 (403), MF46.1 (404), 13b23 (881), T8 (1047), 212A (1317), 522-149 (1318), CA1 (1319), L19 (1320), M90 (1321), MAG 104 (1322), MAG 45 (1323), MAG 95 (1324), MAG 97 (1325), P35 (1326), T9 (1327), p7 (1328)
gp120 C1-C2	polyclonal (1177), L100 (1329)
gp120 C1-C4	8.2A (933), EH21 (985), 2/11c (1330), A32 (1331)
gp120 C1-C5	C11 (1332), L81 (1333)
gp120 C2	1006-30-D (445), 847-D (446), 213.1 (450), B12 (451), B13 (452), C13 (453), M89 (454), B21 (455), B23 (456), B24 (457), B25 (458), B3 (459), B26 (460), B29 (461), B36 (462), 110.E (463), 110.C (464), polyclonal (594)
gp120 C3	B2C (608), 2H1B (611), 2F19C (615), 110.D (616), B32 (617), ICR38.1a (629), polyclonal (1334)
gp120 C4	5C2E5 (624), G3-211 (625), G3-537 (626), ICR38.1a (629), G3-299 (630), G3-42 (631), G3-508 (632), G3-519 (633), G3-536 (634), ICR38.8f (635), MO86/C3 (636), 13H8 (637), G45-60 (638), polyclonal (639), 1662 (640), 1663 (641), 1664 (642), 1697 (643), 1794 (644), 1804 (645), 1807 (646), 1808 (647), 20-2-C8.5F3 (893), 1024 (1335)
gp120 C5	9201 (652), 1C1 (653), 3F5 (654), 5F4/1 (655), 660-178 (656), 9301 (657), B221 (658), H11 (660), W2 (661), M38 (662), 110.1 (664), 42F (665), 43F (666), RV110026 (667), GV1G2 (670), 450-D (672), 670-D (673), 1331A (679), polyclonal (1177), 23A (1337), D7324 (1338)
gp120 CCR5BS	E51 (622), 1.9E (835), 1.9F (836), 2.5E (892), 4.8E (912), 412d (914), 47e (915), E047 (981), ED10 (983), LA15 (1016), LA28 (1018), LF17 (1020), 17b (1433), 21c (1434)

B Cell

Binding type	MAb ID (No.)
gp120 CD4BS	JL413 (623), polyclonal (627), 1795 (628), 102 (842), 13a15 (875), 13a23 (876), 13a3 (877), 13a6 (878), 13a7 (879), 13b18 (880), 13b53 (882), 13b61 (883), 25G (894), 570-D (923), 5E (926), A12 (938), C02-41 (953), C18-2 (956), C8 (958), CD4-IgG2 (959), D02-20 (963), D02-6 (968), D7 (979), F1 (986), m14 (1054), m18 (1056), m22 (1057), m24 (1058), polyclonal (1177), polyclonal (1280), polyclonal (1286), polyclonal (1294), polyclonal (1297), polyclonal (1303), polyclonal (1305), D33 (1315), polyclonal (1316), 10/46c (1339), 1008-D (1340), 1027-30-D (1341), 1125H (1342), 1125H (1343), 120-1B1 (1344), 1202-D (1345), 1331E (1346), 1570 (1347), 1595 (1348), 1599 (1349), 15e (1350), 21h (1351), 28A11/B1 (1352), 2G6 (1353), 35F3/E2 (1354), 38G3/A9 (1355), 428 (1356), 448-D (1357), 46D2/D5 (1358), 48-16 (1359), 50-61A (1360), 5145A (1361), 558-D (1362), 559/64-D (1363), 55D5/F9 (1364), 588-D (1365), 654-D (1366), 67G6/C4 (1367), 729-D (1368), 830D (1369), 9CL (1370), BM12 (1371), D20 (1372), D21 (1373), D24 (1374), D25 (1375), D28 (1376), D35 (1377), D39 (1378), D42 (1379), D52 (1380), D53 (1381), D60 (1382), DA48 (1383), DO8i (1384), F105 (1385), F91 (1386), FG39 (1387), Fbb14 (1388), GP13 (1389), GP44 (1390), GP68 (1391), HF1.7 (1392), HT5 (1393), HT6 (1394), HT7 (1395), ICR 39.13g (1396), ICR 39.3b (1397), Ia3 (1398), Ia7 (1399), IgG1b12 (1400), IgGCD4 (1401), L28 (1402), L33 (1403), L41 (1404), L42 (1405), L52 (1406), L72 (1407), M12 (1408), M13 (1409), M6 (1410), MAG 116 (1411), MAG 12B (1412), MAG 29B (1413), MAG 3B (1414), MAG 55 (1415), MAG 72 (1416), MAG 86 (1417), MAG 96 (1418), MTW61D (1419), S1-1 (1420), T13 (1421), T49 (1422), T56 (1423), TH9 (1424), anti-CD4BS summary (1425), b11 (1426), b13 (1427), b14 (1428), b3 (1429), b6 (1430), polyclonal (1431), (1432)
gp120 CD4i	D19 (498), C12 (614), E51 (622), 19e (885), 412d (914), 47e (915), C02-17 (950), C02-19 (951), C02-53 (954), C02-7 (955), D02-1 (962), D02-24 (964), D02-33 (966), D02-34 (967), D02-7 (969), ED47 (984), Sb1 (1039), m16 (1055), m36 (1059), m6 (1065), polyclonal (1198), polyclonal (1227), polyclonal (1270), polyclonal (1280), polyclonal (1285), polyclonal (1286), polyclonal (1294), polyclonal (1303), (1432), 17b (1433), 21c (1434), 23e (1435), 48d (1436), 49e (1437), Fbb21 (1438), Fbb21 (1439), X5 (1440), 8F101 (1441), 41.1 (1523)
gp120 V1	35D10/D2 (408), 40H2/C7 (409), 43A3/E4 (410), 43C7/B9 (411), 45D1/B7 (412), 46E3/E6 (413), 58E1/B3 (414), 64B9/A6 (415), 69D2/A1 (416), 82D3/C3 (417), P1H6 (418), polyclonal (648), P3B2 (764), P3C8 (765), P4D7 (766), polyclonal (1303)
gp120 V1-V2	polyclonal (1177), polyclonal (1227), polyclonal (1281), 11/68b (1449), 62c (1450), CRA-6 (1451), L15 (1452), T52 (1453), T54 (1454)
gp120 V1-V2 and V3-V5	polyclonal (1455)
gp120 V1-V2-V3	4KG5 (1336)
gp120 V2	6D5 (405), B33 (406), 697-D (419), C108G (421), 11/4c (426), 8.22.2 (427), 12b (428), G3-136 (429), G3-4 (430), polyclonal (648), G34 (1005), (1432), 1088 (1456), 110-B (1457), 1357 (1458), 1361 (1459), 1393A (1460), 2158 (1461), 66a (1462), 66c (1463), 684-238 (1464), 830A (1465), CRA-3 (1466), CRA-4 (1467), L17 (1468), SC258 (1469)
gp120 V2-CD4BS	L25 (1470), L39 (1471), L40 (1472), L78 (1473)

Binding type	MAb ID (No.)
gp120 V3	IIIB-V3-26 (465), IIIB-V3-21 (466), 168B8 (467), polyclonal (468), MO97/V3 (469), polyclonal (470), polyclonal (471), 55/11 (472), 8/38c (473), 8/64b (474), polyclonal (475), polyclonal (476), polyclonal (477), polyclonal (478), 9284 (479), polyclonal (480), polyclonal (481), polyclonal (482), polyclonal (483), MAG 109 (484), MAG 49 (485), MAG 53 (486), MAG 56 (487), 1334-D (488), 1324-E (489), polyclonal (490), MO99/V3 (491), C311E (492), 924 (494), polyclonal (495), polyclonal (496), polyclonal (497), D19 (498), 10F10 (499), 2C4 (500), 412-D (501), polyclonal (502), CGP 47 439 (503), polyclonal (504), 178.1 (505), 257-D (506), 311-11-D (507), 41148D (508), 391/95-D (509), Aw (510), Bw (511), DO142-10 (512), Dv (513), Fv (514), Gv (515), Hv (516), polyclonal (517), 50.1 (518), (519), BAT123 (520), 838-D (521), 1006-15D (522), 782-D (523), 908-D (524), 1027-15D (525), F19.26-4 (527), F19.48-3 (528), F19.57-11 (529), 13105100 (530), M77 (531), polyclonal (532), SP.BAL114 (533), SP.SF2:104 (534), polyclonal (535), loop 2 (536), 4G10 (537), 5F7 (538), G3-523 (539), MN215 (540), Nea 9301 (541), 4117C (542), 419-D (543), 453-D (544), 504-D (545), 83.1 (546), 5023B (547), F58/D1 (548), P1/D12 (549), P4/D10 (550), IIIB-13 V3 (551), IIIB-34 V3 (552), A47/B1 (553), D59/A2 (554), G44/H7 (555), MO96/V3 (556), µ5.5 (557), µ5.5 (558), 19b (559), 268-D (560), 386-D (561), 5042A (562), 5042B (563), 418-D (564), 5021 (565), 5025B (566), 5042 (567), 110.3 (568), 110.4 (569), 110.5 (570), 58.2 (571), KD-247 (573), 537-D (574), 5020 (575), RC25 (576), P3E1 (577), 5023A (578), 110.6 (579), polyclonal (580), 10/36e (581), 10/54 (582), 11/85b (583), polyclonal (584), 0.5β (585), Cβ1, 0.5β (586), C25 (587), 447-52D (588), NM-01 (589), 1026 (590), 1034 (591), 59.1 (592), polyclonal (593), 10E3 (595), polyclonal (596), N11-20 (597), 5025A (598), N70-1.9b (599), 902 (600), 694/98-D (601), 9205 (605), 110.I (606), anti-HIV-2 polyclonal (607), IIIB-V3-01 (609), polyclonal (648), P3C5 (767), 3019 (823), 10/540.w (837), 1101 (858), 12.19 (866), 12.9 (867), 1A3 (886), 2.10H (890), 2.1E (891), 2601 (895), 2B7 (897), 3074 (899), 3224 (902), 4E5 (919), C02-34 (952), CO11 (961), F2A3 (989), F3.9F (990), F39F (991), F425 B4e8 (993), F425B4a1 (994), F530 (995), H211 (1007), LA21 (1017), PA-1 (1035), V3-G2-10 (1048), V3-G2-25 (1049), V3-W1-2 (1050), V3-W1-8 (1051), polyclonal (1177), polyclonal (1180), polyclonal (1185), polyclonal (1188), polyclonal (1207), polyclonal (1213), polyclonal (1227), polyclonal (1228), polyclonal (1234), polyclonal (1280), polyclonal (1284), polyclonal (1285), polyclonal (1294), polyclonal (1295), polyclonal (1297), polyclonal (1303), polyclonal (1305), polyclonal (1308), (1432), (1474), 10D8 (1475), 10F6 (1476), 110.J (1477), 11G5 (1478), 2182 (1479), 2191 (1480), 2219 (1481), 2412 (1482), 2442 (1483), 2456 (1484), 2483 (1485), 2497 (1486), 2557 (1487), 2558 (1488), 2580 (1489), 391/95-D (1490), 39F (1491), 4148d (1492), 55/68b (1493), 5G11 (1494), 6.1 (1495), 6.7 (1496), 8.27.3 (1497), 8E11/A8 (1498), 9305 (1499), A1g8 (1500), AG1121 (1501), Ag1211 (1502), B4a1 (1503), B4e8 (1504), D27 (1505), D47 (1506), D56 (1507), F5.5 (1508), G3-1472 (1509), K24 (1510), TH1 (1511), anti-gp120/V3 (1512), polyclonal (1513), polyclonal (1514), polyclonal (1515), polyclonal (1516), polyclonal (1517), polyclonal (1518), polyclonal (1519), polyclonal (1520), polyclonal (1521), polyclonal (1527)
gp120 V3 discontinuous	11/75a/21/41 (1522), 41.1 (1523), 55/45a/11 (1524)
gp120 V3 mimotope	1108 (1525)
gp120 V3-C4	MO101/V3,C4 (602), polyclonal (1203), polyclonal (1230), polyclonal (1316), polyclonal (1526)
gp120 V3-C5	MO101/V3,C4 (603), MO101/V3,C4 (604)
gp120 V4	D/6D1 (610), 4D7/4 (612), 36.1(ARP 329) (613), C12 (614), polyclonal (618), B15 (619), B34 (620), polyclonal (648), M2 (1021), polyclonal (1527)
gp120 V5	polyclonal (648), polyclonal (649)

B Cell

Binding type	MAb ID (No.)
gp120 V5-C5	CRA1 (650), M91 (651), 8C6/1 (659)
gp120 adjacent to CD4BS	1.4C (833), 1.4G (834), 4.11C (910), 4.6H (911), m9 (1066), A32 (1331)
gp120 carbohydrates at glycosylation residues in C2, C3, C4, and V4	2G12 (898), polyclonal (1294)
gp120-CD4 complex	8F101 (1441), 8F102 (1555), CG-10 (1556), CG-25 (1557), CG-4 (1558), CG-76 (1559), CG-9 (1560)
gp41 MPER (membrane proximal external region)	18F11 (776), 7E10 (777), polyclonal (778), polyclonal (785), 14D9 (788), 2F5 (789), Z13e1 (790), 4E10 (791), Z13 (792), 5A9 (824), 13H11 (873), polyclonal (1198), polyclonal (1280), polyclonal (1305)
gp41 NHR (N-heptad repeat)	13K3 (874), 8K8 (936), D5 (978), DN9 (980), N2 (1029), R21 (1036), R3 (1037), R7 (1038), polyclonal (1310), NC-1 (1566)
gp41 adjacent to cluster II	14D9 (788), 2F5 (789), 13H11 (873)
gp41 alpha-helical hairpin intermediate	98-6 (771), polyclonal (1528)
gp41 cluster I	50-69 (704), Fab T2 (714), 246-D (724), 181-D (727), 240-D (728), F240 (729), D49 (730), D61 (731), T32 (732), T34 (733), 3D6 (760), P1G9 (761), polyclonal (1294), 1367 (1529), 7B2 (1530)
gp41 cluster II	D50 (768), 98-6 (771), 167-7 (772), ND-15G1 (773), 167-D (774), 5A9 (824), D17 (974), D40 (976), polyclonal (1287), 126-6 (1531), 1342 (1532), 1379 (1533), 2.2B (1534), Fab D11 (1535), Fab D5 (1536), Fab G1 (1537), Fab M10 (1538), Fab M12 (1539), Fab M15 (1540), Fab S10 (1541), Fab S6 (1542), Fab S8 (1543), Fab S9 (1544), Fab T3 (1545), Md-1 (1546), 1281 (1553)
gp41 cluster III	Fab A9 (1547), Fab G15 (1548), Fab G5 (1549), Fab L1 (1550), Fab L11 (1551), Fab L2 (1552)
gp41 cytoplasmic domain	polyclonal (1301), Chessie 8 (1554)
gp41 five-helix bundle (one CHR peptide of six helix bundle is missing)	13K3 (874), 8K8 (936), D5 (978), DN9 (980), N2 (1029), R21 (1036), R3 (1037), R7 (1038), NC-1 (1566)
gp41 internal trimeric coiled-coil of N-helices	1034 (852), 1492 (884)
gp41 six-helix bundle and the internal trimeric coiled-coil of N-helices	1010 (838), 1018 (840), 1020 (844), 1022 (845), 13K3 (874)
gp41six-helix bundle	167-D (774), 1014 (839), 1019 (841), D5 (978), Fab 3663 (997), Fab 3670 (998), Fab 3674 (999), N2 (1029), R21 (1036), polyclonal (1310), 1281 (1553), NC-1 (1566)
immunodominant region	3D6 (760), 105-518 (1561)
p24+gp41	31A1 (1562), 39A64 (1563), 39B86 (1564), 9303 (1565)
quaternary structure	2909 (896)
Nef	
C-term	AE6 (1611), AG11 (1612), EH1 (1613), AE6 (1621)
HIV-1	
gp120 CD4i	polyclonal (1668)

IV-B-2 Alphabetical listing of MAbs

Cross reference of MAb names and their order of appearance in the tables. Alphanumeric sorting is symbols, digits and letters.

MAb ID	No.
0.5β	585
1-B-7	69
1-E-4	58
1-E-9	59
1.152 B3	195
1.153 G10	203
1.158 E2	196
1.160 B3	207
1.17.3	90
1.2	281
1.4C	833
1.4G	834
1.9E	835
1.9F	836
10-E-7	60
10-G-9	61
10.1	337
10/36e	581
10/46c	1339
10/54	582
10/540.w	837
10/76b	422
1006-15D	522
1006-30-D	445
1008-D	1340
101-342	1311
101-451	1312
1010	838
1014	839
1018	840
1019	841
102	842
102-135	843
1020	844
1022	845
1024	1335
1025	846
1026	590
1027-15D	525
1027-30-D	1341
103-14E9	847
103-14F5	848
103-16B9	849
103-4E11	850
103-6H7	851
1034	591
1034	852
104-14A2	853
105-134	854
105-306	669
105-518	1561
105-732	759
106-11F10	855
106-9H11	856
106/01	118
108/03	111
1088	1456
10D8	1475
10E3	595
10E7	187
10E9	857
10F10	499
10F6	1476
11	399
11-C-5	62
11/41e	423
11/4b	424
11/4c	426
11/65	394
11/68b	1449
11/75a/21/41	1522
11/85b	583
110-B	1457
110.1	441
110.1	664
110.3	568
110.4	569
110.5	570
110.6	579
110.C	464
110.D	616
110.E	463
110.I	606
110.J	1477
110/015	112
1101	858
1108	1525
1109/01	50
111/052	47
111/073	56
111/182	37
112/021	38
112/047	39
1125H	1342
1125H	1343
113-1B4	859
113-20E11	860
113-2G1	861
113/038	57
113/072	75
1131-A	680
114-12F2	862
114-13A6	863
114-13F6	864
114-4G5	865
115.8	734
11C10B10	106
11D11F2	107
11G5	1478
11H9	26
12	238
12-B-4	103
12.19	866
12.9	867
120-1	1313
120-16	770
120-1B1	1344
1202-D	1345
126-50	868
126-6	1531
126-7	869
1281	1553
12b	428
12G-A8g2	20
12G-D7h11	21
12G-H1c7	22
12G10	400
12H-D3b3	19
12H2	870
12I-D12g2	23
13	239
13-102-100	77
13.10	871
13/035	1570
13/042	1569
13/058	1582
13105100	530
1324-E	489
133/11	356
133/192	364
133/237	354
133/290	355
1331-D	872
1331A	679
1331E	1346
1334-D	488
1342	1532
135/9	401
1357	1458
1361	1459
1367	1529
1379	1533
1393A	1460
13a15	875
13a23	876
13a3	877
13a6	878
13a7	879
13b18	880
13b23	881
13B5	117
13b53	882
13b61	883
13E1	189
13H11	873
13H8	637
13K3	874
14	240
1492	884
14D4E11	51
14D9	788
15-21	33
15.1	298
1570	1347
1575	812
1576	799
1577	820
1578	800
1579	801
1583	802
158F3	674
1595	1348
1599	1349
15e	1350
15F8C7	46
16	241
16/4/2	139
161D7	675
1662	640
1663	641
1664	642
167-7	772
167-D	774
168B8	467
1696	186
1697	643
17	222
178.1	505
1794	644
1795	628
17b	1433
1804	645
1807	646
1808	647
181-D	727
183-H12-5C	140
187.2.1	384
1899	803
18F11	776
19	229
1907	804
1908	805
1909	806
19b	559
19e	885
1A1	683
1A3	886
1A7	91
1B1	887
1B2C12	87
1B8.env	748
1C1	653

B Cell

B Cell

HyHIV-15	25	L72	1407	MAG 109	484	NF3A3	1618
HyHIV-19	157	L78	1473	MAG 116	1411	NF8B4	1619
HyHIV-2	6	L81	1333	MAG 12B	1412	NM-01	589
HyHIV-21	16	LA15	1016	MAG 29B	1413	NT2/4D5.24	295
HyHIV-22	18	LA21	1017	MAG 3B	1414	NT3/2D1.1	280
HyHIV-3	7	LA28	1018	MAG 45	1323	P1/D12	549
HyHIV-4	8	LA9 (121-134)	811	MAG 49	485	P1G9	761
HyHIV-5	9	LE311	1019	MAG 53	486	P1H6	418
HyHIV-6	10	LF17	1020	MAG 55	1415	P2D2	763
i5B11	125	LH-104-A	89	MAG 56	487	P35	1326
Ia3	1398	LH-104-B	119	MAG 6B	1023	P3B2	764
Ia7	1399	LH-104-C	102	MAG 72	1416	P3C5	767
ICR 39.13g	1396	LH-104-E	86	MAG 86	1417	P3C8	765
ICR 39.3b	1397	LH-104-G	124	MAG 95	1324	P3E1	577
ICR38.1a	629	LH-104-I	120	MAG 96	1418	P3G9	825
ICR38.8f	635	LH-104-K	88	MAG 97	1325	p3JB9	121
ID6	1447	loop 2	536	Md-1	1546	P4/D10	550
ID6	1448	M-1	735	Md1	1027	P43110	1033
ID8F6	40	M-11	736	MF119.1	388	P4A3	826
IE8G2	158	M-13	737	MF169.1	447	P4C2	827
IgA6/30λ	1011	M-2	738	MF170.1	448	P4D7	766
IgA6/5k	1012	M-22	739	MF39.1	383	P5-3	1034
IgA6/L4	1013	M-24	740	MF4.1	389	p5F1	113
IgG1b12	1400	M-25	741	MF46.1	404	p6F4	122
IgGCD4	1401	M-28	742	MF49.1	370	p7	1328
IIIB-13 V3	551	M-29	743	MF53.1	390	PA-1	1035
IIIB-34 V3	552	M-36	744	MF58.1	391	PC5009	688
IIIB-V3-01	609	M-4	745	MF77.1	392	polyclonal α577-596	689
IIIB-V3-21	466	M-6	746	MF87.1	449	polyclonal α598-609	747
IIIB-V3-26	465	M12	127	MN215	540	polyclonal HIVIG	185
IVI-4G6	1010	M12	1408	MO101/V3,C4	602	R21	1036
J1	329	M13	1409	MO101/V3,C4	603	R3	1037
J1	443	m14	1054	MO101/V3,C4	604	R7	1038
J3	444	m16	1055	MO28	1024	RC25	576
J3B2	334	m18	1056	MO30	1025	RL4.72.1	78
J4	271	M2	1021	MO43	1026	RSD-33	425
JB7	137	m22	1057	MO86/C3	636	RT-4	255
JF11	138	m24	1058	MO9.42.2	98	RT6H	206
JL413	623	M25	1022	MO9.50.2	99	RT7O	256
K14	1014	m36	1059	MO96/V3	556	RT7U	257
K24	1510	M38	662	MO97/V3	469	RTMAb8	204
KD-247	573	m43	1060	MO99/V3	491	RV110026	667
KU32	1015	m44	1061	MTW61D	1419	S1-1	1420
L-anti-Tat	304	m46	1062	multiple Fabs	1067	SAR1	819
L100	1329	m47	1063	multiple MAbs	1068	Sb1	1039
L14	110	m48	1064	multiple MAbs	1069	sc-FV p17	35
L14.17	1	m6	1065	multiple MAbs	1070	SC258	1469
L15	1452	M6	1410	N03B11	1028	scFvtat1	322
L17	1468	M77	531	N11-20	597	SP.BAL114	533
L19	1320	M85	348	N2	1029	SP.SF2:104	534
L25	1470	M86	352	N2-4	1030	T1.1	371
L28	1402	M89	454	N3C5	1031	T11	396
L33	1403	m9	1066	N70-1.9b	599	T13	1421
L39	1471	M90	1321	N70-2.3a	1032	T15G1	1040
L40	1472	M91	651	NC-1	1566	T2.1	393
L41	1404	M92	351	ND-15G1	773	T20	1041
L42	1405	M96	387	Nea 9301	541	T22	1442
L5.1	360	MAb 35	237	NF1A1	1608	T26	1314
L52	1406	MAG 104	1322	NF2B2	1617	T27	1042

B Cell

IV-B-3 MAbs by order of appearance in tables

No.	MAb ID
p17	
1	L14.17
2	polyclonal
3	32/5.8.42
4	32/5.8.42
5	HyHIV-1
6	HyHIV-2
7	HyHIV-3
8	HyHIV-4
9	HyHIV-5
10	HyHIV-6
11	32/1.24.89
12	3B10
13	3E11
14	polyclonal
15	8H10
16	HyHIV-21
17	B4f8
18	HyHIV-22
19	12H-D3b3
20	12G-A8g2
21	12G-D7h11
22	12G-H1c7
23	12I-D12g2
24	polyclonal
25	HyHIV-15
26	11H9
27	3-H-7
28	C5126
29	1D9
30	4C9
31	4H2B1
32	9G5
33	15-21
34	31-11
35	sc-FV p17
p17-p24	
36	3A6
p24	
37	111/182
38	112/021
39	112/047
40	ID8F6
41	F5-2
42	CB-13/5
43	polyclonal
44	3D3
45	CD-4/1
46	15F8C7
47	111/052
48	polyclonal
49	91-5
50	1109/01
51	14D4E11
52	1G5C8
53	47-2
54	714/01
55	polyclonal
56	111/073
57	113/038
58	1-E-4
59	1-E-9
60	10-E-7
61	10-G-9
62	11-C-5
63	2-E-4
64	2-H-4
65	8-D-2
66	8-G-9
67	8-H-7
68	C5123
69	1-B-7
70	3-B-7
71	6-D-12
72	6-E-7
73	8-D-5
74	FF1
75	113/072
76	25.3
77	13-102-100
78	RL4.72.1
79	406/01
80	polyclonal
81	38:9.6K
82	EB1A9
83	polyclonal
84	30:3E5
85	EF7
86	LH-104-E
87	1B2C12
88	LH-104-K
89	LH-104-A
90	1.17.3
91	1A7
92	1F6
93	23A5G4
94	23A5G5
95	3D10G6
96	polyclonal
97	F5-4
98	MO9.42.2
99	MO9.50.2
100	V10
101	V107
102	LH-104-C
103	12-B-4
104	C5122
105	9A4C4
106	11C10B10
107	11D11F2
108	CD12B4
109	BE3
110	L14
111	108/03
112	110/015
113	p5F1
114	32:32K
115	C5200
116	FH2
117	13B5
118	106/01
119	LH-104-B
120	LH-104-I
121	p3JB9
122	p6F4
123	polyclonal
p24-p2p7p1p6	
124	LH-104-G
p2p7p1p6	
125	i5B11
126	EC6
127	M12
128	DG8
129	EB5
130	HH3
131	AD2
132	CA5
133	DF3
134	EC3
135	FC12
136	GE4
137	JB7
138	JF11
Gag	
139	16/4/2
140	183-H12-5C
141	241-D
142	2A6
143	5E2.A3k
144	71-31
145	91-6
146	98-4.3
147	98-4.9
148	AC2
149	BC1071
150	BE10
151	CD9
152	CH9B2
153	ED8
154	EH12E1
155	G11G1
156	G11H3
157	HyHIV-19
158	IE8G2
159	V7-8
160	anti-Gag
161	anti-p24
162	human sera
163	polyclonal
164	polyclonal
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184	polyclonal
185	polyclonal HIVIG
Protease	
186	1696
187	10E7
188	F11.2.32
189	13E1
190	8B11
191	8C10
192	8G5
RT	
193	1E8
194	polyclonal
195	1.152 B3
196	1.158 E2
197	31D6
198	31G8
199	32E7
200	33D5
201	5B2
202	polyclonal
203	1.153 G10
204	RTMAb8
205	1D4A3
206	RT6H
207	1.160 B3
208	polyclonal
209	C2003
210	anti-RT
Integrase	
211	1C4
212	2C11
213	2E3
214	3E11
215	3F9
216	5F8
217	6G5
218	7B6

B Cell

219 7C6
220 6C5
221 8G4
222 17
223 4D6
224 7-16
225 4F6
226 anti-K159
227 5D9
228 8-6
229 19
230 2-19
231 8-22
232 4-20
233 6-19
234 7C3
235 7F11
236 8E5
237 MAb 35
Pol
238 12
239 13
240 14
241 16
242 1C12B1
243 21
244 32
245 35
246 3D12
247 3F10
248 4
249 5B11
250 6B10
251 6B9
252 6E9
253 7C4
254 E-4
255 RT-4
256 RT7O
257 RT7U
258 anti-HIV-1 RT
259 polyclonal
260 polyclonal
261 polyclonal
262 polyclonal
263 33
264 F-6
265 6B9
266 5F
267 5G
268 7C4
Vif
269 TG002
270 TG001
271 J4
272 polyclonal
Vpr
273 polyclonal
Tat
274 polyclonal
275 polyclonal
276 TA9
277 TD84
278 TE135
279 polyclonal
280 NT3/2D1.1
281 1.2
282 1D9D5
283 polyclonal
284 TB12
285 polyclonal
286 polyclonal
287 polyclonal
288 polyclonal
289 1D2F11
290 2D9E7
291 4B4C4
292 5G7D8
293 polyclonal
294 polyclonal
295 NT2/4D5.24
296 polyclonal
297
298 15.1
299 4A4.8
300 7D5.1
301 7E5
302 8D1.8
303 ABI#161
304 L-anti-Tat
305 Tat1
306 polyclonal
307 polyclonal
308 polyclonal
309 polyclonal
310 polyclonal
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312 polyclonal
313 polyclonal
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315 polyclonal
316 polyclonal
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320 polyclonal
321 polyclonal
322 scFvtat1
323 2D9D5
324 polyclonal
325 polyclonal
326 polyclonal
327 G1
328 G2
329 J1
330 TC15
331 polyclonal
332 polyclonal
333 B1E3
334 J3B2
Rev
335 4G9
336 Ab2
337 10.1
338 3H6
339 8E7
340 9G2
341 Ab4
342 3G4
343 1G10
344 1G7
345 Ab3
346 2G2
Vpu
347 DE7
gp160
348 M85
349 7E2/4
350 4D4#85
351 M92
352 M86
353 polyclonal
354 133/237
355 133/290
356 133/11
357 D/3G5
358 D/6A11
359 D/5E12
360 L5.1
361 4A7C6
362 1D10
363 B242
364 133/192
365 489.1(961)
366 5B3
367 B10
368 B2
369 C6
370 MF49.1
371 T1.1
372 T7.1
373 T9
374 GV4D3
375 B27
376 B9
377 B35
378 D/4B5
379 D/5A11
380 D/6B2
381 B18
382 B20
383 MF39.1
384 187.2.1
385 37.1.1(ARP 327)
386 6D8
387 M96
388 MF119.1
389 MF4.1
390 MF53.1
391 MF58.1
392 MF77.1
393 T2.1
394 11/65
395 W1
396 T11
397 GV1A8
398 CA13
399 11
400 12G10
401 135/9
402 7C10
403 C4
404 MF46.1
405 6D5
406 B33
407 polyclonal
408 35D10/D2
409 40H2/C7
410 43A3/E4
411 43C7/B9
412 45D1/B7
413 46E3/E6
414 58E1/B3
415 64B9/A6
416 69D2/A1
417 82D3/C3
418 P1H6
419 697-D
420 6C4/S
421 C108G
422 10/76b
423 11/41e
424 11/4b
425 RSD-33
426 11/4c
427 8.22.2
428 12b
429 G3-136
430 G3-4
431 BAT085
432 60b
433 74
434 38/12b
435 38/60b
436 polyclonal
437 322-151
438 3D3.B8
439 4C11.D8
440 493-156
441 110.1
442 GV4H3
443 J1
444 J3
445 1006-30-D
446 847-D
447 MF169.1

448	MF170.1
449	MF87.1
450	213.1
451	B12
452	B13
453	C13
454	M89
455	B21
456	B23
457	B24
458	B25
459	B3
460	B26
461	B29
462	B36
463	110.E
464	110.C
465	IIIB-V3-26
466	IIIB-V3-21
467	168B8
468	polyclonal
469	MO97/V3
470	polyclonal
471	polyclonal
472	55/11
473	8/38c
474	8/64b
475	polyclonal
476	polyclonal
477	polyclonal
478	polyclonal
479	9284
480	polyclonal
481	polyclonal
482	polyclonal
483	polyclonal
484	MAG 109
485	MAG 49
486	MAG 53
487	MAG 56
488	1334-D
489	1324-E
490	polyclonal
491	MO99/V3
492	C311E
493	907
494	924
495	polyclonal
496	polyclonal
497	polyclonal
498	D19
499	10F10
500	2C4
501	412-D
502	polyclonal
503	CGP 47 439
504	polyclonal
505	178.1
506	257-D
507	311-11-D
508	41148D
509	391/95-D
510	Aw
511	Bw
512	DO142-10
513	Dv
514	Fv
515	Gv
516	Hv
517	polyclonal
518	50.1
519	
520	BAT123
521	838-D
522	1006-15D
523	782-D
524	908-D
525	1027-15D
526	V3-13
527	F19.26-4
528	F19.48-3
529	F19.57-11
530	13105100
531	M77
532	polyclonal
533	SP.BAL114
534	SP.SF2:104
535	polyclonal
536	loop 2
537	4G10
538	5F7
539	G3-523
540	MN215
541	Nea 9301
542	4117C
543	419-D
544	453-D
545	504-D
546	83.1
547	5023B
548	F58/D1
549	P1/D12
550	P4/D10
551	IIIB-13 V3
552	IIIB-34 V3
553	A47/B1
554	D59/A2
555	G44/H7
556	MO96/V3
557	μ5.5
558	μ5.5
559	19b
560	268-D
561	386-D
562	5042A
563	5042B
564	418-D
565	5021
566	5025B
567	5042
568	110.3
569	110.4
570	110.5
571	58.2
572	polyclonal
573	KD-247
574	537-D
575	5020
576	RC25
577	P3E1
578	5023A
579	110.6
580	polyclonal
581	10/36e
582	10/54
583	11/85b
584	polyclonal
585	0.5β
586	Cβ1, 0.5β
587	C25
588	447-52D
589	NM-01
590	1026
591	1034
592	59.1
593	polyclonal
594	polyclonal
595	10E3
596	polyclonal
597	N11-20
598	5025A
599	N70-1.9b
600	902
601	694/98-D
602	MO101/V3,C4
603	MO101/V3,C4
604	MO101/V3,C4
605	9205
606	110.I
607	anti-HIV-2 polyclonal
608	B2C
609	IIIB-V3-01
610	D/6D1
611	2H1B
612	4D7/4
613	36.1(ARP 329)
614	C12
615	2F19C
616	110.D
617	B32
618	polyclonal
619	B15
620	B34
621	7F11
622	E51
623	JL413
624	5C2E5
625	G3-211
626	G3-537
627	polyclonal
628	1795
629	ICR38.1a
630	G3-299
631	G3-42
632	G3-508
633	G3-519
634	G3-536
635	ICR38.8f
636	MO86/C3
637	13H8
638	G45-60
639	polyclonal
640	1662
641	1663
642	1664
643	1697
644	1794
645	1804
646	1807
647	1808
648	polyclonal
649	polyclonal
650	CRA1
651	M91
652	9201
653	1C1
654	3F5
655	5F4/1
656	660-178
657	9301
658	B221
659	8C6/1
660	H11
661	W2
662	M38
663	polyclonal
664	110.1
665	42F
666	43F
667	RV110026
668	Chim 1
669	105-306
670	GV1G2
671	750-D
672	450-D
673	670-D
674	158F3
675	161D7
676	polyclonal
677	722-D
678	polyclonal
679	1331A
680	1131-A
681	858-D
682	989-D
683	1A1

684	24G3
685	25C2
686	5F3
687	α(566-586)
688	PC5009
689	polyclonal α577-596
690	polyclonal
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693	1F11
694	1H5
695	3D9
696	4B3
697	4D4
698	4G2
699	polyclonal
700	polyclonal
701	
702	polyclonal
703	2A2/26
704	50-69
705	9-11
706	98-43
707	41-1
708	41.4
709	Fab A1
710	Fab A4
711	Fab M12B
712	Fab M26B
713	Fab M8B
714	Fab T2
715	polyclonal
716	86
717	polyclonal
718	V10-9
719	polyclonal
720	anti-P1
721	polyclonal
722	polyclonal
723	2F11
724	246-D
725	polyclonal
726	9G5A
727	181-D
728	240-D
729	F240
730	D49
731	D61
732	T32
733	T34
734	115.8
735	M-1
736	M-11
737	M-13
738	M-2
739	M-22
740	M-24
741	M-25
742	M-28
743	M-29
744	M-36
745	M-4
746	M-6
747	polyclonal α598-609
748	1B8.env
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751	clone 3
752	4
753	41-6
754	41-7
755	68.1
756	68.11
757	75
758	polyclonal
759	105-732
760	3D6
761	P1G9
762	F172-D8
763	P2D2
764	P3B2
765	P3C8
766	P4D7
767	P3C5
768	D50
769	5-21-3
770	120-16
771	98-6
772	167-7
773	ND-15G1
774	167-D
775	polyclonal
776	18F11
777	7E10
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779	polyclonal
780	polyclonal
781	5B2
782	9G11
783	TH-Ab1
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785	polyclonal
786	polyclonal
787	polyclonal
788	14D9
789	2F5
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791	4E10
792	Z13
793	B30
794	polyclonal
795	41S-2
796	C8
797	B31
798	B33
799	1576
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801	1579
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803	1899
804	1907
805	1908
806	1909
807	41-1
808	41-2
809	41-3
810	ED6
811	LA9 (121-134)
812	1575
813	88-158/02
814	88-158/022
815	88-158/079
816	polyclonal
817	polyclonal
818	B8
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820	1577
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822	DZ
823	3019
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826	P4A3
827	P4C2
828	polyclonal
Env	
829	
830	
831	
832	
833	1.4C
834	1.4G
835	1.9E
836	1.9F
837	10/540.w
838	1010
839	1014
840	1018
841	1019
842	102
843	102-135
844	1020
845	1022
846	1025
847	103-14E9
848	103-14F5
849	103-16B9
850	103-4E11
851	103-6H7
852	1034
853	104-14A2
854	105-134
855	106-11F10
856	106-9H11
857	10E9
858	1101
859	113-1B4
860	113-20E11
861	113-2G1
862	114-12F2
863	114-13A6
864	114-13F6
865	114-4G5
866	12.19
867	12.9
868	126-50
869	126-7
870	12H2
871	13.10
872	1331-D
873	13H11
874	13K3
875	13a15
876	13a23
877	13a3
878	13a6
879	13a7
880	13b18
881	13b23
882	13b53
883	13b61
884	1492
885	19e
886	1A3
887	1B1
888	1D10
889	1F7
890	2.10H
891	2.1E
892	2.5E
893	20-2-C8.5F3
894	25G
895	2601
896	2909
897	2B7
898	2G12
899	3074
900	30D
901	31710B
902	3224
903	38B5/C9
904	39H10/A11
905	3C9
906	3D5
907	3F8
908	3F9
909	3H6
910	4.11C
911	4.6H
912	4.8E
913	40D3/C11
914	412d
915	47e
916	49B11/A1
917	4D3
918	4E1

919	4E5
920	52G5/B9
921	55E4/H1
922	56C4/C8
923	570-D
924	57B6/F1
925	57H5/D7
926	5E
927	63G4/E2
928	65B12/C5
929	694/98D
930	6D8
931	6E10
932	7-1054
933	8.2A
934	85G11/D8
935	87E4/A8
936	8K8
937	97B1/E8
938	A12
939	A9
940	ADP421 polyclonal
941	AG10H9
942	AH48
943	B4
944	B5
945	B6
946	B97-11C5
947	BAT267
948	BAT401
949	BAT509
950	C02-17
951	C02-19
952	C02-34
953	C02-41
954	C02-53
955	C02-7
956	C18-2
957	C31
958	C8
959	CD4-IgG2
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961	CO11
962	D02-1
963	D02-20
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967	D02-34
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969	D02-7
970	D1
971	D10
972	D12
973	D16
974	D17
975	D4
976	D40
977	D43
978	D5
979	D7
980	DN9
981	E047
982	E2E
983	ED10
984	ED47
985	EH21
986	F1
987	F223
988	F285
989	F2A3
990	F3.9F
991	F39F
992	F424
993	F425 B4e8
994	F425B4a1
995	F530
996	F7
997	Fab 3663
998	Fab 3670
999	Fab 3674
1000	Fab A12
1001	Fab A2
1002	Fab L9
1003	G12
1004	G2
1005	G34
1006	H2
1007	H211
1008	H8
1009	HBW4
1010	IVI-4G6
1011	IgA6/30λ
1012	IgA6/5k
1013	IgA6/L4
1014	K14
1015	KU32
1016	LA15
1017	LA21
1018	LA28
1019	LE311
1020	LF17
1021	M2
1022	M25
1023	MAG 6B
1024	MO28
1025	MO30
1026	MO43
1027	Md1
1028	N03B11
1029	N2
1030	N2-4
1031	N3C5
1032	N70-2.3a
1033	P43110
1034	P5-3
1035	PA-1
1036	R21
1037	R3
1038	R7
1039	Sb1
1040	T15G1
1041	T20
1042	T27
1043	T3
1044	T30
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1046	T4
1047	T8
1048	V3-G2-10
1049	V3-G2-25
1050	V3-W1-2
1051	V3-W1-8
1052	WR102
1053	WR204
1054	m14
1055	m16
1056	m18
1057	m22
1058	m24
1059	m36
1060	m43
1061	m44
1062	m46
1063	m47
1064	m48
1065	m6
1066	m9
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1068	multiple MAbs
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1192	polyclonal
1193	polyclonal
1194	polyclonal
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1197	polyclonal
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1304	polyclonal
1305	polyclonal
1306	polyclonal
1307	polyclonal
1308	polyclonal
1309	polyclonal
1310	polyclonal
1311	101-342
1312	101-451
1313	120-1
1314	T26
1315	D33
1316	polyclonal
1317	212A
1318	522-149
1319	CA1
1320	L19
1321	M90
1322	MAG 104
1323	MAG 45
1324	MAG 95
1325	MAG 97
1326	P35
1327	T9
1328	p7
1329	L100
1330	2/11c
1331	A32
1332	C11
1333	L81
1334	polyclonal
1335	1024
1336	4KG5
1337	23A
1338	D7324
1339	10/46c
1340	1008-D
1341	1027-30-D
1342	1125H
1343	1125H
1344	120-1B1
1345	1202-D
1346	1331E
1347	1570
1348	1595
1349	1599
1350	15e
1351	21h
1352	28A11/B1
1353	2G6
1354	35F3/E2
1355	38G3/A9
1356	428
1357	448-D
1358	46D2/D5
1359	48-16
1360	50-61A
1361	5145A
1362	558-D
1363	559/64-D
1364	55D5/F9
1365	588-D
1366	654-D
1367	67G6/C4
1368	729-D
1369	830D
1370	9CL
1371	BM12
1372	D20
1373	D21
1374	D24
1375	D25
1376	D28
1377	D35
1378	D39
1379	D42
1380	D52
1381	D53
1382	D60
1383	DA48
1384	DO8i
1385	F105
1386	F91
1387	FG39
1388	Fbb14
1389	GP13
1390	GP44

1391	GP68
1392	HF1.7
1393	HT5
1394	HT6
1395	HT7
1396	ICR 39.13g
1397	ICR 39.3b
1398	Ia3
1399	Ia7
1400	IgG1b12
1401	IgGCD4
1402	L28
1403	L33
1404	L41
1405	L42
1406	L52
1407	L72
1408	M12
1409	M13
1410	M6
1411	MAG 116
1412	MAG 12B
1413	MAG 29B
1414	MAG 3B
1415	MAG 55
1416	MAG 72
1417	MAG 86
1418	MAG 96
1419	MTW61D
1420	S1-1
1421	T13
1422	T49
1423	T56
1424	TH9
1425	anti-CD4BS summary
1426	b11
1427	b13
1428	b14
1429	b3
1430	b6
1431	polyclonal
1432	
1433	17b
1434	21c
1435	23e
1436	48d
1437	49e
1438	Fbb21
1439	Fbb21
1440	X5
1441	8F101
1442	T22
1443	2A2
1444	AC4
1445	AD3
1446	AD3
1447	ID6
1448	ID6
1449	11/68b
1450	62c
1451	CRA-6
1452	L15
1453	T52
1454	T54
1455	polyclonal
1456	1088
1457	110-B
1458	1357
1459	1361
1460	1393A
1461	2158
1462	66a
1463	66c
1464	684-238
1465	830A
1466	CRA-3
1467	CRA-4
1468	L17
1469	SC258
1470	L25
1471	L39
1472	L40
1473	L78
1474	
1475	10D8
1476	10F6
1477	110.J
1478	11G5
1479	2182
1480	2191
1481	2219
1482	2412
1483	2442
1484	2456
1485	2483
1486	2497
1487	2557
1488	2558
1489	2580
1490	391/95-D
1491	39F
1492	4148d
1493	55/68b
1494	5G11
1495	6.1
1496	6.7
1497	8.27.3
1498	8E11/A8
1499	9305
1500	A1g8
1501	AG1121
1502	Ag1211
1503	B4a1
1504	B4e8
1505	D27
1506	D47
1507	D56
1508	F5.5
1509	G3-1472
1510	K24
1511	TH1
1512	anti-gp120/V3
1513	polyclonal
1514	polyclonal
1515	polyclonal
1516	polyclonal
1517	polyclonal
1518	polyclonal
1519	polyclonal
1520	polyclonal
1521	polyclonal
1522	11/75a/21/41
1523	41.1
1524	55/45a/11
1525	1108
1526	polyclonal
1527	polyclonal
1528	polyclonal
1529	1367
1530	7B2
1531	126-6
1532	1342
1533	1379
1534	2.2B
1535	Fab D11
1536	Fab D5
1537	Fab G1
1538	Fab M10
1539	Fab M12
1540	Fab M15
1541	Fab S10
1542	Fab S6
1543	Fab S8
1544	Fab S9
1545	Fab T3
1546	Md-1
1547	Fab A9
1548	Fab G15
1549	Fab G5
1550	Fab L1
1551	Fab L11
1552	Fab L2
1553	1281
1554	Chessie 8
1555	8F102
1556	CG-10
1557	CG-25
1558	CG-4
1559	CG-76
1560	CG-9
1561	105-518
1562	31A1
1563	39A64
1564	39B86
1565	9303
1566	NC-1
Nef	
1567	4H4
1568	polyclonal
1569	13/042
1570	13/035
1571	A6
1572	AM5C6
1573	AM5C6
1574	A7
1575	25/03
1576	26/76
1577	3F2
1578	3D12
1579	polyclonal
1580	polyclonal
1581	3G12
1582	13/058
1583	26/028
1584	polyclonal
1585	2E3
1586	polyclonal
1587	F14.11
1588	31/03
1589	polyclonal
1590	polyclonal
1591	F4
1592	F2
1593	polyclonal
1594	polyclonal
1595	polyclonal
1596	F3
1597	F8
1598	polyclonal
1599	F1
1600	2F2
1601	E9
1602	3E6
1603	E5
1604	2A3
1605	2E4
1606	2H12
1607	3A2
1608	NF1A1
1609	polyclonal
1610	E7
1611	AE6
1612	AG11
1613	EH1
1614	3B4B
1615	3H3E
1616	6.1
1617	NF2B2
1618	NF3A3
1619	NF8B4
1620	polyclonal
1621	AE6
HIV-1	
1622	
1623	
1624	

B Cell

1625	1G12
1626	1H8
1627	polyclonal
1628	polyclonal
1629	polyclonal
1630	polyclonal
1631	polyclonal
1632	polyclonal
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1740	polyclonal
1741	polyclonal
1742	polyclonal
1743	polyclonal
1744	polyclonal
1745	polyclonal
1746	polyclonal

IV-C

HIV Antibodies Tables

All HIV MAbs and polyclonal Abs that bind to linear epitopes 30 amino acids or less in length are arranged by protein position. The table entries are sorted in a nested way—first by protein, then by HXB2 start location, then by antibody type, and finally by antibody name. Abs that bind to conformational epitopes or with unknown epitopes are listed at the end of each protein section.

IV-C-1 Gag p17 Antibodies

No. 1
MAb ID L14.17
HXB2 Location p17 (11–25)
Author Location p17 (11–25 BRU)
Epitope `GELDRWEKIRLRPGG`
Neutralizing no
Immunogen vaccine
Vector/Type: viral lysate *Strain:* B clade BRU *HIV component:* HIV-1
Species (Isotype) mouse (IgG)
References Kanduc *et al.* 2008; Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b; Tatsumi *et al.* 1990

- L14.17: Similarity level of the L14.17 binding site pentapeptide WEKIR to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 1 time, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]

No. 2
MAb ID polyclonal
HXB2 Location p17 (11–25)
Author Location p17 (11–25 LAI)
Epitope `GELDRWEKIRLRPGG`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein, virus-like particle (VLP) *Strain:* B clade LAI *HIV component:* Gag, p17 Gag, p24 Gag *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse
References Truong *et al.* 1997

- An ELISA assay was used to study a panel of Gag peptides – mature p24 CA epitopes mapped to residues 176-192, 201-218, 233-253, 285-304, and were recognized by antibodies elicited by rp24CA – one p17MA epitope, residues 11-25, and one p24CA epitope, residues 176-192, were recognized by antibodies raised against anti-p55 virus-like particles, suggesting a differentantigenic properties for p24CA and p17MA antibodies depending on whether they are produced against the mature soluble protein or the immature assembled form of the gag proteins. Truong *et al.* [1997]

No. 3
MAb ID 32/5.8.42
HXB2 Location p17 (12–19)
Author Location p17 (12–19 IIIB)
Epitope `ELDRWEKI+ALDKIE`
Neutralizing no
Immunogen vaccine
Vector/Type: viral lysate
Species (Isotype) mouse (IgG)
References Papsidero *et al.* 1989

- 32/5.8.42: Binds to two discontinuous regions, positions 12-19 and 100-105, peptides ELDRWEKI and ALDKIE – inhibited infectivity of cell free virus. Papsidero *et al.* [1989]

No. 4
MAb ID 32/5.8.42
HXB2 Location p17 (12–19)
Author Location p17 (IIIB)
Epitope `ELDRWEKI+ALDKIE`
Neutralizing no
Immunogen vaccine
Vector/Type: viral lysate *HIV component:* HIV-1
Species (Isotype) mouse (IgG)
References Papsidero *et al.* 1989

- 32/5.8.42: Inhibited infectivity of cell free virus – bound to two peptides, ELDRWEKI and ALDKIE, at positions 12-19 + 100-105. Papsidero *et al.* [1989]

No. 5
MAb ID HyHIV-1
HXB2 Location p17 (12–29)
Author Location p17 (12–29 JMH1)
Epitope `ELDKWEKIRLRPGGKTLY`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p17 Gag
Species (Isotype) mouse (IgG1)
References Ota & Ueda 1998; Liu *et al.* 1995

- HyHIV-1: This paper compares the results of affinity constant (Ka) measurements of anti-p17 MAbs using double Ab methods versus the faster, isotope-free BIAcore system, and results were found to be similar for HyHIV-(1-6) – six MAbs all bind to the first alpha helix of p17, a functional domain for both membrane binding and nuclear localization. Ota & Ueda [1998]

No. 6
MAb ID HyHIV-2
HXB2 Location p17 (12–29)
Author Location p17 (12–29 JMH1)
Epitope ELDKWEKIRLRPGGKTLY
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p17 Gag
Species (Isotype) mouse (IgG1)
References Ota & Ueda 1998; Liu *et al.* 1995

- HyHIV-2: This paper compares the results of affinity constant (Ka) measurements of anti-p17 MAbs using double Ab methods versus the faster, isotope-free BIAcore system, and results were found to be similar for HyHIV-(1-6) – six MAbs all bind to the first alpha helix of p17, a functional domain for both membrane binding and nuclear localization. Ota & Ueda [1998]

No. 7
MAb ID HyHIV-3
HXB2 Location p17 (12–29)
Author Location p17 (12–29 JMH1)
Epitope ELDKWEKIRLRPGGKTLY
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p17 Gag
Species (Isotype) mouse (IgG1)
References Ota & Ueda 1998; Liu *et al.* 1995

- HyHIV-3: This paper compares the results of affinity constant (Ka) measurements of anti-p17 MAbs using double Ab methods versus the faster, isotope-free BIAcore system, and results were found to be similar for HyHIV-(1-6) – six MAbs all bind to the first alpha helix of p17, a functional domain for both membrane binding and nuclear localization. Ota & Ueda [1998]

No. 8
MAb ID HyHIV-4
HXB2 Location p17 (12–29)
Author Location p17 (12–29 JMH1)
Epitope ELDKWEKIRLRPGGKTLY?
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p17 Gag
Species (Isotype) mouse (IgG1)
References Ota & Ueda 1998; Ota *et al.* 1998; Liu *et al.* 1995

- HyHIV-4: epitope uncertain, based on the best estimate from JMH1 sequence– Ka is 1.8 x 10^7 M-1 for rec p17 – stains the surface of infected cells indicating the antigen is exposed at the cell surface. Ota *et al.* [1998]
- HyHIV-4: This paper compares the results of affinity constant (Ka) measurements of anti-p17 MAbs using double Ab methods versus the faster, isotope-free BIAcore system, and results were found to be similar for HyHIV-(1-6) – six MAbs all bind to the first alpha helix of p17, a functional domain for both membrane binding and nuclear localization. Ota & Ueda [1998]

No. 9
MAb ID HyHIV-5
HXB2 Location p17 (12–29)
Author Location p17 (12–29 JMH1)
Epitope ELDKWEKIRLRPGGKTLY
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p17 Gag
Species (Isotype) mouse (IgG1)
References Ota & Ueda 1998; Liu *et al.* 1995

- HyHIV-5: This paper compares the results of affinity constant (Ka) measurements of anti-p17 MAbs using double Ab methods versus the faster, isotope-free BIAcore system, and results were found to be similar for HyHIV-(1-6) – six MAbs all bind to the first alpha helix of p17, a functional domain for both membrane binding and nuclear localization. Ota & Ueda [1998]

No. 10
MAb ID HyHIV-6
HXB2 Location p17 (12–29)
Author Location p17 (12–29 JMH1)
Epitope ELDKWEKIRLRPGGKTLY
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p17 Gag
Species (Isotype) mouse (IgG1)
References Ota & Ueda 1998; Liu *et al.* 1995

- HyHIV-6: This paper compares the results of affinity constant (Ka) measurements of anti-p17 MAbs using double Ab methods versus the faster, isotope-free BIAcore system, and results were found to be similar for HyHIV-(1-6) – six MAbs all bind to the first alpha helix of p17, a functional domain for both membrane binding and nuclear localization. Ota & Ueda [1998]

No. 11
MAb ID 32/1.24.89
HXB2 Location p17 (17–22)
Author Location p17 (17–22 IIIB)
Epitope EKIRLR
Neutralizing L
Immunogen vaccine
Vector/Type: viral lysate
Species (Isotype) mouse (IgG)
References Papsidero *et al.* 1989

- 32/1.24.89: Inhibited infectivity of cell free virus. Papsidero *et al.* [1989]

No. 12

B Cell

MAb ID 3B10
HXB2 Location p17 (19–38)
Author Location p17 (19–38 SIVmac)
Epitope IRLPGGKKKYMLKHVVWAA
Neutralizing no
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade AGM TYO-7 *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
References Otteken *et al.* 1992

- 3B10: Recognized an epitope present on HIV-2/SIVmac (MAC251/32H) , SIVagm, HIV-1, and SIVmnd, demonstrating that the matrix protein of all nine HIV and SIV isolates tested in this study expresses at least one conserved immunogenic epitope recognized serologically. Otteken *et al.* [1992]

No. 13
MAb ID 3E11
HXB2 Location p17 (19–38)
Author Location p17 (19–38 SIVmac)
Epitope IRLPGGKKKYMLKHVVWAA
Neutralizing no
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade AGM TYO-7 *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
References Nilsen *et al.* 1996; Otteken *et al.* 1992

- 3E11: There is another MAb with this ID that recognizes integrase. Nilsen *et al.* [1996]
- 3E11: Recognized an epitope present on HIV-2/SIVmac (MAC251/32H), SIVagm, HIV-1, and SIVmnd, demonstrating that the matrix protein of all nine HIV and SIV isolates tested in this study expresses at least one highly conserved immunogenic epitope. Otteken *et al.* [1992]

No. 14
MAb ID polyclonal
HXB2 Location p17 (25–34)
Author Location Gag
Epitope GKTHYMINPL
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* Env, Gag, Nef, Pol
Species (Isotype) rabbit
References Li *et al.* 2005b
Keywords mimics

- In early HIV-1 infection, patients develop autoimmune thrombocytopenia, with Ab directed against beta3 integrin, GPIIIa49-66. Panning with a 7-mer phage display library using rabbit anti-GPIIIa49-66 (CAPESIEFPVSEARVLED), the immunodominant epitope of the identified potential molecular mimicry epitopes with HIV-1 Env (sklFDeGLFn, elfnkTIIFP), Pol (geAPEFPskq), Gag (gktHyMINPl) and Nef (qeeeeVgFPVt, qeeeeVgFPVt, edeGigFPVr, fkLVPVSEae, ssnTPTTNaa) proteins. Pools of these peptides elicted Ab in rabbits that induce platelet oxidation in vitro and thrombocytopenia in vivo upon passive transfer. Nef (qeeeeVgFPVt), Gag (gktHyMINPl), and Nef (fkLVPVSEae) all overlap with known HIV-1 epitopes. Li *et al.* [2005b] (**mimics**)

No. 15
MAb ID 8H10
HXB2 Location p17 (30–52)
Author Location p17 (30–52 JMH1)
Epitope KLKHIVWASRELERFAVNPGLLE
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade JMH-1 *HIV component:* p17 Gag *Adjuvant:* BSA
Species (Isotype) mouse (IgM)
References Ota & Ueda 1999; Ota *et al.* 1999

- 8H10: The p17 MAb also can bind to the V3 loop. Ota *et al.* [1999]
- 8H10: Inhibits viral replication of the HIV-1 infected MT-4 cells by decreasing p17 DNA levels in the infected cells, and the effect of growing the 8H10 hybridoma in co-culture with HIV-1 infected MT-4 cells was studied. Ota & Ueda [1999]

No. 16
MAb ID HyHIV-21
HXB2 Location p17 (30–52)
Author Location p17 (30–52 JMH1)
Epitope KLKHIIWASRELERFAVNPGLLE
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p17 Gag
Species (Isotype) mouse (IgG2a)
References Ota *et al.* 1998; Liu *et al.* 1995

- HyHIV-21: epitope uncertain, based on the best estimate from JMH1 sequence – Ka is 3.6 x 10^6 M-1 for rec p17 – stains the surface of infected cells indicating the antigen is exposed at the cell surface –inhibited growth of HIV-1 JMH1 in MT-4 cells when added 24 hours after the initial culture. Ota *et al.* [1998]

No. 17
MAb ID B4f8
HXB2 Location p17 (51–65)
Author Location p17 (51–65)
Epitope LETSEGCRQILGQLQ
Neutralizing no
Immunogen vaccine
Vector/Type: HIV infected-cell lysate *Strain:* B clade IIIB *HIV component:* HIV-1
Species (Isotype) rat (IgG2a)
References Shang *et al.* 1991

- -B4f8: Did not bind live infected cells, only cells that had been made permeable with acetone. Shang *et al.* [1991]

No. 18
MAb ID HyHIV-22
HXB2 Location p17 (52–83)
Author Location p17 (53–87 JMH1)
Epitope ETSEGCRQILGQRQPSLQTGSEELRSLYNTIH

B Cell

Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p17 Gag
Species (Isotype) mouse (IgG1)
References Ota *et al.* 1998; Liu *et al.* 1995

- HyHIV-22: epitope uncertain, based on the best estimate from JMH1 sequence – stains the surface of infected cells indicating the antigen is exposed at the cell surface – Ka is 2.3 x 10^5 M-1 for rec p17. Ota *et al.* [1998]

No. 19
MAb ID 12H-D3b3
HXB2 Location p17 (62–78)
Author Location p17 (62–78)
Epitope GQLQPSLQTGSEELRSL
Neutralizing no
Immunogen vaccine
Vector/Type: HIV infected-cell lysate *Strain:* B clade IIIB *HIV component:* HIV-1
Species (Isotype) rat (IgG2a)
References Shang *et al.* 1991

- 12H-D3b3: Did not bind live infected cells, only cells that had been made permeable with acetone. Shang *et al.* [1991]

No. 20
MAb ID 12G-A8g2
HXB2 Location p17 (86–115)
Author Location p17 (86–115)
Epitope YCVHQRIEIKDTKEALDKIEEEQNKSKKKA
Neutralizing no
Immunogen vaccine
Vector/Type: HIV infected-cell lysate *Strain:* B clade IIIB *HIV component:* HIV-1
Species (Isotype) rat (IgG2a)
References Maksiutov *et al.* 2002; Shang *et al.* 1991

- 12G-A8g2: This epitope is similar to a fragment of the human protein CD40 ligand TNF-related activation protein(T-cell antigen GP39) (CD154), LDKIEDERN, as well as to a fragment of Lens-epithelium-derived growth factor, DIITEEDKSKKKGQ. Maksiutov *et al.* [2002]
- 12G-A8g2: Bound to 30-mer, but not to internal peptides – did not bind live infected cells – antigenic domain known as HPG30. Shang *et al.* [1991]

No. 21
MAb ID 12G-D7h11
HXB2 Location p17 (86–115)
Author Location p17 (86–115)
Epitope YCVHQRIEIKDTKEALDKIEEEQNKSKKKA
Neutralizing no
Immunogen vaccine
Vector/Type: HIV infected-cell lysate *Strain:* B clade IIIB *HIV component:* HIV-1
Species (Isotype) rat (IgG2a)
References Maksiutov *et al.* 2002; Shang *et al.* 1991

- 12G-D7h11: This epitope is similar to a fragment of the human protein CD40 ligand TNF-related activation protein (T-cell antigen GP39) (CD154), LDKIEDERN, as well as to a fragment of Lens-epithelium-derived growth factor, DIITEEDKSKKKGQ. Maksiutov *et al.* [2002]
- 12G-D7h11: Bound to 30-mer, but not to internal peptides – did not bind live infected cells – antigenic domain known as HPG30. Shang *et al.* [1991]

No. 22
MAb ID 12G-H1c7
HXB2 Location p17 (86–115)
Author Location p17 (86–115)
Epitope YCVHQRIEIKDTKEALDKIEEEQNKSKKKA
Neutralizing no
Immunogen vaccine
Vector/Type: HIV infected-cell lysate *Strain:* B clade IIIB *HIV component:* HIV-1
Species (Isotype) rat (IgG)
References Maksiutov *et al.* 2002; Shang *et al.* 1991

- 12G-H1c7: This epitope is similar to a fragment of the human protein CD40 ligand TNF-related activation protein (T-cell antigen GP39) (CD154), LDKIEDERN, as well as to a fragment of Lens-epithelium-derived growth factor, DIITEEDKSKKKGQ. Maksiutov *et al.* [2002]
- 12G-H1c7: Bound to 30-mer, but not to internal peptides – did not bind live infected cells – antigenic domain known as HPG30. Shang *et al.* [1991]

No. 23
MAb ID 12I-D12g2
HXB2 Location p17 (86–115)
Author Location p17 (86–115)
Epitope YCVHQRIEIKDTKEALDKIEEEQNKSKKKA
Neutralizing no
Immunogen vaccine
Vector/Type: HIV infected-cell lysate *Strain:* B clade IIIB *HIV component:* HIV-1
Species (Isotype) rat (IgG2a)
References Maksiutov *et al.* 2002; Shang *et al.* 1991

- 12I-D12g2: This epitope is similar to a fragment of the human protein CD40 ligand TNF-related activation protein (T-cell antigen GP39) (CD154), LDKIEDERN, as well as to a fragment of Lens-epithelium-derived growth factor, DIITEEDKSKKKGQ. Maksiutov *et al.* [2002]
- 12I-D12g2: Bound to 30-mer, but not to internal peptides – did not bind live infected cells – antigenic domain known as HPG30. Shang *et al.* [1991]

No. 24
MAb ID polyclonal
HXB2 Location p17 (86–115)
Author Location p17 (86–115)
Epitope YSVHQRIDVKDTKEALEKIEEEQNKSKKKA
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *HIV component:* p17 Gag *Adjuvant:* Cholera toxin (CT)

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Species (Isotype) mouse (IgA)
References Bukawa *et al.* 1995

- Polyclonal secretory IgA antibody raised by oral mucosal immunization is able to neutralize IIIB, SF2, and MN – HIV-1 neutralization may be due to the V3, CD4 or HPG30 component of the multicomponent peptide immunogen. Bukawa *et al.* [1995]

No. 25
MAb ID HyHIV-15
HXB2 Location p17 (87–115)
Author Location p17 (87–115 JMH1)
Epitope `SVHQRIDVKDTKEALEKIEEEQNKSKKKA?`
Neutralizing L
Immunogen vaccine
Vector/Type: protein *HIV component:* p17 Gag
Species (Isotype) mouse (IgG1)
References Ota *et al.* 1998; Liu *et al.* 1995

- HyHIV-15: epitope uncertain, based on the best estimate from JMH1 sequence – Ka is 1.4 x 10^7 M-1 for rec p17 – stains the surface of infected cells indicating the antigen is exposed at the cell surface – inhibited growth of HIV-1 JMH1 in MT-4 cells when added 24 hours after the initial culture. Ota *et al.* [1998]

No. 26
MAb ID 11H9
HXB2 Location p17 (101–115)
Author Location p17 (101–115 SF2)
Epitope `LEKIEEEQNKSKKKA?`
Neutralizing
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
Research Contact R. B. Ferns and R. S. Tedder
References Maksiutov *et al.* 2002; Ferns *et al.* 1989; Ferns *et al.* 1987

- 11H9: UK Medical Research Council AIDS reagent: ARP344.
- 11H9: This epitope is similar to a fragment of Lens-epithelium-derived growth factor, DIITEEDKSKKKGQ. Maksiutov *et al.* [2002]
- 11H9: Reactive against p18 and p55. Ferns *et al.* [1987]

No. 27
MAb ID 3-H-7 (3H7)
HXB2 Location p17 (113–122)
Author Location p17 (113–122 BH10)
Epitope `KKAQQAAADT`
Neutralizing L
Immunogen vaccine
Strain: B clade IIIB
Species (Isotype) mouse (IgG)
References Levin *et al.* 1997; Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b; Niedrig *et al.* 1989

- 3-H-7: Called 3H7 – using a bicistronic vector, an intracellular Fab intrabody, 3H7, can inhibit HIV-1 infection when expressed in the cytoplasm of dividing CD4+ T cells – HXBIIIB and SI primary isolate virions from 3H7 expressing cells were far less infectious – 3H7 intrabody acts both at the stage of nuclear import and virus particle assembly. Levin *et al.* [1997]
- 3-H-7: No cross-reactivity with HIV-2 ROD or SIV MAC by immunoblot. Niedrig *et al.* [1989]

No. 28
MAb ID C5126
HXB2 Location p17 (113–122)
Author Location p17 (113–122 HXB2)
Epitope `KKAQQAAADT`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: viral lysate *HIV component:* HIV-1
Species (Isotype) mouse (IgG1κ)
References Hinkula *et al.* 1990

- C5126: Defined epitope by peptide blocking of binding to native protein – WB reactive with p53 and p17. Hinkula *et al.* [1990]

No. 29
MAb ID 1D9
HXB2 Location p17 (119–132)
Author Location p17 (121–134 SF2)
Epitope `AAGTGNSSQVSQNY`
Neutralizing
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1
Species (Isotype) mouse (IgG2a)
Research Contact R. B. Ferns and R. S. Tedder
References Theisen *et al.* 2006; Ferns *et al.* 1989; Ferns *et al.* 1987
Keywords antibody interactions, binding affinity

- 1D9: UK Medical Research Council AIDS reagent: ARP316.
- 1D9: This Ab was used as a positive control in the binding activity assay. It was shown, however, that the 1D9 bound slightly weaker to Tat then the PTD-scFvtat1 fusion complex. Theisen *et al.* [2006] (**antibody interactions**, **binding affinity**)
- 1D9: Reactive against p18, but not p55. Ferns *et al.* [1987]

No. 30
MAb ID 4C9
HXB2 Location p17 (119–132)
Author Location p18 (121–134 SF2)
Epitope `AAGTGNSSQVSQNY`
Neutralizing
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1
Species (Isotype) mouse (IgG2a)
Research Contact R. B. Ferns and R. S. Tedder
References Ferns *et al.* 1989; Ferns *et al.* 1987

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- 4C9: UK Medical Research Council AIDS reagent: ARP342.
- 4C9: Reactive against p18, but not p55. Ferns *et al.* [1987]

No. 31
MAb ID 4H2B1
HXB2 Location p17 (119–132)
Author Location p17 (121–134 SF2)
Epitope AAGTGNSSQVSQNY
Neutralizing
Immunogen
Species (Isotype) mouse (IgG1)
Research Contact R. B. Ferns and R. S. Tedder
References Ferns *et al.* 1989; Ferns *et al.* 1987

- 4H2B1: UK Medical Research Council AIDS reagent: ARP315.
- 4H2B1: Reactive against p18 and p55 of multiple isolates. Ferns *et al.* [1987]

No. 32
MAb ID 9G5
HXB2 Location p17 (119–132)
Author Location p17 (121–134 SF2)
Epitope AAGTGNSSQVSQNY
Neutralizing
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1
Species (Isotype) mouse (IgM)
Research Contact R. B. Ferns and R. S. Tedder
References Ferns *et al.* 1989; Ferns *et al.* 1987

- 9G5: UK Medical Research Council AIDS reagent: ARP343.
- 9G5: Reactive against p18, but not p55. Ferns *et al.* [1987]

No. 33
MAb ID 15-21
HXB2 Location p17 (121–132)
Author Location p17 (121–132 BRU)
Epitope DTGHSSQVSQNY
Neutralizing no
Immunogen vaccine
Strain: B clade BRU
Species (Isotype) mouse (IgG)
References Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b

No. 34
MAb ID 31-11
HXB2 Location p17 (121–132)
Author Location p17 (121–132 BRU)
Epitope DTGHSSQVSQNY
Neutralizing no
Immunogen vaccine
Strain: B clade BRU
Species (Isotype) mouse (IgG)
References Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b

No. 35
MAb ID sc-FV p17
HXB2 Location p17 (121–132)
Author Location p17 (121–132 BRU)
Epitope DTGHSSQVSQNY
Neutralizing L
Immunogen vaccine
Strain: B clade BRU
Species (Isotype) mouse (IgG1κ)
Ab Type C-term
Research Contact Paul Zhou, NIH, Bethesda, MD, USA
References Tewari *et al.* 1998; Robert-Hebmann *et al.* 1992a

- A single chain Ab (sc-FV) was made from an anti-p17 MAb, and intracellular binding of sc-FV resulted in inhibition of viral replication that was more pronounced when the sc-FV was expressed in the cytoplasm instead of the nucleus. Tewari *et al.* [1998]

IV-C-2 Gag p17-p24 Antibodies

No. 36
MAb ID 3A6
HXB2 Location p17-p24 (122–17)
Author Location p24 (122–149 BH10)
Epitope TGHSSQVSQNYPIVQNIQGQMVHQAISP
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
References Buchacher *et al.* 1994; Buchacher *et al.* 1992

- 3A6: The reactive peptide spans the p17/p24 border of gag. Buchacher *et al.* [1994]
- 3A6: Human MAbs against HIV generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994]

IV-C-3 Gag p24 Antibodies

No. 37
MAb ID 111/182
HXB2 Location p24 (1–20)
Author Location p24 (134–153 IIIB)
Epitope PIVQNIQGQMVHQAISPRTL
Neutralizing no
Immunogen vaccine
Vector/Type: beta-galactosidase fusion protein *Strain:* B clade IIIB *HIV component:* p24 Gag
Species (Isotype) mouse (IgG1)
References Kanduc *et al.* 2008; Niedrig *et al.* 1991

- 111/182: Similarity level of the 111/182 binding site pentapeptide QMVHQ to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 111/182: Test specific evidence of cross-reactivity between HIV-1, HIV-2 and SIV MAC. Niedrig *et al.* [1991]

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MAb ID 112/021
HXB2 Location p24 (1–20)
Author Location p24 (134–153 IIIB)
Epitope PIVQNIQGQMVHQAISPRTL
Neutralizing no
Immunogen vaccine
Vector/Type: beta-galactosidase fusion protein *Strain:* B clade IIIB *HIV component:* p24 Gag
Species (Isotype) mouse (IgG1)
References Niedrig *et al.* 1991

- 112/021: Test specific evidence of cross-reactivity between HIV-1, HIV-2 and SIV MAC. Niedrig *et al.* [1991]

No. 39
MAb ID 112/047
HXB2 Location p24 (1–20)
Author Location p24 (134–153 IIIB)
Epitope PIVQNIQGQMVHQAISPRTL
Neutralizing no
Immunogen vaccine
Vector/Type: beta-galactosidase fusion protein *Strain:* B clade IIIB *HIV component:* p24 Gag
Species (Isotype) mouse (IgG1)
References Niedrig *et al.* 1991

- 112/047: Test specific evidence of cross-reactivity between HIV-1, HIV-2 and SIV MAC. Niedrig *et al.* [1991]

No. 40
MAb ID ID8F6
HXB2 Location p24 (11–25)
Author Location p24 (143–157 BRU)
Epitope VHQAISPRTLNAWVK
Neutralizing no
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
Research Contact R. B. Ferns and R. S. Tedder
References Kanduc *et al.* 2008; Ferns *et al.* 1989; Ferns *et al.* 1987

- ID8F6: UK Medical Research Council AIDS reagent: ARP348.
- ID8F6: Similarity level of the ID8F6 binding site pentapeptide LNAWV to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- ID8F6: Reacted with both p55 and p24 – showed less than 75% homologous inhibition. Ferns *et al.* [1987]

No. 41
MAb ID F5-2
HXB2 Location p24 (14–23)
Author Location p24 (14–23 HXB2)
Epitope AISPRTLNAW
Subtype B
Neutralizing no
Immunogen
Species (Isotype) mouse
References Kusk *et al.* 1992; Kusk *et al.* 1988

- F5-2: In HIV-1 + individuals, antibody to AISPRTLNAW is associated with CD4 T-cell decline. Kusk *et al.* [1988, 1992]

No. 42
MAb ID CB-13/5 (CB-mab-p24/13-15)
HXB2 Location p24 (21–25)
Author Location p24 (152–156)
Epitope NAWVK
Neutralizing no
Immunogen
Species (Isotype) mouse (IgG1κ)
References Kanduc *et al.* 2008; Glaser & Hausdorf 1996; Kuttner *et al.* 1992; Franke *et al.* 1992; Grunow *et al.* 1990

- CB-13/5 database comment: It is not clear whether the MAbs CD-13/5 and CB-mab-p24/13-15 are the same, but from the shared references in the primary articles they seem to be.
- CB-13/5: Similarity level of the CB-13/5 binding site pentapeptide NAWVK to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 2 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- CB-13/5: Epitope described as VHQAISPRTLNAWVK – binding not affected by bound MAb CB-4/1. Glaser & Hausdorf [1996]
- CB-13/5: Inhibits spread of HIV-1 in cell cultures. Franke *et al.* [1992]
- CB-13/5: Called CB-mab-p24/13-15 – the VDJ H and VJ L regions of CB-mab-p24/13-15 were sequenced. Kuttner *et al.* [1992]

No. 43
MAb ID polyclonal
HXB2 Location p24 (44–60)
Author Location p24 (176–192 LAI)
Epitope SEGATPQDLNTMLNTVG
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein, virus-like particle (VLP) *Strain:* B clade LAI *HIV component:* Gag, p17 Gag, p24 Gag *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse (IgG)
References Kanduc *et al.* 2008; Truong *et al.* 1997

- Similarity level of the polyclonal Ab binding site pentapeptide NTMLN to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 1 time, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- An ELISA assay was used to study a panel of Gag peptides – mature p24 CA epitopes mapped to residues 176-192, 201-218, 233-253, 285-304, and were recognized by antibodies elicited by rp24CA – one p17MA epitope, residues 11-25, and

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one p24CA epitope, residues 176-192, were recognized by antibodies raised against anti-p55 virus-like particles, suggesting a different antigenic properties for p24CA and p17MA antibodies depending on whether they are produced against the mature soluble protein or the immature assembled form of the gag proteins. Truong *et al.* [1997]

No. 44
MAb ID 3D3
HXB2 Location p24 (45–50)
Author Location p24 (177–182 LAI)
Epitope `EGATPQ`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1
Species (Isotype) mouse (IgG2b)
Research Contact R. B. Ferns and R. S. Tedder
References Ferns *et al.* 1989; Ferns *et al.* 1987

- 3D3: UK Medical Research Council AIDS reagent: ARP314.
- 3D3: Most broadly reactive of all the antibodies in this study. Ferns *et al.* [1987]

No. 45
MAb ID CD-4/1 (CB-4/1/1/F6)
HXB2 Location p24 (46–56)
Author Location p24 (182–197)
Epitope `GATPQDLNTML`
Neutralizing no
Immunogen vaccine
Vector/Type: beta-galactosidase fusion protein *HIV component:* p24 Gag
Species (Isotype) mouse (IgG2aκ)
References Ehrhard *et al.* 1996; Glaser & Hausdorf 1996; Hohne *et al.* 1993; Franke *et al.* 1992; Grunow *et al.* 1990

- CD-4/1: Modification of p24 lysine residues by maleic anhydrid increased the affinity of CD-4/1, presumably due to conformational changes exposing a cryptic epitope. Ehrhard *et al.* [1996]
- CD-4/1: Unusual p24-MAb binding kinetics, with biphasic association – probably due to conformational changes in p24, not to p24 dimerization. Glaser & Hausdorf [1996]
- CD-4/1: Affinity of CB-4/1 to native p24 is lower than to peptide or denatured p24 – proposed that the peptide binds in a loop conformation. Hohne *et al.* [1993]
- CD-4/1: Inhibits spread of HIV-1 in cell cultures. Franke *et al.* [1992]

No. 46
MAb ID 15F8C7
HXB2 Location p24 (47–56)
Author Location p24 (183–197)
Epitope `ATPQDLNTML`
Neutralizing no
Immunogen vaccine
Vector/Type: purified HIV-1
Species (Isotype) mouse (IgG1)
References Janvier *et al.* 1992; Janvier *et al.* 1990

- 15F8C7: Mapped to aa209-217 through Pepscan method – cross-reacts with HIV-2 Janvier *et al.* [1990] – maps to aa203-217 through EIA pentadecapeptide Janvier *et al.* [1992]. Janvier *et al.* [1990, 1992]

No. 47
MAb ID 111/052
HXB2 Location p24 (51–60)
Author Location p24 (183–192 IIIB)
Epitope `DLNTMLNTVG`
Neutralizing no
Immunogen vaccine
Vector/Type: beta-galactosidase fusion protein *Strain:* B clade IIIB *HIV component:* p24 Gag
Species (Isotype) mouse (IgG1)
References Kanduc *et al.* 2008; Niedrig *et al.* 1991

- 111/052: Similarity level of the 111/052 binding site pentapeptide TMLNT to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 1 time, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 111/052: Weak cross-reaction with HIV-2 on WB, otherwise not cross-reactive with HIV-2 or SIV MAC. Niedrig *et al.* [1991]

No. 48
MAb ID polyclonal
HXB2 Location p24 (51–82)
Author Location Gag (183–214 LAI)
Epitope `DLNTMLNTVGGHQAAMQMLKETINEEAAEWDR`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* p24 Gag *Adjuvant:* QS21
Species (Isotype) human (IgG)
References Pialoux *et al.* 2001

- 28 subjects were vaccinated with six HIV-1 peptides that were selected to be particularly rich in CTL epitopes, presented in lipopeptides with or without adjuvant QS21 – HIV-specific Ab responses were detected in 25/28 (89%), proliferative in 19/28 (79%), and CTL in 13/24 (54%) of testable volunteers – only 4/28 had Ab responses to peptide G1, 4/28 had proliferative responses, and no patient had a CTL response. Pialoux *et al.* [2001]

No. 49
MAb ID 91-5
HXB2 Location p24 (64–75)
Author Location p24 (196–207)
Epitope `AAMQMLKETINE`
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
References Kanduc *et al.* 2008; Gorny *et al.* 1998; Robinson *et al.* 1990b; Tyler *et al.* 1990; Gorny *et al.* 1989

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- 91-5: NIH AIDS Research and Reference Reagent Program: 1238.
- 91-5: Similarity level of the 91-5 binding site pentapeptide AMQML to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 91-5: Did not enhance HIV-1 IIIB infection. Robinson *et al.* [1990b]
- 91-5: Synthesized by immortalization of peripheral blood cells with Epstein-Barr virus. Gorny *et al.* [1989]

No. 50
MAb ID 1109/01
HXB2 Location p24 (69–86)
Author Location p24 (201–218 BRU)
Epitope LKETINEEAAEWDRVHPV
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse (IgG)
References Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b

No. 51
MAb ID 14D4E11
HXB2 Location p24 (69–86)
Author Location p24 (201–218 BRU)
Epitope LKETINEEAAEWDRVHPV
Neutralizing no
Immunogen vaccine
Vector/Type: purified HIV-1
Species (Isotype) mouse (IgG1)
References Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b; Janvier *et al.* 1992; Janvier *et al.* 1990

- 14D4E11: Mapped to aa209-217 through Pepscan method (original paper, AAEWDRVHP) – cross-reacts with HIV-2 Janvier *et al.* [1990] and to aa203-217 through EIA pentadecapeptide Janvier *et al.* [1992]. Janvier *et al.* [1990, 1992]

No. 52
MAb ID 1G5C8
HXB2 Location p24 (69–86)
Author Location p24 (201–218 BRU)
Epitope LKETINEEAAEWDRVHPV
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p24 Gag
Species (Isotype) mouse (IgG2b)
References Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b; Janvier *et al.* 1992; Janvier *et al.* 1990

- 1G5C8: Mapped to aa209-217 through Pepscan method (original paper, AAEWDRVHP) Janvier *et al.* [1990] and to aa203-217 through EIA pentadecapeptide Janvier *et al.* [1992]. Janvier *et al.* [1990, 1992]

No. 53
MAb ID 47-2
HXB2 Location p24 (69–86)
Author Location p24 (201–218 BRU)
Epitope LKETINEEAAEWDRVHPV
Neutralizing no
Immunogen vaccine
Strain: B clade BRU
Species (Isotype) mouse (IgG)
References Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b

No. 54
MAb ID 714/01
HXB2 Location p24 (69–86)
Author Location p24 (201–218 BRU)
Epitope LKETINEEAAEWDRVHPV
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse (IgG)
References Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b

No. 55
MAb ID polyclonal
HXB2 Location p24 (69–86)
Author Location p24 (201–218 LAI)
Epitope LKETINEEAAEWDRVHPV
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein, virus-like particle (VLP) *Strain:* B clade LAI *HIV component:* Gag, p17 Gag, p24 Gag *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse
References Truong *et al.* 1997

- An ELISA assay was used to study a panel of Gag peptides – mature p24 CA epitopes mapped to residues 176-192, 201-218, 233-253, 285-304, and were recognized by antibodies elicited by rp24CA – one p17MA epitope, residues 11-25, and one p24CA epitope, residues 176-192, were recognized by antibodies raised against anti-p55 virus-like particles, suggesting a different antigenic properties for p24CA and p17MA antibodies depending on whether they are produced against the mature soluble protein or the immature assembled form of the gag proteins. Truong *et al.* [1997]

No. 56
MAb ID 111/073
HXB2 Location p24 (71–81)
Author Location p24 (203–213 IIIB)
Epitope ETINEEAAEWD
Neutralizing no
Immunogen vaccine
Vector/Type: beta-galactosidase fusion protein *Strain:* B clade IIIB *HIV component:* p24 Gag

B Cell

Species (Isotype) mouse (IgG1)
References Niedrig *et al.* 1991

- 111/073: cross-reactive between HIV-1, HIV-2 and SIV MAC by multiple assays. Niedrig *et al.* [1991]

No. 57
MAb ID 113/038
HXB2 Location p24 (71–81)
Author Location p24 (203–213 IIIB)
Epitope ETINEEAAEWD
Neutralizing no
Immunogen vaccine
Vector/Type: beta-galactosidase fusion protein *Strain:* B clade IIIB *HIV component:* p24 Gag
Species (Isotype) mouse (IgG1)
References Niedrig *et al.* 1991

- 113/038: cross-reactive between HIV-1, HIV-2 and SIV MAC by multiple assays. Niedrig *et al.* [1991]

No. 58
MAb ID 1-E-4
HXB2 Location p24 (71–85)
Author Location p24 (203–217)
Epitope ETINEEAAEWDRVHP
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse (IgG)
References Niedrig *et al.* 1989

- 1-E-4: One of nine MAbs that bind to this peptide. Niedrig *et al.* [1989]

No. 59
MAb ID 1-E-9
HXB2 Location p24 (71–85)
Author Location p24 (203–217)
Epitope ETINEEAAEWDRVHP
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse (IgG)
References Niedrig *et al.* 1989

- 1-E-9: One of nine MAbs that bind to this peptide. Niedrig *et al.* [1989]

No. 60
MAb ID 10-E-7
HXB2 Location p24 (71–85)
Author Location p24 (203–217)
Epitope ETINEEAAEWDRVHP
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
References Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 10-E-7: One of nine MAbs that bind to this peptide – cross-reactive with HIV-2 ROD and SIV MAC. Niedrig *et al.* [1989]
- 10-E-7: Cross reactive between HIV-1, HIV-2 and SIV. Niedrig *et al.* [1988]

No. 61
MAb ID 10-G-9
HXB2 Location p24 (71–85)
Author Location p24 (203–217)
Epitope ETINEEAAEWDRVHP
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
References Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 10-G-9: One of nine MAbs that bind to this peptide. Niedrig *et al.* [1989]
- 10-G-9: HIV-1 specific. Niedrig *et al.* [1988]

No. 62
MAb ID 11-C-5
HXB2 Location p24 (71–85)
Author Location p24 (203–217)
Epitope ETINEEAAEWDRVHP
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
References Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 11-C-5: One of nine MAbs that bind to this peptide. Niedrig *et al.* [1989]
- 11-C-5: HIV-1 specific. Niedrig *et al.* [1988]

No. 63
MAb ID 2-E-4
HXB2 Location p24 (71–85)
Author Location p24 (203–217)
Epitope ETINEEAAEWDRVHP
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse (IgG2a)
References Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 2-E-4: One of nine MAbs that bind to this peptide – cross-reactive with HIV-2 ROD. Niedrig *et al.* [1989]
- 2-E-4: Cross reactive between HIV-1, HIV-2 and SIV by ELISA, HIV-1 and HIV-2 by WB. Niedrig *et al.* [1988]

No. 64
MAb ID 2-H-4
HXB2 Location p24 (71–85)
Author Location p24 (203–217)
Epitope ETINEEAAEWDRVHP
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB *HIV component:* HIV-1

B Cell

Species (Isotype) mouse (IgG1)
References Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 2-H-4: One of nine MAbs that bind to this peptide – cross-reactive with HIV-2 ROD. Niedrig *et al.* [1989]
- 2-H-4: Cross reactive between HIV-1, HIV-2 and SIV by ELISA, HIV-1 and HIV-2 by WB. Niedrig *et al.* [1988]

No. 65
MAb ID 8-D-2
HXB2 Location p24 (71–85)
Author Location p24 (203–217)
Epitope ETINEEAAEWDRVHP
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse (IgG2a)
References Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b; Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 8-D-2: One of nine MAbs that bind to this peptide. Niedrig *et al.* [1989]
- 8-D-2: HIV-1 specific. Niedrig *et al.* [1988]

No. 66
MAb ID 8-G-9
HXB2 Location p24 (71–85)
Author Location p24 (203–217)
Epitope ETINEEAAEWDRVHP
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse (IgG)
References Niedrig *et al.* 1989

- 8-G-9: One of nine MAbs that bind to this peptide. Niedrig *et al.* [1989]

No. 67
MAb ID 8-H-7
HXB2 Location p24 (71–85)
Author Location p24 (203–217)
Epitope ETINEEAAEWDRVHP
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse (IgG3)
References Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b; Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 8-H-7: One of nine MAbs that bind to this peptide. Niedrig *et al.* [1989]

No. 68
MAb ID C5123
HXB2 Location p24 (71–85)
Author Location p24 (203–217 HXB2)
Epitope ETINEEAAEWDRVHP
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: viral lysate *HIV component:* HIV-1
Species (Isotype) mouse (IgG1κ)
References Hinkula *et al.* 1990

- C5123: Epitope defined by peptide blocking of binding to native protein – WB reactive with p53 and p24. Hinkula *et al.* [1990]

No. 69
MAb ID 1-B-7
HXB2 Location p24 (76–85)
Author Location p24 (208–217 BH10)
Epitope EAAEWDRVHP
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB
Species (Isotype) mouse (IgG1)
References Kanduc *et al.* 2008; Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 1-B-7: Similarity level of the 1-B-7 binding site pentapeptide AAEWD to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 1-B-7: Reacts with two overlapping peptides, region of overlap is given – reacted with HIV-2 and SIV MAC. Niedrig *et al.* [1989]

No. 70
MAb ID 3-B-7
HXB2 Location p24 (76–85)
Author Location p24 (208–217 BH10)
Epitope EAAEWDRVHP
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB
Species (Isotype) mouse (IgG1)
References Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 3-B-7: Reacts with two overlapping peptides, region of overlap is given – reacted with HIV-2. Niedrig *et al.* [1989]

No. 71
MAb ID 6-D-12
HXB2 Location p24 (76–85)
Author Location p24 (208–217 BH10)
Epitope EAAEWDRVHP
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB
Species (Isotype) mouse (IgG1)
References Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 6-D-12: Reacts with two overlapping peptides, region of overlap is given – reacted with HIV-2. Niedrig *et al.* [1989]

No. 72
MAb ID 6-E-7
HXB2 Location p24 (76–85)

B Cell

Author Location p24 (208–217 BH10)
Epitope EAAEWDRVHP
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB
Species (Isotype) mouse (IgG1)
References Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 6-E-7: Reacts with two overlapping peptides, region of overlap is given – reacted with HIV-2 and SIV MAC. Niedrig *et al.* [1989]

No. 73
MAb ID 8-D-5
HXB2 Location p24 (76–85)
Author Location p24 (208–217 BH10)
Epitope EAAEWDRVHP
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB
Species (Isotype) mouse (IgG)
References Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 8-D-5: Reacts with two overlapping peptides, region of overlap is given – bound only HIV-1. Niedrig *et al.* [1989]

No. 74
MAb ID FF1
HXB2 Location p24 (76–90)
Author Location p24 (208–222 HXB2)
Epitope EAAEWDRVHPVHAGP
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: inactivated HIV
Species (Isotype) mouse (IgG1κ)
References Hinkula *et al.* 1990

- FF1: Epitope defined by peptide blocking of binding to native protein – WB reactive with p53 and p24. Hinkula *et al.* [1990]

No. 75
MAb ID 113/072
HXB2 Location p24 (81–90)
Author Location p24 (213–222 IIIB)
Epitope DRVHPVHAGP
Neutralizing no
Immunogen vaccine
Vector/Type: beta-galactosidase fusion protein *Strain:* B clade IIIB *HIV component:* p24 Gag
Species (Isotype) mouse (IgG1)
References Kanduc *et al.* 2008; Niedrig *et al.* 1991

- 113/072: Similarity level of the 113/072 binding site pentapeptide HPVHA to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 2 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 113/072: Weak cross-reaction with HIV-2 on WB, otherwise not cross-reactive with HIV-2 or SIV MAC. Niedrig *et al.* [1991]

No. 76
MAb ID 25.3
HXB2 Location p24 (82–102)
Author Location p24 (82–102)
Epitope RVHPVHAGPIAPGQMREPRGS
Neutralizing no
Immunogen
Species (Isotype) mouse (IgG1κ)
References Momany *et al.* 1996

- 25.3: Crystal structure of the CA protein bound to Fab 25.3 was solved – monomers form 7 alpha-helices arranged in a coiled-coil – Fab binds to a long antigenic peptide that separates the longest helices, with a salt bridge at CA 82 R, and interactions as far away as positions 100 and 102. Momany *et al.* [1996]

No. 77
MAb ID 13-102-100
HXB2 Location p24 (84–94)
Author Location p24 (102–112 IIIB)
Epitope HPVHAGPIAPG
Neutralizing
Immunogen
Species (Isotype) mouse (IgG)
Research Contact Advanced Technologies, Inc., Columbia, MD
References Qian & Tomer 1998; Parker *et al.* 1996

- 13-102-100: Affinity capillary electrophoresis was used to fine map this epitope, and the optimal peptide was defined as VHAGPIAPGIAP – this method uses migration time shifts to probe relative affinities of Abs – the antibody binds to the cyclophilin A binding domain. Qian & Tomer [1998]
- 13-102-100: Binding site (HPVHAGPIAPG) defined by epitope footprinting – first binding p24 to MAb, then allowing proteolytic cleavage to take place to cleave unprotected residues, then performing mass spectrometry to identify protected residues of epitope. Parker *et al.* [1996]

No. 78
MAb ID RL4.72.1
HXB2 Location p24 (87–101)
Author Location p24 (219–233 BRU)
Epitope HAGPIAPGQMREPRG
Neutralizing no
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* D clade NDK *HIV component:* HIV-1
Species (Isotype) mouse (IgG)
References Kanduc *et al.* 2008; Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b; Tatsumi *et al.* 1990

- RL4.72.1: Similarity level of the RL4.72.1 binding site pentapeptide PGQMR to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- RL4.72.1: Immunized with inactivated HIV NDK, D clade, reacts with B clade peptide. Robert-Hebmann *et al.* [1992a]

B Cell

No. 79
MAb ID 406/01
HXB2 Location p24 (101–121)
Author Location p24 (233–253 BRU)
Epitope GSDIAGTTSTLQEQIGWMTNN
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB
Species (Isotype) mouse (IgG)
References Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b

No. 80
MAb ID polyclonal
HXB2 Location p24 (101–121)
Author Location p24 (233–253 LAI)
Epitope GSDIAGTTSTLQEQIGWMTNL
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein, virus-like particle (VLP) *Strain:* B clade LAI *HIV component:* Gag, p17 Gag, p24 Gag *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse
References Truong *et al.* 1997

- An ELISA assay was used to study a panel of Gag peptides – mature p24 CA epitopes mapped to residues 176-192, 201-218, 233-253, 285-304, and were recognized by antibodies elicited by rp24CA – one p17MA epitope, residues 11-25, and one p24CA epitope, residues 176-192, were recognized by antibodies raised against anti-p55 virus-like particles, suggesting a different antigenic properties for p24CA and p17MA antibodies depending on whether they are produced against the mature soluble protein or the immature assembled form of the gag proteins. Truong *et al.* [1997]

No. 81
MAb ID 38:9.6K (38:96K)
HXB2 Location p24 (121–130)
Author Location p24 (253–262 HXB2)
Epitope NPPIPVGEIY
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p24-p15 Gag
Species (Isotype) mouse (IgG1κ)
References Hinkula *et al.* 1990

- 38:9.6K: UK Medical Research Council AIDS reagent: ARP365.
- 38:9.6K: Called 38:96K – epitope defined by peptide blocking of binding to native protein – WB reactive with p53 and p24. Hinkula *et al.* [1990]

No. 82
MAb ID EB1A9
HXB2 Location p24 (121–135)
Author Location p24 (253–267 LAI)
Epitope NPPIPVGEIYKRWII
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
Research Contact R. B. Ferns and R. S. Tedder
References Kanduc *et al.* 2008; Ferns *et al.* 1989; Ferns *et al.* 1987

- EB1A9: UK Medical Research Council AIDS reagent: ARP345.
- EB1A9: Similarity level of the EB1A9 binding site pentapeptide IYKRW to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- EB1A9: Reacted with both p55 and p24 – showed less than 75% homologous inhibition. Ferns *et al.* [1987]

No. 83
MAb ID polyclonal
HXB2 Location p24 (121–152)
Author Location Gag (253–284 LAI)
Epitope NPPIPVGEIYKRWIILGLNKIVRMYSPTSILD
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* p24 Gag *Adjuvant:* QS21
Species (Isotype) human (IgG)
References Pialoux *et al.* 2001

- 28 subjects were vaccinated with six HIV-1 peptides that were selected to be particularly rich in CTL epitopes, presented in lipopeptides with or without adjuvant QS21 – HIV-specific Ab responses were detected in 25/28 (89%), proliferative in 19/28 (79%), and CTL in 13/24 (54%) of testable volunteers – 25/28 had Ab responses to peptide G2, 14/28 had proliferative responses, and CTL responses were detected. Pialoux *et al.* [2001]

No. 84
MAb ID 30:3E5
HXB2 Location p24 (141–170)
Author Location p24 (273–302 HXB2)
Epitope IVRMYSPTSILDIRQGPKEPFRDYVDRFYK
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* p24-p15 Gag
Species (Isotype) mouse (IgG1λ)
Research Contact B. Wahren
References Hinkula *et al.* 1990

- 30:3E5: UK Medical Research Council AIDS reagent: ARP367.
- 30:3E5: Epitope defined by peptide blocking of binding to native protein – WB reactive with p53 and p24. Hinkula *et al.* [1990]

B Cell

No. 85
MAb ID EF7
HXB2 Location p24 (141–170)
Author Location p24 (273–302 HXB2)
Epitope `IVRMYSPTSILDIRQGPKEPFRDYVDRFYK`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* p24-p15 Gag
Species (Isotype) mouse (IgG1κ)
References Lundin *et al.* 1996; Hinkula *et al.* 1990

- EF7: UK Medical Research Council AIDS reagent: ARP366.
- EF7: Included as a control. Lundin *et al.* [1996]
- EF7: Epitope defined by peptide blocking of binding to native protein – WB reactive with p53. Hinkula *et al.* [1990]

No. 86
MAb ID LH-104-E
HXB2 Location p24 (143–148)
Author Location p24 (275–280 BRU)
Epitope `RMYSPT`
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade BRU
Species (Isotype) mouse (IgG1κ)
References Kanduc *et al.* 2008; Haaheim *et al.* 1991

- LH-104-E: UK Medical Research Council AIDS reagent: ARP319.
- LH-104-E: Similarity level of the LH-104-E binding site pentapeptide MYSPT to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- LH-104-E: Reacts with both p24 and p55. Haaheim *et al.* [1991]

No. 87
MAb ID 1B2C12
HXB2 Location p24 (149–154)
Author Location p24 (273–292 IIIB)
Epitope `SILDIR`
Neutralizing no
Immunogen vaccine
Vector/Type: purified HIV-1
Species (Isotype) mouse (IgG1)
References Kanduc *et al.* 2008; Janvier *et al.* 1992; Janvier *et al.* 1990

- 1B2C12: Similarity level of the 1B2C12 binding site pentapeptide ILDIR to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 4 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 1B2C12: Reacts with HIV-1 and HIV-2– mapped to aa281-286 through Pepscan method Janvier *et al.* [1990], and to aa273-292 through EIA pentadecapeptide method Janvier *et al.* [1992]. Janvier *et al.* [1990, 1992]

No. 88
MAb ID LH-104-K
HXB2 Location p24 (149–154)
Author Location p24 (281–286 BRU)
Epitope `SILDIR`
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade BRU
Species (Isotype) mouse (IgG1κ)
References Haaheim *et al.* 1991

- LH-104-K: UK Medical Research Council AIDS reagent: ARP322.
- LH-104-K: Binds exclusively with p24 (not p55) Haaheim *et al.* [1991]

No. 89
MAb ID LH-104-A
HXB2 Location p24 (152–157)
Author Location p24 (BRU)
Epitope `DIRQGP+QGVGGP`
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *HIV component:* p24 Gag
Species (Isotype) mouse (IgG1κ)
References Haaheim *et al.* 1991

- LH-104-A: UK Medical Research Council AIDS reagent: ARP307.
- LF-104-A: A 104 amino acid peptide was used to immunize mice – hexapeptide scans revealed two reactive p24 peptides – cross-competition studies indicated the region 270-286. Haaheim *et al.* [1991]

No. 90
MAb ID 1.17.3
HXB2 Location p24 (152–172)
Author Location p24 (152–172 SIVmac)
Epitope `CVKQGPKEPFQSYVDRFYKSL`
Neutralizing no
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade AGM TYO-7 *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
References Otteken *et al.* 1992

- 1.17.3: Recognized an epitope present on HIV-2/SIVmac (MAC251/32H) and HIV-2smmH4, but not SIVagmTYO-1, HIV-1 IIIB or SIVmnd. Otteken *et al.* [1992]

No. 91
MAb ID 1A7
HXB2 Location p24 (152–172)
Author Location p24 (152–172 SIVmac)
Epitope `CVKQGPKEPFQSYVDRFYKSL`
Neutralizing no
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade AGM TYO-7 *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)

B Cell

References Otteken *et al.* 1992

- 1A7: Recognized an epitope present on HIV-2/SIVmac (MAC251/32H) and HIV-2smmH4, but not SIVagmTYO-1, HIV-1 IIIB or SIVmnd. Otteken *et al.* [1992]

No. 92
MAb ID 1F6
HXB2 Location p24 (152–172)
Author Location p24 (152–172 SIVmac)
Epitope CVKQGPKEPFQSYVDRFYKSL
Neutralizing no
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade AGM TYO-7 *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
References Otteken *et al.* 1992

- 1F6: Recognized an epitope present on HIV-2/SIVmac (MAC251/32H) and HIV-2smmH4, but not SIVagmTYO-1, HIV-1 IIIB or SIVmnd. Otteken *et al.* [1992]

No. 93
MAb ID 23A5G4
HXB2 Location p24 (153–172)
Author Location p24 (285–304 IIIB)
Epitope IRQGPKEPFRDYVDRFYKTL
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p24 Gag
Species (Isotype) mouse (IgG1)
References Janvier *et al.* 1996; Janvier *et al.* 1992; Janvier *et al.* 1990

- 23A5G4: A few sera which were able to bind the linear sequence 178-192, but not sequence 288-302 in an indirect peptide ELISA inhibited the binding of 23A5G4 to the native p24. Janvier *et al.* [1996]
- 23A5G4: Mapped to aa209-217 through Pepscan method Janvier *et al.* [1990] and to aa285-304 through EIA pentadecapeptide method Janvier *et al.* [1992]. Janvier *et al.* [1990, 1992]

No. 94
MAb ID 23A5G5
HXB2 Location p24 (153–172)
Author Location p24 (285–304 BRU)
Epitope IRQGPKEPFRDYVDRFYKTL
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* p24 Gag
Species (Isotype) mouse (IgG)
References Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b

No. 95
MAb ID 3D10G6
HXB2 Location p24 (153–172)
Author Location p24 (285–304 IIIB)
Epitope IRQGPKEPFRDYVDRFYKTL
Neutralizing no
Immunogen vaccine
Vector/Type: purified HIV-1
Species (Isotype) mouse (IgG1)
References Janvier *et al.* 1992; Janvier *et al.* 1990

- 3D10G6: Epitope cross-reacts with HIV-1 and HIV-2– mapped to aa260-267 through Pepscan method Janvier *et al.* [1990] and to aa285-304 through EIA pentadecapeptide method. Janvier *et al.* [1990, 1992]

No. 96
MAb ID polyclonal
HXB2 Location p24 (153–172)
Author Location p24 (285–304 LAI)
Epitope IRQGPKEPFRDYVDRFYKTL
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein, virus-like particle (VLP) *Strain:* B clade LAI *HIV component:* Gag, p17 Gag, p24 Gag *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse
References Truong *et al.* 1997

- An ELISA assay was used to study a panel of Gag peptides – mature p24 CA epitopes mapped to residues 176-192, 201-218, 233-253, 285-304, and were recognized by antibodies elicited by rp24CA – one p17MA epitope, residues 11-25, and one p24CA epitope, residues 176-192, were recognized by antibodies raised against anti-p55 virus-like particles, suggesting a different antigenic properties for p24CA and p17MA antibodies depending on whether they are produced against the mature soluble protein or the immature assembled form of the gag proteins. Truong *et al.* [1997]

No. 97
MAb ID F5-4
HXB2 Location p24 (153–175)
Author Location p24 (153–174 HXB2)
Epitope IRQGPKEPFRDYVDRFYKTLRAE
Subtype B
Neutralizing no
Immunogen
Species (Isotype) mouse
References Kusk *et al.* 1992; Kusk *et al.* 1988

- F5-4: Binds to a location in the most hydrophilic region of p24. Kusk *et al.* [1988, 1992]

No. 98
MAb ID MO9.42.2
HXB2 Location p24 (153–178)
Author Location p24 (285–310 BRU)
Epitope IRQGPKEPFRDYVDRFYKTLRAEQAS
Neutralizing no
Immunogen vaccine
Vector/Type: virus *Strain:* HIV-2 ROD *HIV component:* HIV-1
Species (Isotype) mouse (IgG)
References Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b

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- MO9.42.2: Reacts with HIV-1s, HIV-2s, and SIVs in rec protein ELISA. Robert-Hebmann *et al.* [1992b]

No. 99
MAb ID MO9.50.2
HXB2 Location p24 (153–178)
Author Location p24 (285–310 BRU)
Epitope IRQGPKEPFRDYVDRFYKTLRAEQAS
Neutralizing no
Immunogen vaccine
Strain: HIV-2 ROD
Species (Isotype) mouse (IgG)
References Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b

- MO9.50.2: Reacts with HIV-1s, HIV-2s, and SIVs in rec protein ELISA. Robert-Hebmann *et al.* [1992b]

No. 100
MAb ID V10
HXB2 Location p24 (155–169)
Author Location p24 (289–303 IIIB)
Epitope QGPKEPFRDYVDRFY
Neutralizing no
Immunogen virus
Species (Isotype) mouse
References Matsuo *et al.* 1992

- V10: Reacts with HIV-1 and SIV AGM analogous peptides. Matsuo *et al.* [1992]

No. 101
MAb ID V107
HXB2 Location p24 (155–177)
Author Location p24 (289–311 IIIB)
Epitope QGPKEPFRDYVDRFYKTLRAEQA
Neutralizing no
Immunogen virus
Species (Isotype) mouse
References Matsuo *et al.* 1992

- V107: Reacts with FIV, HIV-1 and SIV AGM analogous peptides. Matsuo *et al.* [1992]

No. 102
MAb ID LH-104-C
HXB2 Location p24 (156–161)
Author Location p24 (BRU)
Epitope GPKEPF+QGVGGP
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *HIV component:* p24 Gag
Species (Isotype) mouse (IgG3κ)
References Haaheim *et al.* 1991

- LH-104-C: UK Medical Research Council AIDS reagent: ARP309.
- LF-104-C: A 104 amino acid peptide was used to immunize mice – hexapeptide scans revealed two reactive p24 peptides – cross-competition studies indicated the region 351-373. Haaheim *et al.* [1991]

No. 103
MAb ID 12-B-4
HXB2 Location p24 (161–170)
Author Location p24 (293–302 IIIB)
Epitope FRDYVDRFYK
Neutralizing no
Immunogen vaccine
Strain: B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
References Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 12-B-4: Epitope is defined as the overlap between two HIV-1 reactive peptides – cross-reacts with HIV-2 ROD and SIV MAC. Niedrig *et al.* [1988, 1989]

No. 104
MAb ID C5122
HXB2 Location p24 (161–170)
Author Location p24 (293–302 HXB2)
Epitope FRDYVDRFYK
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: viral lysate *HIV component:* HIV-1
Species (Isotype) mouse (IgG1κ)
References Hinkula *et al.* 1990

- C5122: Defined by peptide blocking of binding to native protein – WB reactive with p53 and p24. Hinkula *et al.* [1990]

No. 105
MAb ID 9A4C4
HXB2 Location p24 (170–188)
Author Location p24 (303–317 IIIB)
Epitope KTLRAEQASQEVKNWMTET
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* p24 Gag
Species (Isotype) mouse (IgG1)
References Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b; Janvier *et al.* 1992; Janvier *et al.* 1990

- 9A4C4: Mapped to aa260-267 through Pepscan method Janvier *et al.* [1990] – and to aa303-317 through EIA pentadecapeptide method Janvier *et al.* [1992]. Janvier *et al.* [1990, 1992]

No. 106
MAb ID 11C10B10
HXB2 Location p24 (171–185)
Author Location p24 (303–317 IIIB)
Epitope TLRAEQASQEVKNWM
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p24 Gag
Species (Isotype) mouse (IgG1)
References Janvier *et al.* 1992; Janvier *et al.* 1990

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- 11C10B10: Mapped to aa260-267 through Pepscan method Janvier *et al.* [1990] and to aa303-317 through EIA pentadecapeptide method Janvier *et al.* [1992]. Janvier *et al.* [1990, 1992]

No. 107
MAb ID 11D11F2
HXB2 Location p24 (171–185)
Author Location p24 (303–317 IIIB)
Epitope TLRAEQASQEVKNWM
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p24 Gag
Species (Isotype) mouse (IgG1)
References Janvier *et al.* 1992; Janvier *et al.* 1990

- 11D11F2: Mapped to aa260-267 through Pepscan method Janvier *et al.* [1990] and to aa303-317 through EIA pentadecapeptide method Janvier *et al.* [1992]. Janvier *et al.* [1990, 1992]

No. 108
MAb ID CD12B4
HXB2 Location p24 (171–185)
Author Location p24 (303–317 LAI)
Epitope TLRAEQASQEVKNWM
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
Research Contact R. B. Ferns and R. S. Tedder
References Ferns *et al.* 1989; Ferns *et al.* 1987

- CD12B4: UK Medical Research Council AIDS reagent: ARP346.
- CD12B4: Reacted with both p55 and p24 – strain-specific binding. Ferns *et al.* [1987]

No. 109
MAb ID BE3
HXB2 Location p24 (176–190)
Author Location p24 (308–322 HXB2)
Epitope QASQEVKNWMTETLL
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p24-p15 Gag
Species (Isotype) mouse (IgG1κ)
Research Contact B. Wahren
References Hinkula *et al.* 1990

- BE3: UK Medical Research Council AIDS reagent: ARP368.
- BE3: Defined by peptide blocking of binding to native protein – WB reactive with p53 and p24. Hinkula *et al.* [1990]

No. 110
MAb ID L14
HXB2 Location p24 (176–190)
Author Location p24 (308–322 HXB2)
Epitope QASQEVKNWMTETLL
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p24-p15 Gag
Species (Isotype) mouse (IgG1κ)
Research Contact B. Wahren
References Hinkula *et al.* 1990

- L14: UK Medical Research Council AIDS reagent: ARP369.
- L14: Defined by peptide blocking of binding to native protein – WB reactive with p53 and p24. Hinkula *et al.* [1990]

No. 111
MAb ID 108/03
HXB2 Location p24 (181–190)
Author Location p24 (313–322 IIIB)
Epitope VKNWMTETLL
Neutralizing no
Immunogen vaccine
Vector/Type: beta-galactosidase fusion protein *Strain:* B clade IIIB *HIV component:* p24 Gag
Species (Isotype) mouse (IgG1)
References Kanduc *et al.* 2008; Niedrig *et al.* 1991

- 108/03: Similarity level of the 108/03 binding site pentapeptide KNWMT to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 108/03: Cross-reactive between HIV-1, HIV-2 and SIV MAC by multiple tests. Niedrig *et al.* [1991]

No. 112
MAb ID 110/015
HXB2 Location p24 (181–190)
Author Location p24 (313–322 IIIB)
Epitope VKNWMTETLL
Neutralizing no
Immunogen vaccine
Vector/Type: beta-galactosidase fusion protein *Strain:* B clade IIIB *HIV component:* p24 Gag
Species (Isotype) mouse (IgG1)
References Niedrig *et al.* 1991

- 110/015: Cross-reactive between HIV-1, HIV-2 and SIV MAC by multiple tests. Niedrig *et al.* [1991]

No. 113
MAb ID p5F1
HXB2 Location p24 (197–218)
Author Location Gag (329–350)
Epitope DCKTILKALGPAATLEEMMTAC
Subtype B
Neutralizing
Immunogen vaccine

Vector/Type: protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) mouse (IgG1)
Research Contact Dr. Yongtang Zheng, Laboratory of Molecular Immunopharmacology, Kunming Institute of Zoology, Kunming, Yunnan, China
References Liu *et al.* 2007
Keywords antibody generation, assay standardization/improvement, binding affinity

- p5F1: MAb p5F1 was derived from hybridoma from mice immunized with HIV-1 p24. p5F1 reacted with p24 from HIV-1 IIIB, Ada-M, 74V, and KM018 strains. p5F1 recognized peptide DC-22, Gag 329-350. Detection limit for rp24 in a modified sandwich ELISA of p5F1 was about 15 ng/ml, while p5F1 could detect as low as 40 pg/ml of p24 in standard ELISA. p5F1 showed good specificity and high sensitivity in a modified sandwich ELISA with rabbit anti-p24 serum, indicating its potential use for measurement of p24 antigen levels in research. Liu *et al.* [2007] (**antibody generation**, **binding affinity**, **assay standardization/improvement**)

No. 114
MAb ID 32:32K
HXB2 Location p24 (199–222)
Author Location p24 (331–354 HXB2)
Epitope `KTILKALGPAATLEEMMTACQGVG`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* p24-p15 Gag
Species (Isotype) mouse (IgG1λ)
References Hinkula *et al.* 1990

- 32:32K: UK Medical Research Council AIDS reagent: ARP368.
- 32:32K: Epitope defined by peptide blocking of binding to native protein – WB reactive with p53 and p24. Hinkula *et al.* [1990]

No. 115
MAb ID C5200
HXB2 Location p24 (199–222)
Author Location p24 (331–354 HXB2)
Epitope `KTILKALGPAATLEEMMTACQGVG`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: viral lysate
Species (Isotype) mouse (IgG1κ)
References Hinkula *et al.* 1990

- C5200: Epitope defined by peptide blocking of binding to native protein. Hinkula *et al.* [1990]

No. 116
MAb ID FH2
HXB2 Location p24 (201–215)
Author Location p24 (333–347 HXB2)
Epitope `ILKALGPAATLEEMM`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p24-p15 Gag
Species (Isotype) mouse (IgG1κ)
References Hinkula *et al.* 1990

- FH2: Defined by peptide blocking of binding to native protein – WB reactive with p53 and p24. Hinkula *et al.* [1990]

No. 117
MAb ID 13B5
HXB2 Location p24 (205–214)
Author Location p24 (205–213)
Epitope `LGPAATLEEM`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* p24 Gag
Species (Isotype) mouse
Ab Type C-term
Research Contact bioMerieux
References Berthet-Colominas *et al.* 1999

- 13B5: Fab which was bound to p24 capsid for crystallization and study of p24's structure. Berthet-Colominas *et al.* [1999]

No. 118
MAb ID 106/01
HXB2 Location p24 (211–230)
Author Location p24 (343–362 IIIB)
Epitope `LEEMMTACQGVGGPGHKARV`
Neutralizing no
Immunogen vaccine
Vector/Type: beta-galactosidase fusion protein *Strain:* B clade IIIB *HIV component:* p24 Gag
Species (Isotype) mouse (IgG1)
References Niedrig *et al.* 1991

- 106/01: Cross-reactive between HIV-1, HIV-2 and SIV MAC by multiple tests. Niedrig *et al.* [1991]

No. 119
MAb ID LH-104-B
HXB2 Location p24 (225–230)
Author Location p24 (357–362 BRU)
Epitope `GHKARV`
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade BRU
Species (Isotype) mouse (IgG1κ)
References Haaheim *et al.* 1991

- LH-104-B: UK Medical Research Council AIDS reagent: ARP308.
- LH-104-B: Binds exclusively with p55 (not p24), in contrast to LH-104-I. Haaheim *et al.* [1991]

No. 120
MAb ID LH-104-I
HXB2 Location p24 (226–231)
Author Location p24 (358–363 BRU)

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Epitope HKARVL
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade BRU
Species (Isotype) mouse (IgG1κ)
References Kanduc *et al.* 2008; Haaheim *et al.* 1991

- LH-104-I: UK Medical Research Council AIDS reagent: ARP321.
- LH-104-I: Similarity level of the LH-104-I binding site pentapeptide HKARV to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 3 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- LH-104-I: Binds exclusively with p24 (not p55), in contrast to LH-104-B. Haaheim *et al.* [1991]

No. 121
MAb ID p3JB9
HXB2 Location p24
Author Location p24
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) mouse (IgG1)
Research Contact Dr. Yongtang Zheng, Laboratory of Molecular Immunopharmacology, Kunming Institute of Zoology, Kunming, Yunnan, China
References Liu *et al.* 2007
Keywords antibody generation, assay standardization/improvement, binding affinity

- p3JB9: MAb p3JB9 was derived from hybridoma from mice immunized with HIV-1 p24. p3JB9 reacted with p24 from HIV-1 IIIB, Ada-M, and 74V strains, but not with the p24 from KM018 strain. p3JB9 did not react with any of the five HIV-1 p24 peptides tested. Detection limit for rp24 in a modified sandwich ELISA of p3JB9 was about 15 ng/ml, while p3JB9 could detect as low as 40 pg/ml of p24 in standard ELISA. Liu *et al.* [2007] (**antibody generation**, **binding affinity**, **assay standardization/improvement**)

No. 122
MAb ID p6F4
HXB2 Location p24
Author Location p24
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) mouse (IgG1)
Research Contact Dr. Yongtang Zheng, Laboratory of Molecular Immunopharmacology, Kunming Institute of Zoology, Kunming, Yunnan, China
References Liu *et al.* 2007
Keywords antibody generation, assay standardization/improvement, binding affinity

- p6F4: MAb p6F4 was derived from hybridoma from mice immunized with HIV-1 p24. p6F4 reacted with p24 from HIV-1 IIIB, Ada-M, 74V, and KM018 strains. p6F4 did not react with any of the five HIV-1 p24 peptides tested. Detection limit for rp24 in a modified sandwich ELISA of p6F4 was about 15 ng/ml. Liu *et al.* [2007] (**antibody generation**, **binding affinity**, **assay standardization/improvement**)

No. 123
MAb ID polyclonal
HXB2 Location p24
Author Location p24
Epitope
Subtype A, B, C, CRF02_AG, CRF01_AE, D
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) sheep, mouse
References Kim *et al.* 2008
Keywords assay development

- Sheep polyclonal and mouse monoclonal Abs raised against highly conserved HIV-1 p24 Gag peptides were used in a nanoparticle-based bio-barcode-amplification method. As in the conventional ELISA, the detection specificity of the bio-barcode-amplification method, tested on 112 plasma samples from HIV-1 infected subjects, was 100%. The sensitivity of the bio-barcode-amplification method was 99% compared to 20.5% of the conventional ELISA. p24 Gag was also detected in 60 diverse viruses tested, including ten from each of the most prevalent HIV-1 clades: A, B, C, D, CRF01_AE, and CRF02_AG. Like the quantitative real-time PCR assay, the bio-barcode-amplification method was highly sensitive, although it was not quantitative when low levels of virus were present. Kim *et al.* [2008] (**assay development**)

IV-C-4 Gag p24-p2p7p1p6 Antibodies

No. 124
MAb ID LH-104-G
HXB2 Location p24-p2p7p1p6 (231–5)
Author Location p24 (363–368 BRU)
Epitope LAEAMS
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade BRU
Species (Isotype) mouse (IgG1κ)
References Haaheim *et al.* 1991

- LH-104-G database comment: This epitope overlaps the p24-p2 cleavage site.
- LH-104-G: UK Medical Research Council AIDS reagent: ARP320.
- LH-104-G: Reacts with both p24 and p55, in contrast to LH-104-I. Haaheim *et al.* [1991]

IV-C-5 Gag p2p7p1p6 Antibodies

No. 125
MAb ID i5B11
HXB2 Location p2p7p1p6 (19–28)
Author Location p7 (5–14)
Epitope NFRNQRKIVK
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p7 Gag
Species (Isotype) rat (IgG2a)
References Tanchou *et al.* 1995; Tanchou *et al.* 1994; Otake *et al.* 1994

- i5B11 database comment: i5B11 and 15B11 may be two names for the same MAb.
- i5B11: MAb reacts with NCp7, NCp15, and partially inhibits NCp7-tRNA interaction. Tanchou *et al.* [1995]
- i5B11: Epitope mapped by ELISA and BIAcore – inhibits NCp7 primer tRNA binding. Tanchou *et al.* [1994]

No. 126
MAb ID EC6
HXB2 Location p2p7p1p6 (45–54)
Author Location p15 (408–417 HXB2)
Epitope PRKKGCWKCG
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p24-p15 Gag
Species (Isotype) mouse (IgG2aκ)
References Kanduc *et al.* 2008; Hinkula *et al.* 1990

- EC6: Similarity level of the EC6 binding site pentapeptide CWKCG to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- EC6: Epitope defined by peptide blocking of binding to native protein – WB reactive with p53. Hinkula *et al.* [1990]

No. 127
MAb ID M12
HXB2 Location p2p7p1p6 (45–54)
Author Location p15 (408–417 HXB2)
Epitope PRKKGCWKCG
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p24-p15 Gag
Species (Isotype) mouse (IgG1κ)
References Hinkula *et al.* 1990

- M12 database comment: There is a p15 and a gp120 mouse MAb both called M12 and a human gp41 Fab M12.
- M12: Epitope defined by peptide blocking of binding to native protein – WB reactive with p53. Hinkula *et al.* [1990]

No. 128
MAb ID DG8
HXB2 Location p2p7p1p6 (66–81)
Author Location p7 (52–67)
Epitope RQANFLGKIWPSYKGR
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* p7 Gag
Species (Isotype) mouse
References Kanduc *et al.* 2008; Tanchou *et al.* 1995

- DG8: Similarity level of the DG8 binding site pentapeptide IWPSY to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- DG8: Binds proximal to the second zinc-finger, inhibits NCp7-tRNA interaction. Tanchou *et al.* [1995]

No. 129
MAb ID EB5
HXB2 Location p2p7p1p6 (66–81)
Author Location p7 (52–67)
Epitope RQANFLGKIWPSYKGR
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* p7 Gag
Species (Isotype) mouse
References Tanchou *et al.* 1995

- EB5: Binds proximal to the second zinc-finger – mutation at position 59 (Lys to Ser) results in 10-fold reduction in reactivity. Tanchou *et al.* [1995]

No. 130
MAb ID HH3
HXB2 Location p2p7p1p6 (66–81)
Author Location p7 (52–67)
Epitope RQANFLGKIWPSYKGR
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p7 Gag
Species (Isotype) mouse (IgG2b)
References Tanchou *et al.* 1995; Tanchou *et al.* 1994

- HH3: Binds proximal to the second zinc-finger. Tanchou *et al.* [1995]
- HH3: Epitopes mapped by ELISA and BIAcore – does not inhibit NCp7 primer tRNA binding. Tanchou *et al.* [1994]

No. 131
MAb ID AD2
HXB2 Location p2p7p1p6 (78–86)
Author Location p7 (64–72)
Epitope YKGRPGNFL
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p7 Gag
Species (Isotype) mouse (IgG)

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References Kanduc *et al.* 2008; Tanchou *et al.* 1995

- AD2: Similarity level of the AD2 binding site pentapeptide YKGRP to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 4 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- AD2: Binds at C term of NCp7. Tanchou *et al.* [1995]

No. 132
MAb ID CA5
HXB2 Location p2p7p1p6 (78–86)
Author Location p7 (64–72)
Epitope `YKGRPGNFL`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p7 Gag
Species (Isotype) mouse (IgG)
References Tanchou *et al.* 1995

- CA5: Binds at C term of NCp7. Tanchou *et al.* [1995]

No. 133
MAb ID DF3
HXB2 Location p2p7p1p6 (78–86)
Author Location p7 (64–72)
Epitope `YKGRPGNFL`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p7 Gag
Species (Isotype) mouse (IgG)
References Tanchou *et al.* 1995

- DF3: Binds at C term of NCp7. Tanchou *et al.* [1995]

No. 134
MAb ID EC3
HXB2 Location p2p7p1p6 (78–86)
Author Location p7 (64–72)
Epitope `YKGRPGNFL`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p7 Gag
Species (Isotype) mouse (IgG)
References Tanchou *et al.* 1995

- EC3: Binds at C term of NCp7. Tanchou *et al.* [1995]

No. 135
MAb ID FC12
HXB2 Location p2p7p1p6 (78–86)
Author Location p7 (64–72)
Epitope `YKGRPGNFL`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p7 Gag
Species (Isotype) mouse (IgG)
References Tanchou *et al.* 1995

- FC12: Binds at C term of NCp7, reacts with NCp15, inhibits NCp7-tRNA interaction. Tanchou *et al.* [1995]

No. 136
MAb ID GE4
HXB2 Location p2p7p1p6 (78–86)
Author Location p7 (64–72)
Epitope `YKGRPGNFL`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p7 Gag
Species (Isotype) mouse (IgG)
References Tanchou *et al.* 1995

- GE4: Binds at C term of NCp7. Tanchou *et al.* [1995]

No. 137
MAb ID JB7
HXB2 Location p2p7p1p6 (78–86)
Author Location p7 (64–72)
Epitope `YKGRPGNFL`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p7 Gag
Species (Isotype) mouse (IgG)
References Tanchou *et al.* 1995

- JB7: Binds at C term of NCp7. Tanchou *et al.* [1995]

No. 138
MAb ID JF11
HXB2 Location p2p7p1p6 (78–86)
Author Location p7 (64–72)
Epitope `YKGRPGNFL`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p7 Gag
Species (Isotype) mouse (IgG1)
References Tanchou *et al.* 1995; Tanchou *et al.* 1994

- JF11: Binds at C term of NCp7. Tanchou *et al.* [1995]
- JF11: Epitopes mapped by ELISA and BIAcore – does not inhibit NCp7 primer tRNA binding. Tanchou *et al.* [1994]

IV-C-6 Gag Antibodies

No. 139
MAb ID 16/4/2
HXB2 Location Gag
Author Location p24
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: DNA with CMV promotor, DNA with CMV/MCK hybrid promotor, DNA with MCK promotor
Species (Isotype)
References Bojak *et al.* 2002a

B Cell

- 16/4/2: The ability of three different promoters to induce Gag specific immune responses was compared. The cytomegaliovirus (CMV) early gene promoter, which allows constitutive expression in different cells of host tissue, the tissue specific muscle creatine kinase (MCK) promoter, which may be restricted to differentiated, multinucleated myofibers and so safer, and a hybrid MCK/CMV promoter – intramuscular immunization of BALB/c mice utilizing the MCK promoter in combination with a codon optimized gag gene generated humoral (IgG1 (Th1) and IgG2a (Th2)) and CTL immune responses against HIV-1 Gag, however, the quantified immune parameters were clearly reduced as compared to CMV promotor-driven Gag expression. Bojak *et al.* [2002a]

No. 140
MAb ID 183-H12-5C
HXB2 Location Gag
Author Location p24
Epitope
Neutralizing no
Immunogen
Species (Isotype) mouse (IgG1)
Research Contact Bruce Chesebro and Kathy Wehrly, Rocky Mountain Laboratories, Hamilton, Montana
References Wehrly & Chesebro 1997; Toohey *et al.* 1995; Chesebro *et al.* 1992

- 183-H12-5C: NIH AIDS Research and Reference Reagent Program: 3537.
- 183-H12-5C: Cross-reacts with HIV1 and HIV-2 p24, and SIV p27. Wehrly & Chesebro [1997]
- 183-H12-5C: Used as antigen capture reagent for p24 ELISA. Chesebro *et al.* [1992]; Toohey *et al.* [1995]

No. 141
MAb ID 241-D
HXB2 Location Gag
Author Location p24
Epitope
Neutralizing no
Immunogen
Species (Isotype) human (IgG1λ)
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Robinson *et al.* 1991; Tyler *et al.* 1990; Gorny *et al.* 1989

- 241-D: MH AIDS Research and Reference Reagent program: 1244.
- 241-D: An antibody by this name is available in the NIH AIDS Research and Reference Reagent Program, and they refer to the papers Gorny *et al.* [1989]; Tyler *et al.* [1990]; Robinson *et al.* [1991], but no p24 MAb by this name is discussed in these papers. Gorny *et al.* [1989]; Robinson *et al.* [1991]; Tyler *et al.* [1990]

No. 142
MAb ID 2A6
HXB2 Location Gag
Author Location p17
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact A. O. Arthur, Frederick Cancer Research and Development Center, Frederick, MD
References Pincus *et al.* 1998

- 2A6: Part of a panel of 17 MAbs used as controls testing for the dual specificity of MAb G11H3 for both p17 and mycoplasma. Pincus *et al.* [1998]

No. 143
MAb ID 5E2.A3k
HXB2 Location Gag
Author Location p24 (1–158 SF2)
Epitope
Neutralizing no
Immunogen
Species (Isotype) mouse (IgG1)
Research Contact Biodesign International, Kennebunk, Maine, USA
References Hochleitner *et al.* 2000a

- 5E2.A3k: The Ab binding site was studied with epitope excision (protein is bound in native conformation to immobilized MAb, then digested with proteolytic enzymes) and extraction (protein is digested then allowed to react with Ab), followed by mass spectroscopy, as well as lysine modification – the epitope is discontinuous, but involves the highly conserved N-term proline, and the antibody recognizes SIVs and HIV-2 as well as HIV-1 p24. Hochleitner *et al.* [2000a]

No. 144
MAb ID 71-31
HXB2 Location Gag
Author Location p24
Epitope
Neutralizing no
Immunogen
Species (Isotype) human (IgG1λ)
References Bandres *et al.* 1998; Gorny *et al.* 1998; Gorny *et al.* 1997; Spear *et al.* 1993; Robinson *et al.* 1991; Robinson *et al.* 1990b; Gorny *et al.* 1989

- 71-31: NIH AIDS Research and Reference Reagent Program: 530.
- 71-31: Included as a negative control in studies that demonstrate that CXCR4 can bind to gp120 in the absence of CD4-gp120 interactions, and that this binding can be enhanced by Env deglycosylation. Bandres *et al.* [1998]
- 71-31: Did not mediate deposition of complement component C3 on HIV infected cells. Spear *et al.* [1993]
- 71-31: No enhancing or neutralizing activity. Robinson *et al.* [1991]
- 71-31: Did not enhance HIV-1 IIIB infection. Robinson *et al.* [1990b]

No. 145
MAb ID 91-6
HXB2 Location Gag
Author Location p24 (121–240 IIIB)
Epitope

B Cell

Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
References Robinson *et al.* 1990b; Gorny *et al.* 1989

- 91-6: NIH AIDS Research and Reference Reagent Program: 1239.
- 91-6: No enhancing activity for HIV-1 IIIB. Robinson *et al.* [1990b]

No. 146
MAb ID 98-4.3
HXB2 Location Gag
Author Location p24
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
References Robinson *et al.* 1991

- 98-4.3: No enhancing or neutralizing activity. Robinson *et al.* [1991]

No. 147
MAb ID 98-4.9
HXB2 Location Gag
Author Location p24
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) mouse (IgG3λ)
References Gorny *et al.* 1989

No. 148
MAb ID AC2
HXB2 Location Gag
Author Location p7
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p7 Gag
Species (Isotype) mouse (IgG)
References Tanchou *et al.* 1995

- AC2: Binds NCp7 independent of Zn fingers, does not react with NCp15. Tanchou *et al.* [1995]

No. 149
MAb ID BC1071
HXB2 Location Gag
Author Location p24
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) mouse
Research Contact Aalto BioReagents
References Schonning *et al.* 1999

- BC1071: The stoichiometry of MAb neutralization was tested and MAb BC1071 was used in this study for virion quantification. Schonning *et al.* [1999]

No. 150
MAb ID BE10
HXB2 Location Gag
Author Location p7
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p7 Gag
Species (Isotype) mouse (IgG)
References Tanchou *et al.* 1995

- BE10: Binding NCp7 requires Zn fingers, does not react with NCp15, inhibits NCp7-tRNA interaction. Tanchou *et al.* [1995]

No. 151
MAb ID CD9
HXB2 Location Gag
Author Location p7
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p7 Gag
Species (Isotype) mouse (IgG)
References Tanchou *et al.* 1995

- CD9: Binds NCp7 independent of Zn fingers, does not react with NCp15. Tanchou *et al.* [1995]

No. 152
MAb ID CH9B2
HXB2 Location Gag
Author Location p17
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
Research Contact R. B. Ferns and R. S. Tedder
References Ferns *et al.* 1989; Ferns *et al.* 1987

- CH9B2: UK Medical Research Council AIDS reagent: ARP349.
- CH9B2: Reactive against p18 and p55. Ferns *et al.* [1987]

No. 153
MAb ID ED8
HXB2 Location Gag
Author Location p7
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p7 Gag
Species (Isotype) mouse (IgG)
References Tanchou *et al.* 1995

- ED8: Binds NCp7 independent of Zn fingers, does not react with NCp15. Tanchou *et al.* [1995]

No. 154
MAb ID EH12E1

B Cell

HXB2 Location Gag
Author Location p24
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
Research Contact R. B. Ferns and R. S. Tedder
References Ferns *et al.* 1989; Ferns *et al.* 1987

- EH12E1: UK Medical Research Council AIDS reagent: ARP313.
- EH12E1: Reacted with p55 and p24 in WB. Ferns *et al.* [1987]

No. 155
MAb ID G11G1
HXB2 Location Gag
Author Location p17
Epitope
Neutralizing
Immunogen
Species (Isotype) rat
References Pincus *et al.* 1996; Shang *et al.* 1991

- G11G1: Immunotoxins were generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but only if the antigen was expressed at the cell surface – ricin-G11G1 did not mediate cell killing. Pincus *et al.* [1996]

No. 156
MAb ID G11H3
HXB2 Location Gag
Author Location p17
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Pincus *et al.* 1998; Shang *et al.* 1991

- G11H3: This MAb is cross-reactive between p17 and mycoplasma – this antibody binds strain specifically to the variable lipoprotein (Vlp) F of M. hyorhinis, in the region of the carboxy-terminal repeat CGGSTPTPEQGNNQGGSTPTPE-QGNSQVSK – the p17 epitope is discontinuous, but p17 and Vlp F share the tetrapeptide SQVS. Pincus *et al.* [1998]

No. 157
MAb ID HyHIV-19
HXB2 Location Gag
Author Location p17 (JMH1)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* p17 Gag
Species (Isotype) mouse (IgG1)
References Ota *et al.* 1998; Liu *et al.* 1995

- HyHIV-19: Does not react with p17 peptides – Ka is 3.7 x 10^6 M-1 for rec p17 – inhibited growth of HIV-1 JMH1 in MT-4 cells when added 24 hours after the initial culture. Ota *et al.* [1998]

No. 158
MAb ID IE8G2
HXB2 Location Gag
Author Location p24
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
Research Contact R. B. Ferns and R. S. Tedder
References Ferns *et al.* 1989; Ferns *et al.* 1987

- IE8G2: UK Medical Research Council AIDS reagent: ARP347.
- IE8G2: Reacted with both p55 and p24 – broadly reactive – showed less than 75% homologous inhibition. Ferns *et al.* [1987]

No. 159
MAb ID V7-8
HXB2 Location Gag
Author Location p24
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) mouse (IgG3κ)
References Montefiori *et al.* 1991; Robinson *et al.* 1990b

- V7-8: NIH AIDS Research and Reference Reagent Program: 381.
- V7-8: Reacted with HIV-1IIIB, RF, and MN. Montefiori *et al.* [1991]
- V7-8: Did not enhance HIV-1 IIIB infection. Robinson *et al.* [1990b]

No. 160
MAb ID anti-Gag
HXB2 Location Gag
Author Location Gag
Epitope
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) (IgA)
References Wright *et al.* 2006
Keywords neutralization

- anti-Gag: Intracellular neutralization of HIV by anti-Gag IgA MAbs against internal viral proteins was observed in this study. Wright *et al.* [2006] (**neutralization**)

No. 161
MAb ID anti-p24
HXB2 Location Gag
Author Location p24
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein, virus-like particle (VLP) *HIV component:* Gag, gp120, Nef, Pol
Species (Isotype) mouse (IgG)
Research Contact Intracel Co

B Cell

References Buonaguro *et al.* 2001

- anti-p24: HIV-1 pr55 gag-based virus-like particles (VLP) carrying Nef and Pol open reading frames, as well as gp120 of the clade A isolate 94UG018, were created using a Baculovirus expression system to package additional ORFS into the VLP – anti-V3 and anti-p24 Abs were used to assess the expression levels and Gag and gp120-TM were found to be expressed at comparable levels on the VLP. Buonaguro *et al.* [2001]

No. 162
MAb ID human sera
HXB2 Location Gag
Author Location p24
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Binley *et al.* 1997b

- Retention of anti-Env antibodies and loss of anti-Gag antibodies during progression was studied, and suggested to be the result of the loss of T-cell help and the unique ability of Env to stimulate B cells even in a backdrop of declining CD4 cells, because of the ability of Env to bind to the CD4 molecule. Binley *et al.* [1997b]

No. 163
MAb ID polyclonal
HXB2 Location Gag
Author Location Gag (LAI)
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with protein boost *Strain:* B clade LAI *HIV component:* Gag, Nef, Tat *Adjuvant:* IL-18
Species (Isotype) mouse
References Billaut-Mulot *et al.* 2001

- DNA vaccinated BALB/c mice primed and boosted with a multiepitopic vaccine with IL18 showed lymphoproliferative and CTL responses – co-administration of IL18 increased T-cell responses but decreased anti-HIV Ab levels. Billaut-Mulot *et al.* [2001]

No. 164
MAb ID polyclonal
HXB2 Location Gag
Author Location p24
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: gp120 depleted whole killed virus *Strain:* AG recombinant HZ321 *HIV component:* virus *Adjuvant:* Complete Freund's Adjuvant (CFA), CpG immunostimulatory sequence (ISS)
Species (Isotype) rat
References Moss *et al.* 2000

- Lewis rats co-immunized with HIV-1 antigen in Freund's and with immunostimulatory sequences CpG stimulated increased IFNγ expressing CD4+ and CD8+ T cells and anti-p24 antibodies relative to antigen in Freund's without CpG. Moss *et al.* [2000]

No. 165
MAb ID polyclonal
HXB2 Location Gag
Author Location p24 (SF2)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF2 *HIV component:* gp120, p24 Gag *Adjuvant:* MF59, PLG
Species (Isotype) mouse
References O'Hagan *et al.* 2000

- Microparticles were used as an adjuvant for entrapped HIV-1 gp120 and induced strong serum IgG responses in mice – polylactide co-glycolide polymer (PLG) microparticles in combination with MF-59 had the highest Ab response and also induced p24 specific CTL. O'Hagan *et al.* [2000]

No. 166
MAb ID polyclonal
HXB2 Location Gag
Author Location Gag (SF2)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA, protein *Strain:* B clade SF2 *HIV component:* Gag *Adjuvant:* aluminum phosphate, MF59, PLG
Species (Isotype) macaque, guinea pig, mouse
References O'Hagan *et al.* 2001

- DNA vaccines of codon-optimized Env and Gag genes driven by CMV promotors absorbed on to PLG microparticles were more effective than naked DNA at eliciting strong Ab responses (more rapid, higher titer, more stable), comparable to gp120 in MF-59. O'Hagan *et al.* [2001]

No. 167
MAb ID polyclonal
HXB2 Location Gag
Author Location p24
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* p24 Gag
Species (Isotype) rabbit (IgG)
References Gupta *et al.* 2001

- Gag p24 is the mostly widely used HIV protein for serological based diagnostic kits — phage display libraries of HIV-1 p24 identified 2 epitope-rich regions: 70% of the clones that were identified using immunized rabbit sera had DNA fragments from the N-terminal region spanning 150–240 of Gag, and 30% from the carboxy-terminal region of p24 containing amino acids 310–360 — subtype B and C comparisons were made. Gupta *et al.* [2001]

No. 168
MAb ID polyclonal
HXB2 Location Gag
Author Location p55
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein, virus-like particle (VLP) *Strain:* B clade LAI *HIV component:* CD4BS, Gag, V3
Species (Isotype) mouse
References Truong *et al.* 1996

- Antibodies raised against recombinant anti-p55 virus-like particles with the p24 region 196-226 deleted, bearing inserts of either the V3 or the CD4BS regions of gp120 were studied – no neutralizing responses, weak Env and strong Gag responses were elicited – the major homology region (MHR) and proximal sequences was found to be required for capsid assembly. Truong *et al.* [1996]

No. 169
MAb ID polyclonal
HXB2 Location Gag
Author Location p24 (LAI)
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide, virion, baculovirus, E. Coli recombinant protein *Strain:* B clade LAI *HIV component:* p24 Gag *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) rabbit (IgG)
References Devito *et al.* 2000c

- To compare vaccine strategies, rabbits were immunized with virion HIV-1/Lai, baculovirus recombinant p24, E. coli recombinant p24-15, and p24-derived peptides – the rabbit immunized with peptides had the broadest linear epitope responses – the capture ELISA method using anti-p24 IgG preparations was shown to capture isolates from HIV-1 subtypes or clades A to G – only immunization with virion HIV-1/Lai and baculovirus recombinant p24 developed IgG that was capable of efficiently capturing HIV-1 p24 in ELISA producing Abs able to recognise native configurations. Devito *et al.* [2000c]

No. 170
MAb ID polyclonal
HXB2 Location Gag
Author Location
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA *Adjuvant:* CpG immunostimulatory sequence (ISS), phosphorothioate oligodeoxynucleotides (ODNs)
Species (Isotype) mouse
References Deml *et al.* 2001

- Immunization mice with a codon-optimized Gag was compared with a non-optimized Rev dependent Gag expression vector – Gag expression was at higher levels and Rev independent with the codon-optimized Gag, and i.m. immunization gave a stronger Th1-driven humoral and cellular immune response – intradermal immunization with either Gag DNA induced a Th2 response and no CTL. Deml *et al.* [2001]

No. 171
MAb ID polyclonal
HXB2 Location Gag
Author Location
Epitope
Neutralizing yes
Immunogen HIV-1 infection
Species (Isotype) human
References Montefiori *et al.* 2001

- In 7/9 patients in whom HAART was initiated during early seroconversion, NAbs to autologous strains were not found immediately following treatment interuption after 1-3 years, and Env and Gag Abs were low or undetected by ELISA indicating, that early HAART suppresses the normal antibody response to HIV-1, presumably by limiting the concentration of viral antigens needed to drive B-cell maturation – in 3 patients with a viral rebound autologous NAbs rapidly appeared and correlated with spontaneous down-regulation of viremia – prolonged control of viremia after stopping treatment persisted in the absence of detectable NAbs, suggesting that cellular immune responses alone can control viremia under certain circumstances – these results support the notion that virus-specific B-cell priming, combined with CD8+ CTL induction, may be beneficial for HIV-1 vaccines that aim to suppress viremia in the absence of complete protection to prevent disease and reduce the rate of virus transmission. Montefiori *et al.* [2001]

No. 172
MAb ID polyclonal
HXB2 Location Gag
Author Location
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *HIV component:* Env, Gag *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse (IgG)
References Lebedev *et al.* 2000

- Virus-like particles (VLPs) in the form of spherical particles with yeast dsRNA enveloped in a polysaccharide matrix carrying the protein TBI, that contains fragments of HIV Env and Gag, were used to immunize BALB/c mice and induced specific Abs against HIV-1 as measured by ELISA with TBI. Lebedev *et al.* [2000]

No. 173
MAb ID polyclonal
HXB2 Location Gag

B Cell

Author Location
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: DNA with CMV promotor, DNA with CMV/MCK hybrid promotor, DNA with MCK promotor
Species (Isotype) mouse (IgG1, IgG2a)
References Bojak *et al.* 2002a

- The ability of three different promoters to induce Gag specific immune responses was compared. The cytomegaliovirus (CMV) early gene promoter, which allows constitutive expression in different cells of host tissue, the tissue specific muscle creatine kinase (MCK) promoter, which may be restricted to differentiated, multinucleated myofibers and so safer, and a hybrid MCK/CMV promoter – intramuscular immunization of BALB/c mice utilizing the MCK promoter in combination with a codon optimized gag gene generated humoral (IgG1 (Th1) and IgG2a (Th2)) and CTL immune responses against HIV-1 Gag, however, the quantified immune parameters were clearly reduced as compared to CMV promotor-driven Gag expression. Bojak *et al.* [2002a]

No. 174
MAb ID polyclonal
HXB2 Location Gag
Author Location p24
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human
References Meles *et al.* 2002

- Indeterminant WB in Ethiopians: of 12,124 specimens blood specimens from Ethiopia, 1,437 (11.9%) were HIV-1-positive for antibody, and 91 (0.8%) gave equivocal results, most often due to p24 reactivity – subsequent testing confirmed many of the indeterminants were HIV-negative – the American Red Cross diagnostic criteria was more accurate than CDC or WHO, which would have given some false positive results. Meles *et al.* [2002]

No. 175
MAb ID polyclonal
HXB2 Location Gag
Author Location p24
Epitope
Subtype A
Neutralizing yes
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *Strain:* A clade UG5.94UG018 *HIV component:* Gag, gp120
Species (Isotype) mouse
References Buonaguro *et al.* 2002
Keywords subtype comparisons

- BALB/c mice were immunized with VLPs carrying a subtype A gp120. Humoral immune responses directed against B-clade derived Gag (p24) peptides or gp120-Env V3 loop peptide were readily induced following a multi-dose immunization with VLP particles presenting a gp120 molecule from a HIV-1 isolate of clade A. VLP-immunized mice showed autologous and heterologous (against B-clade HIV-1 IIIB strain) neutralization activity. Proliferative responses and CTL were also observed. Buonaguro *et al.* [2002] (**subtype comparisons**)

No. 176
MAb ID polyclonal
HXB2 Location Gag
Author Location Gag
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA *HIV component:* Gag
Species (Isotype) mouse (IgG1)
References Bojak *et al.* 2002b
Keywords Th1

- Balb/c mice vaccinated by syngag, a DNA plasmid expressing HIV-1 Gag modified for human/mammalian codon usage, gave stronger and longer lasting immune responses than wild type gag. Gag-specific antibody and cellular immune responses were both increased, with a clear T-helper 1 polarization. There was a better IgG1/IgG2 response to intramuscular (i.m.) as compared to subcutaneous (s.c.) vaccination. Bojak *et al.* [2002b] (**Th1**)

No. 177
MAb ID polyclonal
HXB2 Location Gag
Author Location Gag
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA, protein, virus-like particle (VLP), PLG microparticle *Adjuvant:* E. coli heat labile enterotoxin
Species (Isotype) macaque
References Otten *et al.* 2003

- This study evaluates different vaccine technologies that avoid live vectors including plasmid DNA, recombinant p55Gag protein or gag-pol administered by polylactide coglycolide (PLG) microparticles, LTK63 as adjuvant, VLP, and plasmid DNA. 4/4 macaques primed with Gag-PLG and LTK63 showed strong antibody responses after the fourth immunization at week six. The best CTL responses were found for gag DNA, the best Th and Ab were obtained using Gag protein on PLG microparticles; Gag DNA priming with a PLG-protein boost gave high level CTL, Th and Ab responses. Otten *et al.* [2003]

No. 178
MAb ID polyclonal
HXB2 Location Gag
Author Location p24
Epitope
Subtype multiple
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Barin *et al.* 2005

Keywords acute/early infection, assay development

- A combination of 4 antigenic regions was used to differentiate between early (<180 days) and chronic infection. These regions were: p24; the gp41 peptide spanning the immunodominant epitope (IDE) of gp41, RVAVERYLKDQQLLGIWGCSGKICTTAV, and a subtype D version of this peptide; 5 V3 consensus peptides including A, B, C, D, and CRF01-AE; and Integrase. V3 and the IDE provide the best discrimination, with >20 fold higher levels in chronic infection when assayed by EIA using dried serum spots. Antibodies to Integrase and p24 were not as distinctive, and people tend to lose, not increase, responses to p24 over time. This assay can be used to identify samples from early infection with high sensitivity and specificity. Barin *et al.* [2005] (**assay development**, **acute/early infection**)

No. 179
MAb ID polyclonal
HXB2 Location Gag
Author Location Gag
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Lottersberger *et al.* 2004

- Addition of non-immunogenic side chains (AAAC and CAAA) to both N- and C-termini of synthetic alpha helical peptide sequences of HIV-1 p24 and p17 proteins improved Ab reactivity. As diminishing response to these antigens is a harbinger of progression these peptides may by useful in diagnostic assays. Lottersberger *et al.* [2004]

No. 180
MAb ID polyclonal
HXB2 Location Gag
Author Location Gag
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost *Strain:* Other *HIV component:* Gag
Species (Isotype) mouse (IgA, IgG)
References Huang *et al.* 2007c
Keywords genital and mucosal immunity, mucosal immunity

- BALB/c mice were immunized with DNA plasmid and PEI/DNA complexes and boosted with recombinant TianTan vaccinia virus (rTTV) expressing HIV-1 Gag. PEI is polyethylenimine, a polymer with the high cationic charge density. HIV-specific IgG Abs in sera were comparable between DNA and PEI/DNA immunized mice. However, PEI/DNA stimulated significantly higher IgA responses than DNA alone in different mucosal secretions, both with or without rTTV boosting. Intramuscular rTTV boosting enhanced Ab immune responses raised by intranasal priming. Huang *et al.* [2007c] (**genital and mucosal immunity**, **mucosal immunity**)

No. 181
MAb ID polyclonal
HXB2 Location Gag
Author Location Gag
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade HXB2 *HIV component:* Gag
Species (Isotype) macaque, mouse (IgA, IgG)
References Chikhlikar *et al.* 2006
Keywords vaccine antigen design

- DNA encoding Gag as a chimera with the mouse and human lysosome-associated membrane protein (mLAMP/gag and hLAMP/gag) was used in immunization studies in mice and macaques. IgG responses in mice immunized with hLAMP/gag were considerably greater than the response to the mLAMP/gag. Strong HIV-specific IgG response was also observed in hLAMP/gag immunized macaques, which increased after each DNA immunization. Significant Gag-specific IgA levels were detected in 3 of 5 immunized macaques. Serum samples from the macaques recognized 13 of 49 20-aa Gag peptides covering Gag sequence indicating broad B-cell response. Chikhlikar *et al.* [2006] (**vaccine antigen design**)

No. 182
MAb ID polyclonal
HXB2 Location Gag
Author Location
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: Salmonella *HIV component:* p24 Gag *Adjuvant:* Cholera toxin (CT)
Species (Isotype) mouse (IgA, IgG)
References Tsunetsugu-Yokota *et al.* 2007
Keywords dendritic cells, mucosal immunity, vaccine antigen design

- Mice immunized with oral gag-expressing Salmonella (ST-coGag) vaccine were shown to develop Gag-specific IgG responses in the serum and to secrete Gag-specific IgA in the intestine, while intestinal IgA was not detected in nasally immunized mice. These results suggest that oral ST-coGag can be useful in directing Gag-specific immunity to the intestinal mucosa. Tsunetsugu-Yokota *et al.* [2007] (**vaccine antigen design**, **mucosal immunity**, **dendritic cells**)

No. 183
MAb ID polyclonal
HXB2 Location Gag
Author Location Gag
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: Other *Strain:* B clade HXB2 *HIV component:* Gag-Pol, p17/p24 Gag, Rev, Tat, Vif, Vpr *Adjuvant:* CpG immunostimulatory sequence (ISS)
Species (Isotype) mouse
References Racek *et al.* 2006
Keywords vaccine antigen design

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- Immunization of mice with DNA-prime, VSV-G pseudotyped HIV-1-derived pseudovirion-boost vaccine resulted in a Gag-specific Ab response and high titers of neutralizing Abs directed against the VSV-G protein. The level of Gag-specific Ab responses was similar in sera from mice immunized with vGJ2-hgag and vGJ2-gfp indicating that the transgene expression from the hgag gene (p17/p24 gag) did not further activate the humoral immune response. Racek *et al.* [2006] (**vaccine antigen design**)

No. 184
MAb ID polyclonal
HXB2 Location Gag
Author Location Gag
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Krachmarov *et al.* 2006
Keywords neutralization

- A pool of anti-V3b MAbs did not neutralize the YU-2 Env while a SF162 variant containing the JR-FL V1/V2 and V3 domains was more sensitive. The substitutions in the V3 sequence of YU-2 were shown not to contribute to the resistance of this virus while the removal of glycosylation sites in the V1/V2 region increased the sensitivity of this virus over 2,500-fold, indicating that it is the masking of V1/V2 that is responsible for the resistance of YU-2. Krachmarov *et al.* [2006] (**neutralization**)

No. 185
MAb ID polyclonal HIVIG
HXB2 Location Gag
Author Location p24
Epitope
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
References Nichols *et al.* 2002

- NYBC-HIVIG derived from patients with high NAb titers and NABI-HIVIG derived from patients with high anti-p24 Ab titers were compared in neutralizing assay against a panel of six primary isolates—both could neutralize all isolates tested but the NYBC-HIVIG dose required for 50% neutralization was of 3.2 fold lower, showing that the source plasmas influence the effective concentration of NAb present in HIVIG. Nichols *et al.* [2002]

IV-C-7 Protease Antibodies

No. 186
MAb ID 1696
HXB2 Location Protease (1–7)
Author Location Protease (1–7 BH10)
Epitope `PQIYLWQ`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Protease
Species (Isotype) mouse (IgG)
Ab Type N-term
References Kanduc *et al.* 2008; Bartoňová *et al.* 2008; Lescar *et al.* 2003; Rezacova *et al.* 2002; Rezacova *et al.* 2001; Lescar *et al.* 1999
Keywords drug resistance, review, structure

- 1696: The antibody fragment scFv1696 is a potent inhibitor of wild-type Protease and also has a strong inhibitory effect on Protease variants resistant to active-site inhibitors used as anti-AIDS drugs. Bartoňová *et al.* [2008] (**drug resistance**)
- 1696: Similarity level of the 1696 binding site pentapeptide QIYLW to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 1696: Study compares the crystal structure of the scFv-1696 in the non-complexed form compared to the complexed Fab-1696 and the Ag-bound scFv-1696 structures. Changes in the three conformational tertiary structures of CDR-H3 as well as in the different relative orientations of the light-chain variable domains of the different structures were observed, demonstrating plasticity in the antibody binding site. Lescar *et al.* [2003] (**structure**)
- 1696: Review of the implications of antibody structure and antigen peptide binding for the mechanisms of inhibition of protease activity by two MABs with different binding sites in protease. Rezacova *et al.* [2002] (**review**, **structure**)
- 1696: The crystal structure of the single chain Fv fragment of 1696 bound to a cross-reactive peptide (PQITLWQRR) was obtained. This sturcture suggests that 1696 inhibits portease activity by favoring dissociation of the active homodimer. Rezacova *et al.* [2001] (**structure**)
- 1696: MAb binds to HIV-1 and HIV-2, putative epitopes are PQIYLWQ and PQFSLWK respectively – Pro1 is critical, QIYLWQR residues 2-8, does not compete - MAb disrupts catalytic activity – crystal structure of the ligand-free Fab at 3 A resolution reveals a deep cavity lined by acidic and hydrophobic residues – the binding region is located within the region required for dimerization and the Fab structure could serve as a basis for drug design targeting this region. Lescar *et al.* [1999] (**structure**)

No. 187
MAb ID 10E7
HXB2 Location Protease (36–46)
Author Location Protease (38–45 HXB2)
Epitope `MSLPGRWKPKM`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Protease
Species (Isotype) hamster (IgG)
References Kanduc *et al.* 2008; Bjorling *et al.* 1992; Croix *et al.* 1993

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- 10E7: Similarity level of the 10E7 binding site pentapeptide WKPKM to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 10E7: Immunodominant region of protease in Armenian hamster (but only weakly reactive in people, see: Bjorling *et al.* [1992]) – peptide MSLPGRWKP blocks protease binding Croix *et al.* [1993]. Bjorling *et al.* [1992]; Croix *et al.* [1993]

No. 188
MAb ID F11.2.32
HXB2 Location Protease (36–46)
Author Location Protease (36–46 BH10)
Epitope `MSLPGRWKPKM`
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* Protease
Species (Isotype) mouse (IgG1κ)
Ab Type flap region
References Bartoňová *et al.* 2008; Rezacova *et al.* 2002; Lescar *et al.* 1999; Lescar *et al.* 1997; Lescar *et al.* 1996
Keywords drug resistance, review, structure

- F11.2.32: The antibody fragment scFvF11.2.32 inhibits of wild-type Protease and also has an inhibitory effect on Protease variants resistant to active-site inhibitors used as anti-AIDS drugs. Bartoňová *et al.* [2008] (**drug resistance**)
- F11.2.32: Review of the implications of antibody structure and antigen peptide binding for the mechanisms of inhibition of protease activity by two MABs with different binding sites in protease. Rezacova *et al.* [2002] (**review**, **structure**)
- F11.2.32: Crystal strucutre of a Fab peptide complex was obtained. Distortion may occur in the flap region of the protein, important for regulating access of substrate to the catalytic site. Lescar *et al.* [1999] (**structure**)
- F11.2.32: Binding leads to significant inhibition in proteolytic activity – crystal structure of Fab-peptide was determined to 2.2 A resolution – bound peptide shows no structural similarity to the corresponding segment in native protease suggesting binding may distort protein structure. Lescar *et al.* [1997] (**structure**)

No. 189
MAb ID 13E1
HXB2 Location Protease (38–45)
Author Location Protease (38–45 HXB2)
Epitope `LPGRWKPK`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Protease
Species (Isotype) hamster (IgG)
References Croix *et al.* 1993

- 13E1: Binds to MSLPGRWKPKM with sightly higher affinity. Croix *et al.* [1993]

No. 190
MAb ID 8B11
HXB2 Location Protease (38–45)
Author Location Protease (38–45 HXB2)
Epitope `LPGRWKPK`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Protease
Species (Isotype) hamster (IgG)
References Croix *et al.* 1993

- 8B11: Binds to MSLPGRWKPKM with sightly higher affinity. Croix *et al.* [1993]

No. 191
MAb ID 8C10
HXB2 Location Protease (38–45)
Author Location Protease (38–45 HXB2)
Epitope `LPGRWKPK`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Protease
Species (Isotype) hamster (IgG)
References Croix *et al.* 1993

- 8C10: Binds to MSLPGRWKPKM with sightly higher affinity. Croix *et al.* [1993]

No. 192
MAb ID 8G5
HXB2 Location Protease (38–45)
Author Location Protease (38–45 HXB2)
Epitope `LPGRWKPK`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Protease
Species (Isotype) hamster (IgG)
References Croix *et al.* 1993

- 8G5: Binds to MSLPGRWKPKM with sightly higher affinity. Croix *et al.* [1993]

IV-C-8 RT Antibodies

No. 193
MAb ID 1E8
HXB2 Location RT (65–73)
Author Location RT (65–73)
Epitope `KKDSTKWRK`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* RT *Adjuvant:* nitrocellulose
Species (Isotype) mouse (IgG1)

B Cell

References Kanduc *et al.* 2008; Gu *et al.* 1996; Wu *et al.* 1993

- 1E8: Similarity level of the 1E8 binding site pentapeptide DSTKW to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 1E8: Significantly inhibits DNA polymerase activity of RT by hindering binding of dNTPs – additive or synergistic RT inhibition with nevirapine and delavirdine. Gu *et al.* [1996]
- 1E8: Inhibits RT activity, binding site overlaps with two AZT resistance mutations. Wu *et al.* [1993]

No. 194
MAb ID polyclonal
HXB2 Location RT (249–263)
Author Location RT (249–263)
Epitope KDSWTVNDIQKLVGK
Neutralizing
Immunogen vaccine, in vitro stimulation or selection
Vector/Type: peptide presented on icosahedral protein scaffold *HIV component:* RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (Isotype) human (IgG)
References Kanduc *et al.* 2008; Domingo *et al.* 2003
Keywords vaccine antigen design

- Similarity level of the polyclonal Ab binding site pentapeptide KDSWT to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- A virus-like protein scaffold, called E2DISP, derived from pyruvate dehydrogenase multienzyme from Bacillus stearothermophilus has been engineered to display 60 copies of one or more epitopes on a single molecule. An E2DISP scaffold which displayed pep23, a 15-residue B and T helper HIV-1 RT epitope elicited a pep23-specific T-helper response *in vitro*. The E2DISP scaffold displaying peptide RT2, which is a CTL HIV-1 RT epitope, was able to elicit a CD8+ T cell response *in vitro* and in a vaccinated HLA-A2 transgenic mouse. Thus the E2DISP scaffold allows cell-entry and access to both the class I and class II processing pathways. The Th response in vaccinated mice supported Pep23-specific IgG responses. Domingo *et al.* [2003] (**vaccine antigen design**)

No. 195
MAb ID 1.152 B3
HXB2 Location RT (294–302)
Author Location RT (294–302)
Epitope PLTEEAELE
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* RT
Species (Isotype) mouse (IgG1)
References Orvell *et al.* 1991

- 1.152 B3: Weakly positive by immunofluorescence – binding inhibits RT enzymatic activity. Orvell *et al.* [1991]

No. 196
MAb ID 1.158 E2
HXB2 Location RT (294–302)
Author Location RT (294–302)
Epitope PLTEEAELE
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* RT
Species (Isotype) mouse (IgG1)
References Orvell *et al.* 1991

- 1.158 E2: Negative by immunofluorescence – binding inhibits RT enzymatic activity. Orvell *et al.* [1991]

No. 197
MAb ID 31D6
HXB2 Location RT (294–318)
Author Location RT (294–319)
Epitope PLTEEAELELAENREILKEPVHGVY
Neutralizing no
Immunogen vaccine
Vector/Type: E. coli Trp fusion protein *HIV component:* RT
Species (Isotype) mouse (IgG1)
References Szilvay *et al.* 1992

- 31D6: Strong inhibitor of RT, > 50% inhibition. Szilvay *et al.* [1992]

No. 198
MAb ID 31G8
HXB2 Location RT (294–318)
Author Location RT (294–319)
Epitope PLTEEAELELAENREILKEPVHGVY
Neutralizing no
Immunogen vaccine
Vector/Type: E. coli Trp fusion protein *HIV component:* RT
Species (Isotype) mouse (IgG1)
References Szilvay *et al.* 1992

- 31G8: Weak inhibitor of RT, reactive by immunofluorescence. Szilvay *et al.* [1992]

No. 199
MAb ID 32E7
HXB2 Location RT (294–318)
Author Location RT (294–319)
Epitope PLTEEAELELAENREILKEPVHGVY
Neutralizing no
Immunogen vaccine
Vector/Type: E. coli Trp fusion protein *HIV component:* RT
Species (Isotype) mouse (IgG1)
References Szilvay *et al.* 1992

- 32E7: Weak inhibitor of RT, reactive by immunofluorescence. Szilvay *et al.* [1992]

No. 200
MAb ID 33D5
HXB2 Location RT (294–318)
Author Location RT (294–319)
Epitope PLTEEAELELAENREILKEPVHGVY

Neutralizing no
Immunogen vaccine
Vector/Type: E. coli Trp fusion protein *HIV component:* RT
Species (Isotype) mouse (IgG1)
References Szilvay *et al.* 1992

- 33D5: Weak inhibitor of RT, reactive by immunofluorescence. Szilvay *et al.* [1992]

No. 201
MAb ID 5B2
HXB2 Location RT (294–318)
Author Location RT (294–319)
Epitope `PLTEEAELELAENREILKEPVHGVY`
Neutralizing no
Immunogen vaccine
Vector/Type: E. coli Trp fusion protein *HIV component:* RT
Species (Isotype) mouse (IgG1)
References Szilvay *et al.* 1992

- 5B2: UK Medical Research Council AIDS reagent: ARP3018.
- 5B2: There is an RT specific Ab Szilvay *et al.* [1992] and a gp41 specific Ab Tian *et al.* [2001] both called 5B2. Szilvay *et al.* [1992]
- 5B2: Weak inhibitor of RT, reactive by immunofluorescence. Szilvay *et al.* [1992]

No. 202
MAb ID polyclonal
HXB2 Location RT (295–304)
Author Location RT (295–304 PV22)
Epitope `LTEEAELELA`
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Grimison & Laurence 1995

No. 203
MAb ID 1.153 G10
HXB2 Location RT (350–354)
Author Location RT (350–354)
Epitope `KTGKY`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* RT
Species (Isotype) mouse (IgG1)
References Orvell *et al.* 1991

No. 204
MAb ID RTMAb8
HXB2 Location RT (376–383)
Author Location RT (532–539)
Epitope `TTESIVIW`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* RT
Species (Isotype) mouse (IgG)
References Ferns *et al.* 1991; Tisdale *et al.* 1988

No. 205
MAb ID 1D4A3
HXB2 Location RT (384–387)
Author Location RT (540–543)
Epitope `GKIP`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* RT
Species (Isotype) mouse (IgG)
References Ferns *et al.* 1991

No. 206
MAb ID RT6H
HXB2 Location RT (384–387)
Author Location RT (540–543)
Epitope `GKIP`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* RT
Species (Isotype) mouse (IgG)
References Ferns *et al.* 1991

No. 207
MAb ID 1.160 B3
HXB2 Location RT (442–450)
Author Location RT (442–450)
Epitope `VDGAANRET`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* RT
Species (Isotype) mouse (IgG1)
References Orvell *et al.* 1991

No. 208
MAb ID polyclonal
HXB2 Location RT (521–531)
Author Location RT (521–531 PV22)
Epitope `IIEQLIKKEKV`
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Grimison & Laurence 1995

No. 209
MAb ID C2003
HXB2 Location RT (536–549)
Author Location RT (703–716 BH10)
Epitope `VPAHKGIGGNEQVD`
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade BH10
Species (Isotype) rabbit (IgG)
References DeVico *et al.* 1991

- C2003: Inhibits polymerase activity from a variety of retroviruses – RT protected from inhibition by preincubation with template primer. DeVico *et al.* [1991]

No. 210
MAb ID anti-RT
HXB2 Location RT

Author Location RT
Epitope
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) (IgA)
References Wright *et al.* 2006
Keywords neutralization

- anti-RT: Intracellular neutralization of HIV by anti-RT IgA MAbs against internal viral proteins was observed in this study. Wright *et al.* [2006] (**neutralization**)

IV-C-9 Integrase Antibodies

No. 211
MAb ID 1C4
HXB2 Location Integrase (1–16)
Author Location Integrase (1–16 HXB2)
Epitope FLDGIDKAQDEHEKYH
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2
HIV component: Int
Species (Isotype) mouse (IgG1κ)
Ab Type N-term
References Nilsen *et al.* 1996; Haugan *et al.* 1995

- 1C4: One of a large set of MAbs that interact with the N-terminal part of integrase: 1C4, 2C11, 2E3, 3E11, 3F9, 5F8, 6G5, 7B6, 7C6 – these MAbs inhibit end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]
- 1C4: MAb interferes with integrase binding to DNA. Haugan *et al.* [1995]

No. 212
MAb ID 2C11
HXB2 Location Integrase (1–16)
Author Location Integrase (1–16 HXB2)
Epitope FLDGIDKAQDEHEKYH
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2
HIV component: Int
Species (Isotype) mouse (IgG1κ)
Ab Type N-term
References Nilsen *et al.* 1996

- 2C11: One of a large set of MAbs that interact with the N-terminal part of integrase: 1C4, 2C11, 2E3, 3E11, 3F9, 5F8, 6G5, 7B6, 7C6 – these MAbs inhibit end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]

No. 213
MAb ID 2E3
HXB2 Location Integrase (1–16)
Author Location Integrase (1–16 HXB2)
Epitope FLDGIDKAQDEHEKYH
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2
HIV component: Int
Species (Isotype) mouse (IgG1κ)
Ab Type N-term
References Ovod *et al.* 1992; Nilsen *et al.* 1996

- 2E3: One of a large set of MAbs that interact with the N-terminal part of integrase: 1C4, 2C11, 2E3, 3E11, 3F9, 5F8, 6G5, 7B6, 7C6 – these MAbs inhibit end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]
- 2E3: There are two MAbs called 2E3 – the other one binds to Nef. Ovod *et al.* [1992]

No. 214
MAb ID 3E11
HXB2 Location Integrase (1–16)
Author Location Integrase (1–16 HXB2)
Epitope FLDGIDKAQDEHEKYH
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2
HIV component: Int
Species (Isotype) mouse (IgG1κ)
Ab Type N-term
References Nilsen *et al.* 1996; Otteken *et al.* 1992

- 3E11: One of a large set of MAbs that interact with the N-terminal part of integrase: 1C4, 2C11, 2E3, 3E11, 3F9, 5F8, 6G5, 7B6, 7C6 – these MAbs inhibit end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]
- 3E11: There is another MAb with this ID that recognizes p17. Otteken *et al.* [1992]
- 3E11: Recognized an epitope present on HIV-2/SIVmac, SIVagm, HIV-1, and SIVmnd. Otteken *et al.* [1992]

No. 215
MAb ID 3F9
HXB2 Location Integrase (1–16)
Author Location Integrase (1–16 HXB2)
Epitope FLDGIDKAQDEHEKYH
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2
HIV component: Int
Species (Isotype) mouse (IgG1κ)
Ab Type N-term
References Nilsen *et al.* 1996

- 3F9: One of a large set of MAbs that interact with the N-terminal part of integrase: 1C4, 2C11, 2E3, 3E11, 3F9, 5F8, 6G5, 7B6, 7C6 – these MAbs inhibit end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]

No. 216
MAb ID 5F8

B Cell

HXB2 Location Integrase (1–16)
Author Location Integrase (1–16 HXB2)
Epitope `FLDGIDKAQDEHEKYH`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2
HIV component: Int
Species (Isotype) mouse (IgG1κ)
Ab Type N-term
References Nilsen *et al.* 1996; Haugan *et al.* 1995

- 5F8: One of a large set of MAbs that interact with the N-terminal part of integrase: 1C4, 2C11, 2E3, 3E11, 3F9, 5F8, 6G5, 7B6, 7C6 – these MAbs inhibit end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]
- 5F8: MAb interferes with integrase binding to DNA. Haugan *et al.* [1995]

No. 217
MAb ID 6G5
HXB2 Location Integrase (1–16)
Author Location Integrase (1–16 HXB2)
Epitope `FLDGIDKAQDEHEKYH`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2
HIV component: Int
Species (Isotype) mouse (IgG1κ)
Ab Type N-term
References Nilsen *et al.* 1996

- 6G5: One of a large set of MAbs that interact with the N-terminal part of integrase: 1C4, 2C11, 2E3, 3E11, 3F9, 5F8, 6G5, 7B6, 7C6 – these MAbs inhibit end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]

No. 218
MAb ID 7B6
HXB2 Location Integrase (1–16)
Author Location Integrase (1–16 HXB2)
Epitope `FLDGIDKAQDEHEKYH`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2
HIV component: Int
Species (Isotype) mouse (IgG1κ)
Ab Type N-term
References Nilsen *et al.* 1996

- 7B6: One of a large set of MAbs that interact with the N-terminal part of integrase: 1C4, 2C11, 2E3, 3E11, 3F9, 5F8, 6G5, 7B6, 7C6 – these MAbs inhibit end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]

No. 219
MAb ID 7C6
HXB2 Location Integrase (1–16)
Author Location Integrase (1–16 HXB2)
Epitope `FLDGIDKAQDEHEKYH`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2
HIV component: Int
Species (Isotype) mouse (IgG1κ)
Ab Type N-term
References Nilsen *et al.* 1996

- 7C6: One of a large set of MAbs that interact with the N-terminal part of integrase: 1C4, 2C11, 2E3, 3E11, 3F9, 5F8, 6G5, 7B6, 7C6 – these MAbs inhibit end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]

No. 220
MAb ID 6C5
HXB2 Location Integrase (17–38)
Author Location Integrase (17–38 HXB2)
Epitope `SNWRAMASDFNLPPVVAKEIVA`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2
HIV component: Int
Species (Isotype) mouse (IgG1κ)
Ab Type N-term
References Nilsen *et al.* 1996; Haugan *et al.* 1995

- 6C5: This MAb inhibits end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]
- 6C5: MAb interferes with integrase binding to DNA. Haugan *et al.* [1995]

No. 221
MAb ID 8G4
HXB2 Location Integrase (22–31)
Author Location Integrase (12–42 HXB2)
Epitope `MASDFNLPPV+GYIEAEVIPAETGQETAYFI?`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2
HIV component: Int
Species (Isotype) mouse (IgG1κ)
References Nilsen *et al.* 1996; Haugan *et al.* 1995

- 8G4: This MAb reacted strongly with peptides IN(12-31) and IN(22-42), and less strongly with peptide IN(82-101) – it did not react with a deletion mutant of positions 17-38 – this MAb inhibits end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]
- 8G4: MAb interferes with integrase binding to DNA. Haugan *et al.* [1995]

No. 222
MAb ID 17 (mAb17)
HXB2 Location Integrase (25–35)
Author Location Integrase (25–35)
Epitope `DFNLPPVVAKE`
Neutralizing no

B Cell

Immunogen vaccine
Vector/Type: protein *HIV component:* Int
Species (Isotype) mouse (IgG1)
References Yi *et al.* 2000; Levy-Mintz *et al.* 1996; Bizub-Bender *et al.* 1994

- 17: Epitope mapped to helix-turn-helix motif in the N-term domain of Integrase, positions 25-35 – Zn binding stabilizes the Integrase-mAb17 complex – both MAb and Fab form of mAb17 inhibit Integrase activity – epitope region likely to be involved in protein-protein interaction. Yi *et al.* [2000]
- 17: Used for the creation of single chain variable antibody fragments (SFvs) for internal cellular expression – neutralization of IN activity prior to integration, whether the Ab is expressed in the nucleolus or the cytoplasm – relative binding affinity to IN: 12 > 17 = 33 > 21 > 4. Levy-Mintz *et al.* [1996]
- 17: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized – the Zn finger motif is in the binding region – MAbs 14 and 17 form a competition group. Bizub-Bender *et al.* [1994]

No. 223
MAb ID 4D6
HXB2 Location Integrase (42–55)
Author Location Integrase (42–55 HXB2)
Epitope KCQLKGEAMHGQVD
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2 *HIV component:* Int
Species (Isotype) mouse (IgG1κ)
Ab Type N-term
References Kanduc *et al.* 2008; Nilsen *et al.* 1996; Haugan *et al.* 1995

- 4D6: Similarity level of the 4D6 binding site pentapeptide AMHGQ to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 4D6: This MAb inhibits end processing and DNA joining, and reduces reintegration activity. Nilsen *et al.* [1996]
- 4D6: MAb interferes with integrase binding to DNA. Haugan *et al.* [1995]

No. 224
MAb ID 7-16 (7-19)
HXB2 Location Integrase (50–159)
Author Location Integrase (50–159 HXB2)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: chimeric maltose binding protein (MBP) *Strain:* B clade IIIB *HIV component:* Int
Species (Isotype) mouse (IgG2b)
Ab Type Integrase catalytic core
Research Contact Yoshihiro Kitamura, Div of Mol Genetics, Nat Inst of Infectious Diseases, Musashimurayama, Japan
References Ishikawa *et al.* 1999

- 7-16: Binds to the central catalytic domain – the paper seems to sometimes call this antibody 7-16, sometimes 7-19, a possible typo. Ishikawa *et al.* [1999]

No. 225
MAb ID 4F6
HXB2 Location Integrase (56–102)
Author Location Integrase (56–102 HXB2)
Epitope CSPGIWQLDCTHLEGKVILVAVHVASGYIEAE-VIPAETGQETAYFLL
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2 *HIV component:* Int
Species (Isotype) mouse (IgG1κ)
Ab Type Integrase catalytic core
References Nilsen *et al.* 1996; Haugan *et al.* 1995

- 4F6: MAb binding had minimal effects on IN *in vitro* activities. Nilsen *et al.* [1996]
- 4F6: MAb interferes with integrase binding to DNA. Haugan *et al.* [1995]

No. 226
MAb ID anti-K159
HXB2 Location Integrase (151–163)
Author Location Integrase (163–175)
Epitope VESMNKELKKIIG
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* Int
Species (Isotype) rabbit (IgG)
References Maksiutov *et al.* 2002; Maroun *et al.* 1999

- anti-K159: This epitope is similar to a fragment of the human protein Apoptosis regulator BCL-W (KIAA0271), ESVNKEMEPLVGQV. Maksiutov *et al.* [2002]
- anti-K159: Both the peptide K159, SQGVVESMNKELKKIIGQVRDQAEHLKTA, and the Abs raised against this peptide inhibit Integrase activity – K159 was found to fulfill condition of minimal number of helical heptads to achieve the formation of a stable coiled-coil structure – Integrase is proposed to function as a dimer interacting in this region. Maroun *et al.* [1999]

No. 227
MAb ID 5D9
HXB2 Location Integrase (186–250)
Author Location Integrase (186–250 HXB2)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2 *HIV component:* Int
Species (Isotype) mouse (IgG1κ)
Ab Type Integrase DNA binding domain

References Nilsen *et al.* 1996; Haugan *et al.* 1995

- 5D9: MAb binding had minimal effects on IN *in vitro* activities. Nilsen *et al.* [1996]
- 5D9: While C-term and N-term anti-Integrase MAbs interfere with Integrase-DNA binding, 5D9 which binds more centrally, does not. Haugan *et al.* [1995]

No. 228
MAb ID 8-6
HXB2 Location Integrase (211–227)
Author Location Integrase (211–227 HXB2)
Epitope `KELQKQITKIQNFRVYY`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: chimeric maltose binding protein (MBP) *Strain:* B clade IIIB *HIV component:* Int
Species (Isotype) mouse (IgG1)
Research Contact Yoshihiro Kitamura, Div of Mol Genetics, Nat Inst of Infectious Diseases, Musashimurayama, Japan
References Kanduc *et al.* 2008; Ishikawa *et al.* 1999

- 8-6: Similarity level of the 8-6 binding site pentapeptide ITKIQ to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 8-6: Antibody binds proximal to the DNA binding region. Ishikawa *et al.* [1999]

No. 229
MAb ID 19 (2-19, scAb2-19)
HXB2 Location Integrase (228–236)
Author Location Integrase (228–236 LAI)
Epitope `RDSRNPLWK`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Int
Species (Isotype) mouse (IgG1)
References Kanduc *et al.* 2008; Kitamura *et al.* 1999; Levy-Mintz *et al.* 1996; Bizub-Bender *et al.* 1994

- 19: Similarity level of the 19 binding site pentapeptide RNPLW to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 19: Called 2-19, scAb2-19 is a single-chain Ab made from MAb 2-19 –acts intra-cellularly to block infection at low MOI by binding to integrase – scAb interfered with the folding of Gag-Pol polyprotein, the Ab did not affect viral production in LAI transfected cells, but the virus produced was less infectious – authors suggest that the epitope may be conformational. Kitamura *et al.* [1999]
- 19: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized – 19 has a low binding affinity. Bizub-Bender *et al.* [1994]

No. 230
MAb ID 2-19
HXB2 Location Integrase (228–236)
Author Location Integrase (228–236 HXB2)
Epitope `RDSRNPLWK`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: chimeric maltose binding protein (MBP) *Strain:* B clade IIIB *HIV component:* Int
Species (Isotype) mouse (IgG2b)
Ab Type Integrase DNA binding domain
Research Contact Yoshihiro Kitamura, Div of Mol Genetics, Nat Inst of Infectious Diseases, Musashimurayama, Japan
References Ishikawa *et al.* 1999

- 2-19: MAb inhibits RT-Integrase interaction, and the terminal cleavage and strand transfer functions of Integrase, but not the disintegration activity. Ishikawa *et al.* [1999]

No. 231
MAb ID 8-22
HXB2 Location Integrase (237–252)
Author Location Integrase (237–252 HXB2)
Epitope `GPAKLLWKGEGAVVIQ`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: chimeric maltose binding protein (MBP) *Strain:* B clade IIIB *HIV component:* Int
Species (Isotype) mouse (IgG1)
Ab Type Integrase DNA binding domain
Research Contact Yoshihiro Kitamura, Div of Mol Genetics, Nat Inst of Infectious Diseases, Musashimurayama, Japan
References Ishikawa *et al.* 1999

- 8-22: MAb inhibits the terminal cleavage and strand transfer functions of Integrase, but not the disintegration activity. Ishikawa *et al.* [1999]

No. 232
MAb ID 4-20
HXB2 Location Integrase (253–261)
Author Location Integrase (253–261 HXB2)
Epitope `DNSDIKVVP`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: chimeric maltose binding protein (MBP) *Strain:* B clade IIIB *HIV component:* Int
Species (Isotype) mouse (IgG1)
Ab Type Integrase DNA binding domain

B Cell

Research Contact Yoshihiro Kitamura, Div of Mol Genetics, Nat Inst of Infectious Diseases, Musashimurayama, Japan
References Ishikawa *et al.* 1999

- 4-20: Inhibits the terminal cleavage and strand transfer functions of Integrase, but not the disintegration activity. Ishikawa *et al.* [1999]

No. 233
MAb ID 6-19
HXB2 Location Integrase (262–270)
Author Location Integrase (261–270 HXB2)
Epitope `RRKAKIIRD`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: chimeric maltose binding protein (MBP) *Strain:* B clade IIIB *HIV component:* Int
Species (Isotype) mouse (IgG2b)
Ab Type Integrase DNA binding domain
Research Contact Yoshihiro Kitamura, Div of Mol Genetics, Nat Inst of Infectious Diseases, Musashimurayama, Japan
References Ishikawa *et al.* 1999

- 6-19: Inhibits the terminal cleavage and strand transfer functions of Integrase, but not the disintegration activity. Ishikawa *et al.* [1999]

No. 234
MAb ID 7C3
HXB2 Location Integrase (262–271)
Author Location Integrase (262–271 HXB2)
Epitope `RRKAKIIRDY`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2 *HIV component:* Int
Species (Isotype) mouse (IgG1κ)
References Nilsen *et al.* 1996; Haugan *et al.* 1995

- 7C3: A set of three MAbs recognize an epitope in this region, 7C3, 7F11, and 8E5 – all three HIV-1 MAbs cross-react with HIV-2 IN – these MAbs inhibit end-processing, DNA joining and reintegration, and had little effect on disintegration. Nilsen *et al.* [1996]
- 7C3: MAb interferes with integrase binding to DNA. Haugan *et al.* [1995]

No. 235
MAb ID 7F11
HXB2 Location Integrase (262–271)
Author Location Integrase (262–271 HXB2)
Epitope `RRKAKIIRDY`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2 *HIV component:* Int
Species (Isotype) mouse (IgG1κ)
References Lasky *et al.* 1987; Nilsen *et al.* 1996

- 7F11: A set of three MAbs recognize an epitope in this region, 7C3, 7F11, and 8E5 – all three HIV-1 MAbs cross-react with HIV-2 IN – these MAbs inhibit end-processing, DNA joining and reintegration, and had little effect on disintegration. Nilsen *et al.* [1996]
- 7F11: There is another MAb with this name that binds to gp120. Lasky *et al.* [1987]

No. 236
MAb ID 8E5
HXB2 Location Integrase (262–271)
Author Location Integrase (262–271 HXB2)
Epitope `RRKAKIIRDY`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2 *HIV component:* Int
Species (Isotype) mouse (IgG1κ)
References Nilsen *et al.* 1996; Haugan *et al.* 1995

- 8E5: A set of three MAbs recognize an epitope in this region, 7C3, 7F11, and 8E5 – all three HIV-1 MAbs cross-react with HIV-2 IN – these MAbs inhibit end-processing, DNA joining and reintegration, and had little effect on disintegration. Nilsen *et al.* [1996]
- 8E5: MAb interferes with integrase binding to DNA. Haugan *et al.* [1995]

No. 237
MAb ID MAb 35
HXB2 Location Integrase (264–273)
Author Location Integrase (264–273)
Epitope `KAKIIRDYGK`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Int
Species (Isotype) mouse (IgGκ)
References Kanduc *et al.* 2008; Acel *et al.* 1998; Barsov *et al.* 1996

- MAb 35: Similarity level of the MAb 35 binding site pentapeptide IRDYG to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- MAb 35: Integrase was shown to have intrinsic DNA polymerase activity that can catalyze gap repair – MAb 35 inhibits this activity. Acel *et al.* [1998]
- MAb 35: There appears to be two different IN Abs with similar names: MAb 35 and 35. Barsov *et al.* [1996]
- MAb 35: Although MAb 35 does not inhibit HIV-1 IN, Fab 35 inhibits 3'-end processing, strand transfer and disintegration. Barsov *et al.* [1996]

B Cell

IV-C-10 Pol Antibodies

No. 238
MAb ID 12
HXB2 Location Pol
Author Location Integrase (1–58)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Int
Species (Isotype) mouse (IgG2a)
References Levy-Mintz *et al.* 1996; Bizub-Bender *et al.* 1994

- 12: Used for the creation of single-chain variable antibody fragments (SFvs) for internal cellular expression – neutralization of IN activity prior to integration, whether the Ab is expressed in the nucleolus or the cytoplasm – relative binding affinity to IN: 12 > 17 = 33 > 21 > 4. Levy-Mintz *et al.* [1996]
- 12: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized – the Zn finger motif is in the binding region – MAbs 12, 13 and 35 form a competition group. Bizub-Bender *et al.* [1994]

No. 239
MAb ID 13
HXB2 Location Pol
Author Location Integrase (1–58)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Int
Species (Isotype) mouse (IgG1)
References Bizub-Bender *et al.* 1994

- 13: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized – the Zn finger motif is in the binding region – MAbs 12, 13 and 35 form a competition group. Bizub-Bender *et al.* [1994]

No. 240
MAb ID 14
HXB2 Location Pol
Author Location Integrase (1–58)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Int
Species (Isotype) mouse (IgG1)
References Bizub-Bender *et al.* 1994

- 14: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized – the Zn finger motif is in the binding region – MAbs 14 and 17 form a competition group. Bizub-Bender *et al.* [1994]

No. 241
MAb ID 16
HXB2 Location Pol
Author Location Integrase
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Int
Species (Isotype) mouse (IgG2a)
References Bizub-Bender *et al.* 1994

- 16: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized. Bizub-Bender *et al.* [1994]

No. 242
MAb ID 1C12B1
HXB2 Location Pol
Author Location RT (431–521)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* RT
Species (Isotype) mouse
References Ferns *et al.* 1991

- 1C12B1: UK Medical Research Council AIDS reagent: ARP384.
- 1C12B1: Recognized both p66 and p51 in Western blot, binds to C terminus. Ferns *et al.* [1991]

No. 243
MAb ID 21
HXB2 Location Pol
Author Location Integrase (58–141)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Int
Species (Isotype) mouse (IgG2b)
References Levy-Mintz *et al.* 1996; Bizub-Bender *et al.* 1994

- 21: Used for the creation of single chain variable antibody fragments (SFvs) for internal cellular expression – neutralization of IN activity prior to integration, whether the Ab is expressed in the nucleolus or the cytoplasm – relative binding affinity to IN: 12 > 17 = 33 > 21 > 4. Levy-Mintz *et al.* [1996]
- 21: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized. Bizub-Bender *et al.* [1994]

No. 244
MAb ID 32 (mAb32, Fab32)
HXB2 Location Pol
Author Location Integrase (223–266)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Int
Species (Isotype) mouse (IgG2b)
References Yi *et al.* 2002; Yi & Skalka 2000; Bizub-Bender *et al.* 1994

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- 32: Called mAb32 – mAb33 and mAb32 compete for binding to the C-term domain of Integrase – while mAb32 only weakly inhibits IN activity, mAb33 inhibits strongly, mAb32 has a lower affinity than mAb33, and Fab32 does not inhibit at all while Fab33 inhibits DNA binding a catalytic activity. Yi *et al.* [2002]
- 32: Limited proteolysis combined with mass spectrometric analysis indicates Fab32 binds to two strands of the beta sheet, beta1 223F, 224R, 226Y, and 228R and beta5 264K and 266K. Yi & Skalka [2000]
- 32: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized – MAbs 32 and 33 form a competition group. Bizub-Bender *et al.* [1994]

No. 245
MAb ID 35
HXB2 Location Pol
Author Location Integrase (1–58)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Int
Species (Isotype) mouse (IgG2b)
References Bizub-Bender *et al.* 1994

- 35: There appears to be two IN Abs with similar names: MAb 35 and 35. Bizub-Bender *et al.* [1994]
- 35: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized – the Zn finger motif is in the binding region – MAbs 12, 13 and 35 form a competition group. Bizub-Bender *et al.* [1994]

No. 246
MAb ID 3D12
HXB2 Location Pol
Author Location RT
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* RT
Species (Isotype) mouse (IgG2a)
References Chiba *et al.* 1997

- 3D12: There is an anti-Nef MAb that also has this name (see Chiba *et al.* [1997]) Chiba *et al.* [1997]

No. 247
MAb ID 3F10
HXB2 Location Pol
Author Location RT
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* RT
Species (Isotype) mouse (IgG2a)
References Chiba *et al.* 1997

No. 248
MAb ID 4
HXB2 Location Pol
Author Location Integrase (141–172)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Int
Species (Isotype) mouse (IgG2b)
References Levy-Mintz *et al.* 1996; Bizub-Bender *et al.* 1994

- 4: Used for the creation of single chain variable antibody fragments (SFvs) for internal cellular expression – neutralization of IN activity prior to integration, whether the Ab is expressed in the nucleolus or the cytoplasm – relative binding affinity to IN: 12 > 17 = 33 > 21 > 4. Levy-Mintz *et al.* [1996]
- 4: There is another MAb with this ID that reacts with gp41. Bizub-Bender *et al.* [1994]
- 4: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized – 4 has a low binding affinity. Bizub-Bender *et al.* [1994]

No. 249
MAb ID 5B11
HXB2 Location Pol
Author Location RT (BH-10)
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Research Contact Amon Hizi, Sackler School of Medicine, Tel Aviv, Isreal
References Herschhorn *et al.* 2003
Keywords antibody generation, antibody sequence variable domain, immunotherapy

- 5B11: One of five human single chain Fv (ScFv) Abs isolated from an phage display library. F-6 was shown to the carboxyl terminal segment of the p66 RT polypeptide, corresponding to RNase H. F-6 inhibited the DNA and RNA-dependent DNA polymerase (RDDP) activities of HIV-1 RT; two others, 6E9 and 5B11, inhibited RDDP and so have possible therapeutic potential. Herschhorn *et al.* [2003] (**antibody generation**, **immunotherapy**, **antibody sequence variable domain**)

No. 250
MAb ID 6B10
HXB2 Location Pol
Author Location RT (BH-10)
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Research Contact Amon Hizi, Sackler School of Medicine, Tel Aviv, Isreal
References Herschhorn *et al.* 2003
Keywords antibody generation, antibody sequence variable domain

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- 6B10:One of five human single chain Fv (ScFv) Abs isolated from an phage display library. F-6 was shown to the carboxyl terminal segment of the p66 RT polypeptide, corresponding to RNase H. F-6 inhibited the DNA and RNA-dependent DNA polymerase (DDDP and RDDP) activities of HIV-1 RT; two others, 6E9 and 5B11, inhibited RDDP and so have possible therapeutic potential. In contrast, 6B10 seemed to enhance DDDP activity and did not effect RDDP. Herschhorn *et al.* [2003] (**antibody generation**, **antibody sequence variable domain**)

No. 251
MAb ID 6B9
HXB2 Location Pol
Author Location RT
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* RT
Species (Isotype) mouse (IgG2a)
References Chiba *et al.* 1997

No. 252
MAb ID 6E9
HXB2 Location Pol
Author Location RT (BH-10)
Epitope
Subtype B
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human
Research Contact Amon Hizi, Sackler School of Medicine, Tel Aviv, Isreal
References Herschhorn *et al.* 2003
Keywords antibody generation, antibody sequence variable domain, immunotherapy

- 6E9: One of five human single chain Fv (ScFv) Abs isolated from an phage display library. F-6 was shown to the carboxyl terminal segment of the p66 RT polypeptide, corresponding to RNase H. F-6 inhibited the DNA and RNA-dependent DNA polymerase (RDDP) activities of HIV-1 RT; two others, 6E9 and 5B11, inhibited RDDP and so have possible therapeutic potential. Herschhorn *et al.* [2003] (**antibody generation**, **immunotherapy**, **antibody sequence variable domain**)

No. 253
MAb ID 7C4
HXB2 Location Pol
Author Location RT
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* RT
Species (Isotype) mouse (IgG1)
References Chiba *et al.* 1997

- 7C4: Dose-dependent inhibition of polymerase activity of RT of strains IIIB, Bru and IMS-1, but not HIV-2 strains GH-1 or LAV-2 or SIV strains MAC or MND. Chiba *et al.* [1997]

No. 254
MAb ID E-4
HXB2 Location Pol
Author Location RT (BH-10)
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Research Contact Amon Hizi, Sackler School of Medicine, Tel Aviv, Isreal
References Herschhorn *et al.* 2003
Keywords antibody generation, antibody sequence variable domain

- E-4:One of five human single chain Fv (ScFv) Abs isolated from an phage display library. F-6 was shown to the carboxyl terminal segment of the p66 RT polypeptide, corresponding to RNase H. F-6 inhibited the DNA and RNA-dependent DNA polymerase (RDDP) activities of HIV-1 RT; two others, 6E9 and 5B11, inhibited RDDP and so have possible therapeutic potential. In contrast, E-4 seemed to enhance RDDP. Herschhorn *et al.* [2003] (**antibody generation**, **antibody sequence variable domain**)

No. 255
MAb ID RT-4
HXB2 Location Pol
Author Location RT
Epitope
Neutralizing no
Immunogen
Species (Isotype) mouse (IgG2b)
References Gu *et al.* 1996; Li *et al.* 1993

- RT-4: Increased nevirapine and delavirdine inhibition, no effect on AZT inhibition. Gu *et al.* [1996]

No. 256
MAb ID RT7O
HXB2 Location Pol
Author Location RT (231–315)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* RT
Species (Isotype) mouse (IgG1)
Research Contact B. Ferns and R. Tedder
References Ferns *et al.* 1991

- RT7O: UK Medical Research Council AIDS reagent: ARP381.
- RT7O: Conformational epitope located centrally in the protein – inhibited RT enzyme activity and thus may bind close to the active site of the enzyme. Ferns *et al.* [1991]

No. 257
MAb ID RT7U
HXB2 Location Pol
Author Location RT (231–315)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* RT

B Cell

Species (Isotype) mouse
Research Contact B. Ferns and R. Tedder
References Ferns *et al.* 1991
- RT7U: UK Medical Research Council AIDS reagent: ARP380.
- RT7U: Has a conformational epitope – reacts with p66 and p51 in WB. Ferns *et al.* [1991]

No. 258
MAb ID anti-HIV-1 RT
HXB2 Location Pol
Author Location RT
Epitope
Neutralizing
Immunogen
Species (Isotype) mouse (IgG)
References Wainberg & Gu 1995; Maciejewski *et al.* 1995; di Marzo Veronese *et al.* 1986
- anti-HIV-1 RT: Cloned heavy and light chains to express Fab intracellularly, preventing HIV infection *in vitro* – this MAb was broadly cross-reactive with clinical strains and even HIV-2. Maciejewski *et al.* [1995]
- Commentary on Maciejewski *et al.* Wainberg & Gu [1995]

No. 259
MAb ID polyclonal
HXB2 Location Pol
Author Location p55
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *HIV component:* Gag, gp120, V3
Species (Isotype) macaque
References Wagner *et al.* 1998b
- A VLP is a non-infectious virus-like particle self-assembled from HIV Pr55 gag – macaques were immunized with VLPs bound to either gp120 or V3+CD4 linear domains – gag and env CTL specific CTL were stimulated in each case, and Ab response to gag and gp120 and was elicited, but the gp120 neutralizing response occurred only with whole gp120, not V3+CD4 – despite the CTL and Ab response, immunized macaques were infected by intervenous challenge with SHIV chimeric challenge stock. Wagner *et al.* [1998b]

No. 260
MAb ID polyclonal
HXB2 Location Pol
Author Location RT
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA *HIV component:* Env, Gag, Pol, Vif *Adjuvant:* B7, IL-12
Species (Isotype) mouse
References Kim *et al.* 1997b
- A gag/pol, vif or CMN160 DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules B7 and IL-12, gave a dramatic increase in both the cytotoxic and proliferative responses in mice, as well as Ab response detected by ELISA. Kim *et al.* [1997b]

No. 261
MAb ID polyclonal
HXB2 Location Pol
Author Location RT (203–219)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: Salmonella *HIV component:* RT
Species (Isotype) mouse (IgA)
References Burnett *et al.* 2000
- A live attenuated bacterial vaccine, Salmonella SL3261-pHART, with an inserted HIV RT gene fragment in the Lpp-OmpA-HIV fusion protein, induced a lymphoproliferative Th response and fecal RT-specific IgA in BALB/c mice. Burnett *et al.* [2000]

No. 262
MAb ID polyclonal
HXB2 Location Pol
Author Location Integrase
Epitope
Subtype multiple
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V3
References Barin *et al.* 2005
Keywords acute/early infection, assay development
- A combination of 4 antigenic regions was used to differentiate between early (<180 days) and chronic infection. These regions were: p24; the gp41 peptide spanning the immunodominant epitope (IDE) of gp41, RVAVERYLKDQQLLGIWGC-SGKICTTAV, and a subtype D version of this peptide; 5 V3 consensus peptides including A, B, C, D, and CRF01-AE; and Integrase. V3 and the IDE provide the best discrimination, with >20 fold higher levels in chronic infection when assayed by EIA using dried serum spots. Antibodies to Integrase and p24 were not as distinctive, and people tend to lose, not increase, responses to p24 over time. Integrase antibodies are among the last to appear after infection. This assay can be used to identify samples from early infection with high sensitivity and specificity. Barin *et al.* [2005] (**assay development**, **acute/early infection**)

No. 263
MAb ID 33 (mAb33, Fab33, 33D5, mab 33)
HXB2 Location Pol
Author Location Integrase (223–268 HXB2)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Int

B Cell

Species (Isotype) mouse (IgG2b)
Ab Type C-term
References Schreiber *et al.* 2005; Yi *et al.* 2002; Yi & Skalka 2000; Levy-Mintz *et al.* 1996; Bizub-Bender *et al.* 1994
Keywords antibody binding site definition and exposure, computational epitope prediction, mimotopes, structure

- 33: Called Fab33. A new computer program designed to recognize conformational epitopes in 3D structures that correspond to linear peptide mimotopes (3DEX) was tested using the known conformational epitope of this Fab. 223F, 224R, 226Y, 244K, 267I, and 268I, previously defined as the epitope from NMR structural studies (Yi2002) were confirmed, along with two additional amino acids, (A265 and K266). Schreiber *et al.* [2005] (**antibody binding site definition and exposure**, **mimotopes**, **computational epitope prediction**, **structure**)
- 33: Called mAb33 – mAb33 and mAb32 compete for binding to the C-term domain of Integrase – while mAb32 only weakly inhibits IN activity, mAb33 inhibits strongly, mAb32 has a lower affinity than mAb33, and Fab32 does not inhibit at all while Fab33 inhibits catalytic activity and DNA binding – heteronuclear NMR indicated eight residues of Integrase are immobilized upon Fab33 binding, two in the core of the protein, and 6 on the outer face that form a contiguous patch likely to contain the epitope – 223F, 224R, 226Y, 244K, 267I, and 268I, which may be a useful target for drug design – the Fab33-IN complex is far more soluble than IN alone and may be useful for crystallization. Yi *et al.* [2002] (**antibody binding site definition and exposure**)
- 33: Limited proteolysis combined with mass spectrometric analysis were used to define the binding site for Fab32, but Fab33 binding to the Intergrase C-term domain left it resistant to proteolytic digestion. Yi & Skalka [2000]
- 33: Used for the creation of single chain variable antibody fragments (SFvs) for internal cellular expression – neutralization of IN activity prior to integration, whether the Ab is expressed in the nucleolus or the cytoplasm – relative binding affinity to IN: 12 > 17 = 33 > 21 > 4. Levy-Mintz *et al.* [1996]
- 33: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized – MAbs 32 and 33 form a competition group. Bizub-Bender *et al.* [1994]

No. 264
MAb ID F-6
HXB2 Location Pol
Author Location RT (BH-10)
Epitope
Subtype B
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human
Ab Type C-term
Research Contact Amon Hizi, Sackler School of Medicine, Tel Aviv, Isreal
References Herschhorn *et al.* 2003
Keywords antibody generation, antibody sequence variable domain, immunotherapy

- F-6: One of five human single chain Fv (ScFv) Abs isolated from an phage display library. F-6 was shown to bind to the carboxyl terminal segment of the p66 RT polypeptide, corresponding to RNase H. F-6 inhibited the DNA and RNA-dependent DNA polymerase (RDDP) activities of HIV-1 RT; two others, 6E9 and 5B11, inhibited RDDP and so have possible therapeutic potential. To pinpoint the mechanism of inhibition, three peptides were synthesized corresponding to the CDR3 sequences of F-6, and a cyclic version of the CDR H3 region bound to purified RT and blocked RDDP. Herschhorn *et al.* [2003] (**antibody generation**, **immunotherapy**, **antibody sequence variable domain**)

No. 265
MAb ID 6B9
HXB2 Location Pol
Author Location RT (155–250)
Epitope
Neutralizing yes
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade HXB2 *HIV component:* RT
Species (Isotype) mouse (IgG)
Ab Type RT palm domain
References Ohba *et al.* 2001; Chiba *et al.* 1997; Chiba *et al.* 1996

- 6B9: In contrast to MAb 7C4, which binds to the thumb region of RT, 6B9 binds to the palm subdomain and does not inhibit RT activity. Chiba *et al.* [1996]

No. 266
MAb ID 5F
HXB2 Location Pol
Author Location RT (252–335)
Epitope
Neutralizing yes
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade HXB2 *HIV component:* RT
Species (Isotype) mouse
Ab Type RT thumb domain
References Ohba *et al.* 2001

- 5F: BALB/c mice were vaccinated with vaccinia carrying RT and a phage display library was produced and panned with RT – Fabs 5F and 5G were cloned, both recognizing an immunodominant neutralizing RT epitope in the region of the template primer-binding site in the thumb domain also recognized by MAb 7C4 – sequencing revealed the heavy chains and light chains of 7C4, 5G and 7C4 are related. Ohba *et al.* [2001]

No. 267
MAb ID 5G
HXB2 Location Pol
Author Location RT (252–335)
Epitope
Neutralizing yes
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade HXB2 *HIV component:* RT
Species (Isotype) mouse

B Cell

Ab Type RT thumb domain
References Ohba *et al.* 2001

- 5G: BALB/c mice were vaccinated with vaccinia carrying RT and a phage display library was produced and panned with RT – Fabs 5F and 5G were cloned, both recognizing an immunodominant neutralizing RT epitope in the region of the template primer-binding site in the thumb domain also recognized by MAb 7C4 – sequencing revealed the heavy chains and light chains of 7C4, 5G and 7C4 are related. Ohba *et al.* [2001]

No. 268
MAb ID 7C4
HXB2 Location Pol
Author Location RT (252–335)
Epitope
Neutralizing yes
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade HXB2 *HIV component:* RT
Species (Isotype) mouse (IgG2a)
Ab Type RT thumb domain
References Ohba *et al.* 2001; Chiba *et al.* 1997; Chiba *et al.* 1996

- 7C4: Fabs 5F and 5G both recognize the same immunodominant neutralizing RT epitope in the region of the template primer-binding site in the thumb domain recognized by MAb 7C4 – sequencing revealed the heavy chains and light chains of 7C4, 5G and 7C4 are related. Ohba *et al.* [2001]
- 7C4: 7C4 inhibits RT from HIV-1 strains IIIB, Bru, and IMS-1 but not HIV-2 strains GH-1 and LAV-2, SIV MAC, nor SIV MND. Chiba *et al.* [1997]
- 7C4: 7C4 was produced from a hybridoma cell line derived from a BALB/c mouse repeatedly immunized with RT in a vaccinia construct, and was found to inhibit RT through binding to the template primer-binding site, a possible target for RT inhibitors. Chiba *et al.* [1996]

IV-C-11 Vif Antibodies

No. 269
MAb ID TG002
HXB2 Location Vif (34–47)
Author Location Vif (34–47)
Epitope `KARGWFYRHHYESP?`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Vif
Species (Isotype) mouse
Research Contact Transgene
References Kanduc *et al.* 2008

- TG002: This MAb was raised in response to a rec Vif protein derived from E. coli.
- TG002: NIH AIDS Research and Reference Reagent Program: 2746.
- TG002: Similarity level of the TG002 binding site pentapeptide FYRHH to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]

No. 270
MAb ID TG001
HXB2 Location Vif (176–192)
Author Location Vif (176–192)
Epitope `KPQKTKGHRGSHTMNGH?`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Vif
Species (Isotype) mouse
Ab Type C-term
Research Contact Transgene
References Kanduc *et al.* 2008

- TG001: This antibody was raised in response to a rec Vif protein derived from E. coli.
- TG001: NIH AIDS Research and Reference Reagent Program: 2745.
- TG001: Similarity level of the TG001 binding site pentapeptide HTMNG to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 1 time, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]

No. 271
MAb ID J4
HXB2 Location Vif
Author Location (HXB2)
Epitope
Subtype B
Neutralizing
Immunogen
Species (Isotype) humanized rabbit
References Goncalves *et al.* 2002

- J4: The authors developed a Vif-specific intrabody single-chain FAb fragment of J4 called 14BL. When expressed intracellularly in the cytoplasm this intrabody efficiently bound Vif protein and neutralized its infectivity enhancing function. Intrabody-expressing transduced cells were highly refractory to challenge with the laboratory strain NL43 and with primary isolate strains of HIV-1. Goncalves *et al.* [2002]

No. 272
MAb ID polyclonal
HXB2 Location Vif
Author Location Vif
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA *HIV component:* Env, Gag, Pol, Vif *Adjuvant:* B7, IL-12
Species (Isotype) mouse
References Kim *et al.* 1997b

B Cell

- A gag/pol, vif or CMN160 DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules B7 and IL-12, gave a dramatic increase in both the cytotoxic and proliferative responses in mice, as well as an Ab response detected by ELISA. Kim *et al.* [1997b]

IV-C-12 Vpr Antibodies

No. 273
MAb ID polyclonal
HXB2 Location Vpr
Author Location Vpr (89.6)
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Richardson *et al.* 2003
Keywords rate of progression

- Serum samples were obtained from the French GRIV (genetic resistance to HIV) cohort and tested for anti-Tat and anti-Vpr responses, as both may contribute as extracellular proteins to pathogenesis. Serum anti-Vpr IgG responses were significantly higher in stable non-progressors (CD4+ T cell counts greater than 500 cell/ul after being positive for 8 years with no ART) and unstable non-progressors (declined during a 20 month follow up), than fast progressors (CD4+ T less than 300 cells/ul within 2 years of seroconversion, some HAART). Serum anti-Tat IgG was found to be significantly higher in stable non-progressors compared to unstable non-progressors and fast progressors indicating that higher levels of serum anti-Tat IgG are associated with maintenance of non-progression status. Richardson *et al.* [2003] (**rate of progression**)

IV-C-13 Tat Antibodies

No. 274
MAb ID polyclonal
HXB2 Location Tat (1–15)
Author Location Tat (1–15 89.6)
Epitope MEPVDRPLEPWKHPG
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6, B clade HXBc2 *HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (Isotype) macaque (IgG)
Ab Type C-term, N-term, Tat basic region
References Silvera *et al.* 2002
Keywords antibody binding site definition and exposure, vaccine antigen design

- Anti-Tat and Tat toxoid responses were raised in rhesus macaques using HxBc2 and 89.6P Tat, and Tat toxoids.High anti-Tat IgG responses were observed in all animals, and helper responses were detected in 8/16, and IFN gamma CTL in 11/16.. Ab and proliferative responses were observed, and the trucated 86 amino acid IIIB Tat was more immunogenic than the full 102 amino acid Tat. Tat vaccinated animals when challenged with SHIV89.6 were infected despite a robust immune response. The most consistent reactions to the vaccinations were to peptides in regions: N-term, 1-15 (MEPVDRPLEPWKHPG), basic domain 46-60 (SYGRKKRRQRRRAHQ), and 61-91, particularly C-term 76-90 (QPRGDPTGPKQKKK). Silvera *et al.* [2002] (**antibody binding site definition and exposure**, **vaccine antigen design**)

No. 275
MAb ID polyclonal
HXB2 Location Tat (1–20)
Author Location Tat (1–20 IIIB BH10)
Epitope MEPVDPRLEPWKHPGSQPKT?
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA), macrophage activating lipopeptide-2 (MALP-2)
Species (Isotype) mouse (IgA, IgG)
References Borsutzky *et al.* 2003
Keywords adjuvant comparison, genital and mucosal immunity, immunodominance, mucosal immunity, Th1, Th2, vaccine-induced epitopes

- Intranasal immunization of BALB/c mice Tat with MALP-2 induced stronger immune responses than i.p. vaccination of Tat with IFA. Also i.n. MALP-2 vaccination favored Th1 responses, while i.p IFA favored Th2. Ab, T help and CTL responses were observed. MALP-2 enhanced Tat-specific IgA responses in the lung and in the genital tract. Three linear Ab epitopes were recognized. The most frequent response (80% of vaginal lavage, 100% of sera and lung lavage) was to Tat peptide 1-20. The second strongest to Tat 46-60 (20% of vaginal lavage, 50% of lung lavage, 50% of sera). Finally, 50% of the sera of Tat+ IFA i.p. immunized mice recognized Tat 73-86. Borsutzky *et al.* [2003] (**adjuvant comparison**, **genital and mucosal immunity**, **vaccine-induced epitopes**, **immunodominance**, **mucosal immunity**, **Th1**, **Th2**)

No. 276
MAb ID TA9
HXB2 Location Tat (1–20)
Author Location Tat (1–20 Lai/Bru)
Epitope MEPVDPRLEPGSQPKT
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU *HIV component:* Tat *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse (IgG)
Ab Type N-term
Research Contact Dr. J.-L. Guesdon, Institut Pasteur, Paris
References Kanduc *et al.* 2008; Belliard *et al.* 2003
Keywords subtype comparisons

B Cell

- TA9: Similarity level of the TA9 binding site pentapeptide MEPVD to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 1 time, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- This is one of 5 anti-Tat murine monoclonal antibodies generated in this study. TA9 is clade B specific, and does not recognize Tat from clade A, C, D, or CRF01 (AE).TA9 binds to the Tat peptide aa 1-61 strongly, and is also able to bind to Tat aa 1-20, and Tat peptide aa 8-53. Belliard *et al.* [2003] (**subtype comparisons**)

No. 277
MAb ID TD84
HXB2 Location Tat (1–20)
Author Location Tat (1–20 Lai/Bru)
Epitope MEPVDPRLEPGSQPKT
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU *HIV component:* Tat *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse (IgG)
Ab Type N-term
Research Contact Dr. J.-L. Guesdon, Institut Pasteur, Paris
References Belliard *et al.* 2003
Keywords subtype comparisons

- This is one of 5 anti-Tat murine monoclonal antibodies generated in this study. TD84 is clade B specific, and does not recognize Tat from clade A, C, D, or CRF01 (AE). It reacts strongly with aa 1-61, and is able to react with aa 1-20. Belliard *et al.* [2003] (**subtype comparisons**)

No. 278
MAb ID TE135
HXB2 Location Tat (1–20)
Author Location Tat (1–20 Lai/Bru)
Epitope MEPVDPRLEPGSQPKT
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU *HIV component:* Tat *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse (IgG)
Ab Type N-term
Research Contact Dr. J.-L. Guesdon, Institut Pasteur, Paris
References Belliard *et al.* 2003
Keywords subtype comparisons

- This is one of 5 anti-Tat murine monoclonal antibodies generated in this study. TE135 is clade B specific, and does not recognize Tat from clade A, C, D, or CRF01 (AE). It reacts strongly with aa 1-61, and is able to react with aa 1-20. Belliard *et al.* [2003] (**subtype comparisons**)

No. 279
MAb ID polyclonal
HXB2 Location Tat (1–24)
Author Location Tat (1–24)
Epitope MEPVDPRLEPWKHPGSQPKTACTN
Neutralizing
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* Tat *Adjuvant:* Montanide (ISA 51)
Species (Isotype) human (IgG)
Ab Type N-term
References Noonan *et al.* 2003
Keywords immunotherapy, vaccine-specific epitope characteristics

- Intramuscular injection of Tat-toxoid induced high titers of anti-Tat reactivity in serum samples of six HIV-1 positive and of four HIV negative study subjects. Anti-Tat antibodies successfully blocked extracellular Tat from transactivating HIV Tat-sensitive promotors. The anti-Tat IgG response in sera from two healthy and HIV infected patients inhibited cell entry of synthetic Tat, thus blocking its functional activity. Additionally, the anti-Tat antibodies inhibited intercellular Tat transfer as demonstrated by a co-culture cell system. All HIV-1 infected patients had Ab responses to the N-term region of Tat, and 4/4 HIV-1 + and 5/6 HIV-1 negative patients responded to the basic domain. Several additional peptides were recognized either exclusively or more commonly in the HIV+ people. The N-terminus region of Tat mediates binding to CD26, that may be involved in modulation of chemokine function, and may also mediate T-cell apotosis. Noonan *et al.* [2003] (**vaccine-specific epitope characteristics**, **immunotherapy**)

No. 280
MAb ID NT3/2D1.1
HXB2 Location Tat (2–15)
Author Location Tat
Epitope EPVDPNLEPWNHPS
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* Tat
Species (Isotype) mouse (IgG1a)
Ab Type N-term
References Kanduc *et al.* 2008; Karasev *et al.* 2005; Dingwall *et al.* 1989
Keywords antibody binding site definition and exposure

- NT3/2D1.1: UK Medical Research Council AIDS reagent: ARP352.
- NT3/2D1.1: Similarity level of the NT3/2D1.1 binding site pentapeptide PWNHP to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- #4138 (NT3/2D1.1): Tat gene was cloned into a plant-based tobacco mosaic virus which was used to inoculate spinach plants. The produced Tat protein expression and its immunoreactivity was tested against six different Tat-specific MAbs, including #4138. The spinach-expressed Tat reacted against the #4138 MAb. Karasev *et al.* [2005] (**antibody binding site definition and exposure**)

B Cell

- NT3/2D1.1: Immunoprecipitates and immunoblots HIV-1 tat protein. Dingwall *et al.* [1989]

No. 281
MAb ID 1.2
HXB2 Location Tat (2–17)
Author Location Tat (1–16)
Epitope EPVDPRLEWKHPGSQ
Neutralizing
Immunogen
Species (Isotype) mouse
References Ranki *et al.* 1995; Ovod *et al.* 1992

- 1.2: Weak expression of Tat observed in HIV+ brain tissue sample, in contrast to Nef. Ranki *et al.* [1995]

No. 282
MAb ID 1D9D5
HXB2 Location Tat (2–21)
Author Location Tat
Epitope EPVDPRLEWKHPGSQPKTA
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Tat
Species (Isotype) mouse (IgG1)
Ab Type N-term
References Kanduc *et al.* 2008; Valvatne *et al.* 1996; Mhashilkar *et al.* 1995

- 1D9D5: Similarity level of the 1D9D5 binding site pentapeptide EWKHP to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 1D9D5: Exogenously delivered Tat can efficiently transactivate an HIV-LTR-CAT construct in HeLa cells in the presence of 1D9D5, suggesting when considered with the results of Mhashilkar *et al.* [1995], that free Tat and not Ab bound is taken up by cells Valvatne *et al.* [1996]. Mhashilkar *et al.* [1995]; Valvatne *et al.* [1996]
- 1D9D5: Single chain antibodies, intrabodies, were engineered that can be stably expressed in the cytoplasm of mammalian cells – co-expression of an N-term intrabody can inhibit transactivation of an HIV LTR-CAT construct and block import into nucleus, but intrabody specific for exon 2 did not inhibit activity. Mhashilkar *et al.* [1995]

No. 283
MAb ID polyclonal
HXB2 Location Tat (21–40)
Author Location Tat (21–40)
Epitope ACTNCYCKKCCFHCQVCFTT
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* Tat *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) mouse
Ab Type Tat Cys-rich domain
References Devadas *et al.* 2007
Keywords subtype comparisons, therapeutic vaccine, vaccine-specific epitope characteristics

- Immunization of mice with a multiple-peptide conjugate system consisting of modified Tat peptides (HIV-1-Tat-MPC) induced an effective immune response. The antibodies induced against HIV-1-Tat-MPC efficiently suppressed viral replication of HIV-1 clinical isolates of subtypes A, B and F but not C. Devadas *et al.* [2007] (**therapeutic vaccine**, **vaccine-specific epitope characteristics**, **subtype comparisons**)

No. 284
MAb ID TB12
HXB2 Location Tat (44–60)
Author Location Tat (44–61 Lai/Bru)
Epitope GISYGRKKRRQRRPPQG
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU *HIV component:* Tat *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse (IgG)
Ab Type Tat basic region
Research Contact Dr. J.-L. Guesdon, Institut Pasteur, Paris
References Belliard *et al.* 2003
Keywords subtype comparisons

- This is one of 5 anti-Tat murine monoclonal antibodies generated in this study. TB12 is clade B and D specific, and does not recognize Tat from clade A, C, or CRF01 (AE). It reacts strongly with aa 1-61, and is also able to react with aa 44-61, in the basic region involved in Tat uptake. Belliard *et al.* [2003] (**subtype comparisons**)

No. 285
MAb ID polyclonal
HXB2 Location Tat (46–60)
Author Location Tat (46–60 IIIB BH10)
Epitope SYGRKKRRQRRRAHQ?
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA), macrophage activating lipopeptide-2 (MALP-2)
Species (Isotype) mouse (IgA, IgG)
References Kanduc *et al.* 2008; Borsutzky *et al.* 2003
Keywords adjuvant comparison, genital and mucosal immunity, immunodominance, mucosal immunity, Th1, Th2, vaccine-induced epitopes

- Similarity level of the polyclonal Ab binding site pentapeptide SYGRK to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 1 time, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]

B Cell

- Intranasal immunization of BALB/c mice Tat with MALP-2 induced stronger immune responses than i.p. vaccination of Tat with IFA. Also i.n. MALP-2 vaccination favored Th1 responses, while i.p IFA favored Th2. Ab, T help and CTL responses were observed. MALP-2 enhanced Tat-specific IgA responses in the lung and in the genital tract. Three linear Ab epitopes were recognized. The most frequent response (80% of vaginal lavage, 100% of sera and lung lavage) was to Tat peptide 1-20. The second strongest to Tat 46-60 (20% of vaginal lavage, 50% of lung lavage, 50% of sera). Finally, 50% of the sera of Tat+ IFA i.p. immunized mice recognized Tat 73-86. Borsutzky *et al.* [2003] (**adjuvant comparison**, **genital and mucosal immunity**, **vaccine-induced epitopes**, **immunodominance**, **mucosal immunity**, **Th1**, **Th2**)

No. 286
MAb ID polyclonal
HXB2 Location Tat (46–60)
Author Location Tat (46–60 89.6)
Epitope SYGRKKRRQRRRAHQ
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6, B clade HXBc2 *HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (Isotype) macaque (IgG)
Ab Type C-term, N-term, Tat basic region
References Silvera *et al.* 2002
Keywords antibody binding site definition and exposure, vaccine antigen design

- Anti-Tat and Tat toxoid responses were raised in rhesus macaques using HxBc2 and 89.6P Tat, and Tat toxoids.High anti-Tat IgG responses were observed in all animals, and helper responses were detected in 8/16, and IFN gamma CTL in 11/16.. Ab and proliferative responses were observed, and the trucated 86 amino acid IIIB Tat was more immunogenic than the full 102 amino acid Tat. Tat vaccinated animals when challenged with SHIV89.6 were infected despite a robust immune response. The most consistent reactions to the vaccinations were to peptides in regions: N-term, 1-15 (MEPVDRPLEPWKHPG), basic domain 46-60 (SYGRKKRRQRRRAHQ), and 61-91, particularly C-term 76-90 (QPRGDPTGPKQKKK). Silvera *et al.* [2002] (**antibody binding site definition and exposure**, **vaccine antigen design**)

No. 287
MAb ID polyclonal
HXB2 Location Tat (46–60)
Author Location Tat (46–60 89.6)
Epitope SYGRKKRRQRRRAHQ
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6, B clade HXBc2 *HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (Isotype) macaque (IgG)
Ab Type C-term, N-term, Tat basic region
References Silvera *et al.* 2002
Keywords antibody binding site definition and exposure, vaccine antigen design

- Anti-Tat and Tat toxoid responses were raised in rhesus macaques using HxBc2 and 89.6P Tat, and Tat toxoids.High anti-Tat IgG responses were observed in all animals, and helper responses were detected in 8/16, and IFN gamma CTL in 11/16.. Ab and proliferative responses were observed, and the trucated 86 amino acid IIIB Tat was more immunogenic than the full 102 amino acid Tat. Tat vaccinated animals when challenged with SHIV89.6 were infected despite a robust immune response. The most consistent reactions to the vaccinations were to peptides in regions: N-term, 1-15 (MEPVDRPLEPWKHPG), basic domain 46-60 (SYGRKKRRQRRRAHQ), and 61-91, particularly C-term 76-90 (QPRGDPTGPKQKKK). Silvera *et al.* [2002] (**antibody binding site definition and exposure**, **vaccine antigen design**)

No. 288
MAb ID polyclonal
HXB2 Location Tat (47–60)
Author Location Tat (46–60)
Epitope YGRKKRRQRRRPPQ
Neutralizing
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* Tat *Adjuvant:* Montanide (ISA 51)
Species (Isotype) human (IgG)
Ab Type Tat basic region
References Noonan *et al.* 2003
Keywords immunotherapy, vaccine-specific epitope characteristics

- Intramuscular injection of Tat-toxoid induced high titers of anti-Tat reactivity in serum samples of six HIV-1 positive and of four HIV negative study subjects. Anti-Tat Abs successfully blocked extracellular Tat from transactivating HIV Tat-sensitive promotors. The anti-Tat IgG response in sera from two healthy and HIV infected patients inhibited cell entry of synthetic Tat, thus blocking its functional activity. Additionally, the anti-Tat Abs inhibited intercellular Tat transfer in a co-culture cell system. All HIV-1 infected patients had Ab responses to the N-term region of Tat, and 4/4 HIV-1 + and 5/6 HIV-1 negative patients responded to the basic domain. Several additional peptides were recognized either exclusively or more commonly in the HIV+ people. The basic region of Tat mediates binding to VEGFR2 on Kaposi's sarcoma cells and endothelial cells, and HIV patients with Kaposi's sarcoma lack Abs to this domain. Noonan *et al.* [2003] (**vaccine-specific epitope characteristics**, **immunotherapy**)

No. 289
MAb ID 1D2F11
HXB2 Location Tat (49–86)
Author Location Tat
Epitope RKKRRQRRRPPQGSQTHQVSLSKQPTSQSRGD-PTGPKE
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Tat
Species (Isotype) mouse (IgG1)

Ab Type C-term
References Valvatne *et al.* 1996

- 1D2F11: MAb did not bind shorter peptides – this MAb inhibited exogenously delivered Tat transactivation of an HIV-LTR-CAT construct in HeLa cells by inhibition of cellular uptake of Tat. Valvatne *et al.* [1996]

No. 290
MAb ID 2D9E7
HXB2 Location Tat (49–86)
Author Location Tat
Epitope RKKRRQRRRPPQGSQTHQVSLSKQPTSQSRGD-PTGPKE
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Tat
Species (Isotype) mouse (IgG1)
Ab Type C-term
References Valvatne *et al.* 1996

- 2D9E7: MAb did not bind shorter peptides – this MAb inhibited exogenously delivered Tat transactivation of an HIV-LTR-CAT construct in HeLa cells by inhibition of cellular uptake of Tat, but less efficiently than MAbs 1D2F11 or 4B4C4. Valvatne *et al.* [1996]

No. 291
MAb ID 4B4C4 (4B4)
HXB2 Location Tat (49–86)
Author Location Tat
Epitope RKKRRQRRRPPQGSQTHQVSLSKQPTSQSRGD-PTGPKE
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Tat
Species (Isotype) mouse (IgG1)
Ab Type C-term
References Jensen *et al.* 1997; Valvatne *et al.* 1996

- 4B4C4: MAb did not bind shorter peptides – this MAb inhibited exogenously delivered Tat transactivation of an HIV-LTR-CAT construct in HeLa cells by inhibition of cellular uptake of Tat. Valvatne *et al.* [1996]

No. 292
MAb ID 5G7D8
HXB2 Location Tat (49–86)
Author Location Tat
Epitope RKKRRQRRRPPQGSQTHQVSLSKQPTSQSRGD-PTGPKE
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Tat
Species (Isotype) mouse (IgG1)
Ab Type C-term
References Valvatne *et al.* 1996

- 5G7D8: MAb did not bind shorter peptides – this MAb inhibited exogenously delivered Tat transactivation of an HIV-LTR-CAT construct in HeLa cells by inhibition of cellular uptake of Tat, but less efficiently than 1D2F11 or 4B4C4. Valvatne *et al.* [1996]

No. 293
MAb ID polyclonal
HXB2 Location Tat (53–68)
Author Location Tat (53–68)
Epitope RQRRRAHQNSQTHQAS
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* Tat *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) mouse
Ab Type Tat basic region
References Devadas *et al.* 2007
Keywords antibody generation, subtype comparisons, therapeutic vaccine

- Immunization of mice with a multiple-peptide conjugate system consisting of modified Tat peptides (HIV-1-Tat-MPC) induced an effective immune response. The antibodies induced against HIV-1-Tat-MPC efficiently suppressed viral replication of HIV-1 clinical isolates of subtypes A, B and F but not C. Devadas *et al.* [2007] (**antibody generation**, **therapeutic vaccine**, **subtype comparisons**)

No. 294
MAb ID polyclonal
HXB2 Location Tat (73–86)
Author Location Tat (73–86 IIIB BH10)
Epitope PTSQPRGDPTGPKE?
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA), macrophage activating lipopeptide-2 (MALP-2)
Species (Isotype) mouse (IgA, IgG)
References Borsutzky *et al.* 2003
Keywords adjuvant comparison, genital and mucosal immunity, immunodominance, mucosal immunity, Th1, Th2, vaccine-induced epitopes

- Intranasal immunization of BALB/c mice Tat with MALP-2 induced stronger immune responses than i.p. vaccination of Tat with IFA. Also i.n. MALP-2 vaccination favored Th1 responses, while i.p IFA favored Th2. Ab, T help and CTL responses were observed. MALP-2 enhanced Tat-specific IgA responses in the lung and in the genital tract. Three linear Ab epitopes were recognized. The most frequent response (80% of vaginal lavage, 100% of sera and lung lavage) was to Tat peptide 1-20. The second strongest to Tat 46-60 (20% of vaginal lavage, 50% of lung lavage, 50% of sera). Finally, 50% of the sera of Tat+ IFA i.p. immunized mice recognized Tat 73-86. Borsutzky *et al.* [2003] (**adjuvant comparison**, **genital and mucosal immunity**, **vaccine-induced epitopes**, **immunodominance**, **mucosal immunity**, **Th1**, **Th2**)

No. 295
MAb ID NT2/4D5.24
HXB2 Location Tat (73–86)
Author Location Tat

B Cell

Epitope PTSQPRGDPTGPKE
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* Tat
Species (Isotype) mouse
Ab Type C-term
References Dingwall *et al.* 1989

- NT2/4D5.24: Immunoprecipitates and immunoblots HIV-1 tat protein. Dingwall *et al.* [1989]

No. 296
MAb ID polyclonal
HXB2 Location Tat (76–89)
Author Location Tat (76–90 89.6)
Epitope QPRGDPTGPKQKKK
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6, B clade HXBc2 *HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (Isotype) macaque (IgG)
Ab Type C-term, N-term, Tat basic region
References Silvera *et al.* 2002
Keywords antibody binding site definition and exposure, vaccine antigen design

- Anti-Tat and Tat toxoid responses were raised in rhesus macaques using HxBc2 and 89.6P Tat, and Tat toxoids.High anti-Tat IgG responses were observed in all animals, and helper responses were detected in 8/16, and IFN gamma CTL in 11/16.. Ab and proliferative responses were observed, and the trucated 86 amino acid IIIB Tat was more immunogenic than the full 102 amino acid Tat. Tat vaccinated animals when challenged with SHIV89.6 were infected despite a robust immune response. The most consistent reactions to the vaccinations were to peptides in regions: N-term, 1-15 (MEPVDRPLEPWKHPG), basic domain 46-60 (SYGRKKRRQRRRAHQ), and 61-91, particularly C-term 76-90 (QPRGDPTGPKQKKK). Silvera *et al.* [2002] (**antibody binding site definition and exposure**, **vaccine antigen design**)

No. 297
MAb ID
HXB2 Location Tat
Author Location Tat
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA), Montanide (ISA 51)
Species (Isotype) human
References Gringeri *et al.* 1998
Keywords immunotherapy

- 14 HIV-1 infected individuals were vaccinated with inactivated Tat (called Tat-toxoid), with the intent of enhancing Tat Ab levels to suppress the negative impact of secreted Tat on immune function. Tat vaccinations were safe and patients developed increased levels of Tat-specific Abs; some patients had increased Tat-specific proliferative responses. CD4 T cells tended to increase a small but significant amount after immunization, and in several patients viral load decreased. Gringeri *et al.* [1998] (**immunotherapy**)

No. 298
MAb ID 15.1
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Dr. Jonathan Karn, AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH
References Karasev *et al.* 2005
Keywords antibody binding site definition and exposure

- 15.1: Tat gene was cloned into a plant-based tobacco mosaic virus which was used to inoculate spinach plants. The produced Tat protein expression and its immunoreactivity was tested against six different Tat-specific MAbs, including 15.1. The spinach-expressed Tat had moderate reactivity against 15.1 MAb. Karasev *et al.* [2005] (**antibody binding site definition and exposure**)

No. 299
MAb ID 4A4.8 (NT7 4A4.8)
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Dr. Jonathan Karn, AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH
References Karasev *et al.* 2005
Keywords antibody binding site definition and exposure

- NT7 4A4.8: Tat gene was cloned into a plant-based tobacco mosaic virus which was used to inoculate spinach plants. The produced Tat protein expression and its immunoreactivity was tested against six different Tat-specific MAbs, including NT7 4A4.8. The spinach-expressed Tat had moderate reactivity against the NT7 4A4.8 MAb. Karasev *et al.* [2005] (**antibody binding site definition and exposure**)

No. 300
MAb ID 7D5.1 (NT7 7D5.1)
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen
Species (Isotype) mouse (IgG1)

Research Contact Dr. Jonathan Karn, AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH
References Karasev *et al.* 2005
Keywords antibody binding site definition and exposure

- NT7 7D5.1: Tat gene was cloned into a plant-based tobacco mosaic virus which was used to inoculate spinach plants. The produced Tat protein expression and its immunoreactivity was tested against six different Tat-specific MAbs, including NT7 7D5.1. The spinach-expressed Tat did not react against the NT7 7D5.1 MAb. Karasev *et al.* [2005] (**antibody binding site definition and exposure**)

No. 301
MAb ID 7E5
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Theisen *et al.* 2006
Keywords antibody interactions, binding affinity

- 7E5: This mouse alpha-RT mAb was used as negative control in the binding activity assay and did not bind to Tat. Theisen *et al.* [2006] (**antibody interactions**, **binding affinity**)

No. 302
MAb ID 8D1.8 (NT8 8D1.8)
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen
Species (Isotype) mouse (IgG1κ)
Research Contact Dr. Jonathan Karn, AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH
References Ramírez *et al.* 2007; Karasev *et al.* 2005
Keywords antibody binding site definition and exposure

- 8D1.8: Tat antigen was successfully expressed in tomatoes. The plant-expressed protein was able to bind to 8D1.8, indicating that its native immunologic properties were retained. Ramírez *et al.* [2007]
- NT8 8D1.8: Tat gene was cloned into a plant-based tobacco mosaic virus which was used to inoculate spinach plants. The produced Tat protein expression and its immunoreactivity was tested against six different Tat-specific MAbs, including NT8 8D1.8. The spinach-expressed Tat reacted against the NT8 8D1.8 MAb. Karasev *et al.* [2005] (**antibody binding site definition and exposure**)

No. 303
MAb ID ABI#161
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact ABI (Columbia MD)
References Karasev *et al.* 2005
Keywords antibody binding site definition and exposure

- 161: Tat gene was cloned into a plant-based tobacco mosaic virus which was used to inoculate spinach plants. The produced Tat protein expression and its immunoreactivity was tested against six different Tat-specific MAbs, including 161. The spinach-expressed Tat showed reactivity against the 161 MAb. Karasev *et al.* [2005] (**antibody binding site definition and exposure**)

No. 304
MAb ID L-anti-Tat
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing L P (when lipidated)
Immunogen vaccine
Vector/Type: protein *HIV component:* Tat
Species (Isotype) mouse (IgG1)
Research Contact AGMED, Inc., Bedford, MA USA
References Cruikshank *et al.* 1997

- L-anti-Tat: Lipidated antibody can be taken up by cells and effectively block IIIB and primary virus HIV-1 replication in actively and latently infected cells. Cruikshank *et al.* [1997]

No. 305
MAb ID Tat1
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen
Species (Isotype) human (IgG1)
References Mancini *et al.* 2006
Keywords autoantibody, binding affinity

- Tat1: This natural Ab was cloned an characterized from an HIV-1 seronegative patient. It was a polyreactive Ab of IgG1 isotype. The clone showed a pattern of mutations suggesting antigen-driven mechanisms of selection. Its heavy chain was derived from a V-gene subfamily highly represented in fetal life. Antibodies belonging to this class are also frequently described as autoantibodies. The heavy chain of the Ab exhibited an unusual and extremely long hydrophilic CDR3 and was mainly responsible for the Ab polyreactivity. Mancini *et al.* [2006] (**autoantibody**, **binding affinity**)

No. 306
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat
Epitope
Subtype A, B, C, CRF01_AE, D
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Belliard *et al.* 2003
Keywords rate of progression, subtype comparisons

B Cell

- Sera from 20 HIV-1 positive individuals were tested for their ability to react with Tat proteins from different clades, and were found to react with subtype A, B, and D, but not with subtype C or CRF01 (AE). Sera from 101 slow progressors and 42 fast progressors were tested for responses to Tat peptides, and compared to responses to gp41 peptide, as anti-Tat antibodies have been shown by others to be elevated in slow progressors. In this study, overall levels of Tat antibodies were not different in the two groups, however relative levels of antibodies to different Tat and gp41 peptides were observed. Belliard *et al.* [2003] (**subtype comparisons**, **rate of progression**)

No. 307
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing yes
Immunogen vaccine
Vector/Type: protein *HIV component:* Tat *Adjuvant:* Complete Freund's Adjuvant (CFA), red blood cells
Species (Isotype) mouse (IgG1, IgG2a, IgG3)
References Dominici *et al.* 2003
Keywords adjuvant comparison, immunotherapy, Th1, Th2

- BALB/c mice were immunized intra-peritineally with Tat protein bound to red blood cells via biotin-avidin conjugation. This antigen delivery system was successfully internalized by dendritic cells, and induced more consistent anti-Tat NAbs responses and sightly increased Tat-specific CTL responses relative to Tat protein with CFA. RBC-Tat immunization induced Th1 (IgG2a)and Th2 (IgG1 and IgG3)type immune responses. Dominici *et al.* [2003] (**adjuvant comparison**, **immunotherapy**, **Th1**, **Th2**)

No. 308
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: chitosan nanoparticles *HIV component:* Tat *Adjuvant:* adjuvant oily structure (IMS)
Species (Isotype) mouse (IgA, IgG)
References Le Buanec *et al.* 2001
Keywords adjuvant comparison, mucosal immunity

- Mice were immunized with Tat toxoid (Tat detoxified by carboxamidation) either intranasally or orally using either adjuvant oily structure (IMS), nanoparticles of chitosan, or microparticles of polylactide-co-glycolide. Each of these strategies triggered IgG and IgA that inhibited Tat activity. Le Buanec *et al.* [2001] (**adjuvant comparison**, **mucosal immunity**)

No. 309
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat (IIIB)
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* Tat *Adjuvant:* Cholera toxin (CT), E. coli mutant heat labile enterotoxin (LT-R72), E. coli heat labile enterotoxin
Species (Isotype) mouse (IgG)
References Marinaro *et al.* 2003
Keywords adjuvant comparison, mucosal immunity

- Intranasal immunization of BALB/c mice with Tat and e.coli heat-labile enterotoxin (LT) and non-toxic LT-R72 LT induced strong antigen-specific IgG Abs which remained stable for one year. Tat-specific IgA reponses were measured in vaginal and intestinal secretions. Immunization of BALB/c mice with native Tat (aa1-86) induced serum IgG directed against an immunodominant epitope (aa1-20) and against a second epitope (aa 46-60). CTL responses were also observed. Anti-Tat serum Abs neutralized Tat activity in a dose-independent manner. C57BL/6 remained unresponsive to Tat immunizations when Tat was co-adminstered with LT or cholera toxin (CT) as adjuvant; BALB/c mice are H-2d, C57BL/6 are H-2b. Congenic BALB.C mice that express H-2b rather than H-2d also could not respond to Tat, suggesting the repsonse to Tat is constrained by the haplotype. Marinaro *et al.* [2003] (**adjuvant comparison**, **mucosal immunity**)

No. 310
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein, vaccinia *Strain:* B clade MN *HIV component:* gp160, Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA), polyphosphazene
Species (Isotype) macaque (IgG)
References Pauza *et al.* 2000

- 16 Macaques mulatta were immunized with Tat toxoid, or with Tat plus gp160, and challenged with the SHIV 89.6PD isolate. Sera from 14/16 animals neutralized Tat *in vitro*. 8 macaques developed both cellular and humoral responses to Tat, and 7/8 of these had low viral set points after rectal challenge with SHIV89.6PD. CD4+ T cells in Tat vaccinated infected animals had lower IFN-alpha and chemokine receptor expression, features of infection associated with extracellular Tat. Pauza *et al.* [2000]

No. 311
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat
Epitope
Subtype B
Neutralizing

B Cell

Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120, Nef, Tat *Adjuvant:* AS02A (oil-in-water emulsion, 3D-monophosphoryl lipid A, QS21), AS06 (CpG, aluminum hydroxide)
Species (Isotype) macaque (IgG)
References Voss *et al.* 2003
Keywords adjuvant comparison, variant cross-recognition or cross-neutralization

- Monkeys were immunized with different combinations of gp120/NefTat/SIV-Tat three times over a three-month time period and intravenously challenged with SHIV 89.6P four weeks after the last immunzation. Vaccination induced anti-Tat, -Nef and -gp120 Ab responses that decreased until challenge. Neutralizing Ab responses against HIV-1 MN and HIV-1 W61D were observed. Vaccination with the combination of all three proteins reduced viral load and kept animals from a CD4+ T cell decline, preventing AIDS for more than 2.5 years. The adjuvant AS02A elicited NAbs and protected from disease, while AS06 did not. gp120 alone or TatNef/SIV-Tat without gp120 could not protect from disease. Voss *et al.* [2003] (**adjuvant comparison**, **variant cross-recognition or cross-neutralization**)

No. 312
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Zagury *et al.* 1998
Keywords immunotherapy, rate of progression

- Comparing 67 fast progressors with 182 non-progressors in the GRIV cohort, only anti-Tat Ab levels, not Abs to Env, Gag, or Nef, were correlated as a serological indicator of rate of progression. This suggests that raising Tat Abs may be beneficial as immunotherapy or in a vaccine. Zagury *et al.* [1998] (**immunotherapy**, **rate of progression**)

No. 313
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: Other *HIV component:* Tat *Adjuvant:* Other
Species (Isotype) mouse (IgG, IgG1, IgG2a, IgG2b)
Ab Type Tat basic region
References Mascarell *et al.* 2005
Keywords antibody binding site definition and exposure, dendritic cells, neutralization, Th1, Th2, vaccine antigen design, vaccine-induced epitopes

- Immunization of mice with recombinant adenylate cyclase molecule carrying HIV-1 Tat (CyaA-E5-Tat) without adjuvant generated strong anti-Tat humoral responses that exhibited potent Tat neutralizing capacities. Sera from these mice were shown to recognize Tat peptides containing amino acids 1 to 20 and 46 to 65. The IgG1/IgG2a ratio observed in these sera was consistent with a Th1 polarization. In contrast, immunization of mice with Tat toxoid in presence or absence of alum adjuvant failed to induce responses comparable to those in CyaA-E5-Tat immunized animals. Sera from Tat toxoid immunized mice recognized Tat peptide containing amino acids 73 to 86 and showed prevalence of IgG1 indicating Th2 polarization. Insertion of Tat into CyaA did not modify the function of CyaA, the inserted Tat protein had no transactivating activity, and the complex was not toxic to bone-marrow derived dendritic cells. Mascarell *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **vaccine-induced epitopes**, **Th1**, **Th2**, **dendritic cells**)

No. 314
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Tat *Adjuvant:* Other, poly(I:C)
Species (Isotype) mouse (IgA, IgG)
References Partidos *et al.* 2005
Keywords mucosal immunity, neutralization, Th1, Th2, vaccine antigen design

- dsRNA motifs poly(A):poly(U) and poly(I):poly(C) were used as adjuvants in immunizations of mice with Tat protein. Both dsRNA motifs enhanced serum and mucosal Ab responses, which were comparable to those elicited in the presence of CT adjuvant. Anti-Tat IgG Abs from both Pi:pC and pA:pU mice sera showed strong reactivity with Tat peptides 1-20 and 44-61, but only sera from mice immunized with Tat+pI:pC inhibited Tat-driven transactivation. Neutralization was detectable only at low dilutions of sera. Partidos *et al.* [2005] (**neutralization**, **vaccine antigen design**, **mucosal immunity**, **Th1**, **Th2**)

No. 315
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA, Other *Strain:* B clade MN *HIV component:* Tat
Species (Isotype) mouse
References Karasev *et al.* 2005
Keywords vaccine antigen design

- Tat gene was cloned into a plant-based tobacco mosaic virus which was used to inoculate spinach plants. The protein was successfully expressed in spinach plants which were fed to mice. Sera from spinach-fed mice showed no detectable induction of Tat-specific Abs. The mice were subsequently immunized with plasmid Tat-DNA. Mice that were fed Tat-producing spinach showed increased levels of Tat-specific Abs compared to mice fed non-Tat-producing spinach, indicating that orally delivered Tat can prime mice for DNA immunization. Karasev *et al.* [2005] (**vaccine antigen design**)

No. 316
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* Tat *Adjuvant:* Montanide (ISA 720)
Species (Isotype) macaque (IgG)
References Belliard *et al.* 2005
Keywords vaccine antigen design, variant cross-recognition or cross-neutralization

- Seven of eight macaques immunized with a pool of tat peptides, encompassing residues 1-20, 1-61, and 44-61, developed significant cross-reactive Ab responses and elevated titers of IgG reacting with the three peptides. The serum from two macaques that showed highest reactivity with Tat also strongly inhibited Tat transactivation. When challenged with a partially heterologous SHIV BX08, only one of seven macaques was found to control infection. Belliard *et al.* [2005] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 317
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Tat *Adjuvant:* aluminum hydroxide
Species (Isotype) african green monkey (IgG)
References Mascarell *et al.* 2006
Keywords antibody binding site definition and exposure, binding affinity, early-expressed proteins, kinetics, vaccine antigen design

- African Green Monkeys were immunized with adenylate cyclase (CyaA) carrying HIV-Tat (CyaA-E5-Tat) in presence or absence of alum. Both were shown to induce production of anti-Tat Abs that mainly recognized the N-terminal domain of Tat protein. All sera from immunized animals displayed the capacity to bind to Tat and neutralize its function in vitro. It is also suggested that a high rate of association of the Abs with immobilized Tat might be associated with their Tat neutralizing capacity. Mascarell *et al.* [2006] (**antibody binding site definition and exposure**, **vaccine antigen design**, **kinetics**, **binding affinity**, **early-expressed proteins**)

No. 318
MAb ID polyclonal
HXB2 Location Tat
Author Location
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: nanoparticle *Strain:* B clade consensus *HIV component:* Tat *Adjuvant:* aluminum hydroxide, Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) mouse (IgG, IgG1, IgG2a)
References Patel *et al.* 2006
Keywords adjuvant comparison, antibody binding site definition and exposure, early-expressed proteins, neutralization, Th1, Th2

- Tat coated on nanoparticles (NP) was shown to induce greater Tat-specific Ab titers at lower doses of Tat compared to alum adjuvant in immunized mice. Significantly lower tat-specific IgG2a titers were produced with alum compared to NP. Tat-coated NPs generated Abs that recognized both the N-terminal and basic regions of the protein and showed superior Tat neutralization activity over other forms of delivery. Patel *et al.* [2006] (**adjuvant comparison**, **antibody binding site definition and exposure**, **neutralization**, **Th1**, **Th2**, **early-expressed proteins**)

No. 319
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen HIV-2 infection
Species (Isotype) human (IgG)
References Rodriguez *et al.* 2006
Keywords HIV-2, rate of progression

- 68% of the HIV-2 infected subjects studied here were shown positive for anti-Tat Abs. The Ab response was shown to be established early after seroconversion and maintained over the course of HIV-2 infection. Subjects who progressed to HIV-2 AIDS had significantly lower anti-Tat IgG levles than those who did not, indicating a correlation between the rate of disease progression and anti-Tat Ab status. Rodriguez *et al.* [2006] (**HIV-2**, **rate of progression**)

No. 320
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Tat
Species (Isotype) mouse (IgG1)
References Lecoq *et al.* 2008
Keywords neutralization, vaccine antigen design

- Tat complexed with a low-molecular-weight heparin fragment (Hep6000) had altered cell-binding capacity and transactivating activity, and was less susceptible to proteolysis. Mice immunized with Tat-Hep6000 complex had an anti-Tat Ab response that was 10- and 100- fold higher than mice immunized with Tat alone or with a Tat toxoid, respectively. The Ab responses were predominantly of IgG1 isotype. Sera from mice immunized with Tat-Hep6000 neutralized the transactivating activity of Tat more efficiently than sera from mice immunized with Tat only. Both sera bound mainly to the N-terminal region of the protein, indicating that formation of the complex does not alter the B-cell immunodominant region. These results indicate that the immunogenic properties of Tat can be increased by a ligand-stabilizing strategy. Lecoq *et al.* [2008] (**neutralization**, **vaccine antigen design**)

No. 321
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Tat
Species (Isotype) mouse (IgA, IgG)
References Ramírez *et al.* 2007
Keywords genital and mucosal immunity, neutralization, vaccine antigen design

- Tat antigen was successfully expressed in tomatoes while it retained the immunological properties of native Tat. Mice immunized with tomato-derived Tat, either intraperitoneally, intramuscularly, or orally, developed a strong anti-Tat response which increased over time. Oral immunizations induced IgG and IgA responses, the latter found in the gut and genital tract, indicating that oral immunizations with tomato-derived Tat can elicit both systemic and mucosal immunity. The anti-Tat Abs elicited upon immunization were able to neutralize the activity of extracellular Tat. Ramírez *et al.* [2007] (**genital and mucosal immunity**, **neutralization**, **vaccine antigen design**)

No. 322
MAb ID scFvtat1
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Theisen *et al.* 2006
Keywords antibody interactions

- scFvtat1: Single chain anti-Tat Ab scFvtat1 was fused to the protein transduction domain (PTD) of Tat that mediates nuclear localization. It was shown that the PTD targets the scFvtat1 Ab directly to the site of Tat action inside the nucleus, where the PTD competes with Tat binding to TAR and the scFvtat1 simultaneously binds to Tat interfering with its interactions with cyclinT. The PTD-scFvtat1 fusion complex potentially inhibits Tat-mediated transactivation both when expressed inracellularly or when added as purified protein but that it does not inhibit HIV-1 Tat translocation to the nucleus, suggesting that Tat traffic can only marginally be affected by anti-Tat Abs. Theisen *et al.* [2006] (**antibody interactions**)

No. 323
MAb ID 2D9D5
HXB2 Location Tat
Author Location Tat
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Tat
Species (Isotype) mouse (IgG)
Ab Type C-term
References Mhashilkar *et al.* 1995

- 2D9D5: Single chain antibodies, intrabodies, were engineered that can be stably expressed in the cytoplasm of mammalian cells – co-expression of C-term intrabody did not inhibit transactivation of an HIV LTR-CAT construct, in contrast to MAb 1D9D5. Mhashilkar *et al.* [1995]

No. 324
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat (IIIB, 89.6, CMU08)
Epitope
Subtype B, CRF01_AE
Neutralizing
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* Tat
Species (Isotype) human (IgG)
Ab Type C-term, N-term, Tat basic region
References Richardson *et al.* 2003
Keywords antibody binding site definition and exposure, rate of progression, subtype comparisons, vaccine-specific epitope characteristics

- Serum samples were obtained from the French GRIV (genetic resistance to HIV) cohort and tested for anti-Tat and anti-Vpr responses as both may contribute as extracellular proteins to pathogenesis. Serum anti-Tat IgG responses were significantly higher and maintained for up to 20 months in stable non-progressors (CD4+ T cell counts greater than 500 cell/ul after being positive for 8 years with no ART) compared to unstable non-progressors and fast progressors (CD4+ T less than 300 cells/ul within 2 years of seroconversion, some HAART). Anti-Tat IgG from GRIV stable non-progressors recognized linear epitopes located within the N-terminal, basic and the C-terminal domains of Tat. Humoral responses of fast-progressors and of one unstable non-progressor were restricted to the basic region of Tat. Tat toxoid vaccinees from Milan tended to recognize N-terminal and C-terminal domains. Sera from some GRIV and Tat toxoid vaccinees cross-reacted in an ELISA assay with a truncated 89.6 S/HIV 89.6P Tat, 89.6P Tat, HIv-1 subtype E (CMU08) and with SIVmac251 Tat (one sample). Richardson *et al.* [2003] (**antibody binding site definition and exposure**, **vaccine-specific epitope characteristics**, **subtype comparisons**, **rate of progression**)

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MAb ID polyclonal
HXB2 Location Tat
Author Location Tat
Epitope
Subtype B, CRF01_AE
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6, B clade IIIB *HIV component:* Tat
Species (Isotype) macaque (IgG)
Ab Type C-term, N-term, Tat basic region
References Richardson *et al.* 2002
Keywords antibody binding site definition and exposure, vaccine antigen design, variant cross-recognition or cross-neutralization

- Anti-Tat responses were raised in rhesus macaques using IIIB Tat, SHIV89.6P Tat, carboxymethylated Tat and 89.6P Tat toxoids. Tat IgG responses to the vaccine were cross-reactive with subtype E and MAC 251. Ab and proliferative responses were observed, and the trucated 86 amino acid IIIB Tat was more immunogenic than the full 102 amino acid Tat. Tat vaccinated animals when challenged with SHIV89.6 were infected despite a robust immune response and were not distinguishable from controls. Richardson *et al.* [2002] (**antibody binding site definition and exposure**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 326
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat (IIIB, 89.6, CMU08)
Epitope
Subtype B, CRF01_AE
Neutralizing
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* Tat
Species (Isotype) human (IgG)
Ab Type C-term, N-term, Tat basic region
References Richardson *et al.* 2003
Keywords antibody binding site definition and exposure, rate of progression, subtype comparisons, vaccine-specific epitope characteristics

- Serum samples were obtained from the French GRIV (genetic resistance to HIV) cohort and tested for anti-Tat and anti-Vpr responses as both may contribute as extracellular proteins to pathogenesis. Serum anti-Tat IgG responses were significantly higher and maintained for up to 20 months in stable non-progressors (CD4+ T cell counts greater than 500 cell/ul after being positive for 8 years with no ART) compared to unstable non-progressors and fast progressors (CD4+ T less than 300 cells/ul within 2 years of seroconversion, some HAART). Anti-Tat IgG from GRIV stable non-progressors recognized linear epitopes located within the N-terminal, basic and the C-terminal domains of Tat. Humoral responses of fast-progressors and of one unstable non-progressor were restricted to the basic region of Tat. Tat toxoid vaccinees from Milan tended to recognize N-terminal and C-terminal domains. Sera from some GRIV and Tat toxoid vaccinees cross-reacted in an ELISA assay with a truncated 89.6 S/HIV 89.6P Tat, 89.6P Tat, HIv-1 subtype E (CMU08) and with SIVmac251 Tat (one sample). Richardson *et al.* [2003] (**antibody binding site definition and exposure**, **vaccine-specific epitope characteristics**, **subtype comparisons**, **rate of progression**)

No. 327
MAb ID G1
HXB2 Location Tat
Author Location Tat (1–15)
Epitope
Subtype B
Neutralizing yes
Immunogen vaccine
Strain: B clade *HIV component:* Tat
Species (Isotype) human (IgG1κ)
Ab Type N-term
References Moreau *et al.* 2004
Keywords antibody binding site definition and exposure, antibody sequence variable domain, subtype comparisons

- G1: G1 is a single-chain fragment-variable scFv antibody derived from a Tat-toxoid vaccinated uninfected volunteer. G1 binds strongly to soluble rTAT protein and to denatured rTAT, suggesting that the epitope is linear. G1 recognized HIV-1 clade B Tat proteins Bru and HXB2, but did not bind to clade E (CM240), clade C (92Br), clade D (Eli) and clade A (Ug11RP). G1 inhibited Tat-transactivation of viral replication. The VH3 heavy chains of the two phage scFvG1 VH3 heavy chain sequences of scFvG1 and scFvG2 vary (G1 CDR3, RGSTGKALDYCSPRTL; G2 CDR3, ERSQQHCNPLLHSNGKNYAE) although both share identical Vk light chain sequences. Moreau *et al.* [2004] (**antibody binding site definition and exposure**, **subtype comparisons**, **antibody sequence variable domain**)

No. 328
MAb ID G2
HXB2 Location Tat
Author Location Tat (1–15)
Epitope
Subtype B
Neutralizing yes
Immunogen vaccine
Strain: B clade *HIV component:* Tat
Species (Isotype) human (IgG1κ)
Ab Type N-term
References Moreau *et al.* 2004
Keywords antibody binding site definition and exposure, antibody sequence variable domain, subtype comparisons

- G2: G2 is a single-chain fragment-variable scFv antibody derived from a Tat-toxoid vaccinated uninfected volunteer. G2 binds strongly to soluble rTAT protein and to denatured rTAT, suggesting that the epitope is linear. G2 recognized HIV-1 clade B Tat proteins Bru and HXB2, but did not bind to clade E (CM240), clade C (92Br), clade D (Eli) and clade A (Ug11RP). G2 inhibited Tat-transactivation of viral replication. The VH3 heavy chains of the two phage scFvG1 VH3 heavy chain sequences of scFvG1 and scFvG2 vary (G1

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CDR3, RGSTGKALDYCSPRTL; G2 CDR3, ERSQQHCNPLLHSNGKNYAE) although both share identical Vk light chain sequences and Tat binding sites. Moreau *et al.* [2004] (**antibody binding site definition and exposure**, **subtype comparisons**, **antibody sequence variable domain**)

No. 329
MAb ID J1
HXB2 Location Tat
Author Location Tat (1–15)
Epitope
Subtype B
Neutralizing yes
Immunogen vaccine
Strain: B clade *HIV component:* Tat
Species (Isotype) human (IgG1λ)
Ab Type N-term
References Moreau *et al.* 2004
Keywords antibody binding site definition and exposure, antibody sequence variable domain, subtype comparisons

- J1: J1 is a single-chain fragment-variable scFv antibody derived from a Tat-toxoid vaccinated uninfected volunteer. J1 binds strongly to soluble rTAT protein and to denatured rTAT, suggesting that the epitope is linear. J1 recognized HIV-1 clade B Tat proteins Bru and HXB2, but did not bind to clade E (CM240), clade C (92Br), clade D (Eli) and clade A (Ug11RP). J1 inhibited Tat-transactivation of viral replication. Of three scFv antibodies, all bound the N-terminal amino acids 1-15, but G1 and G2 had kappa light chains and J1 had lambda, and the CDR3 of each was distinct, with J1's CDR3 sequence being: RDRYCSSPGCYKGADGGRLKDY. Moreau *et al.* [2004] (**antibody binding site definition and exposure**, **subtype comparisons**, **antibody sequence variable domain**)

No. 330
MAb ID TC15
HXB2 Location Tat
Author Location Tat (Lai/Bru)
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU *HIV component:* Tat *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse (IgG)
Ab Type N-term
Research Contact Dr. J.-L. Guesdon, Institut Pasteur, Paris
References Belliard *et al.* 2003
Keywords subtype comparisons

- TC15: This is one of 5 anti-Tat murine monoclonal antibodies generated in this study. It is conformational reacting only with intact protein. It reacts with B and D clade Tat proteins, and does not recognize Tat from clade A, C, or CRF01 (AE). Belliard *et al.* [2003] (**subtype comparisons**)

No. 331
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat (Lai/Bru)
Epitope
Subtype B
Neutralizing
Immunogen SHIV infection, vaccine
Vector/Type: peptide *Strain:* B clade BRU *HIV component:* Tat *Adjuvant:* aluminum phosphate, CpG immunostimulatory sequence (ISS), Montanide (ISA 720)
Species (Isotype) macaque (IgG)
Ab Type N-term
References Belliard *et al.* 2003
Keywords rate of progression

- Macaques were immunized with different combinations of Tat peptides. Serum from these animals was able to inhibit Tat-induced apoptosis, and Tat antibodies are associated with long term survival. Anti-Tat antibodies generated in infected macaques tended to be restricted to the peptide 44-61, while sera from infected humans could react with several different peptides. Belliard *et al.* [2003] (**rate of progression**)

No. 332
MAb ID polyclonal
HXB2 Location Tat
Author Location Tat (Lai/Bru)
Epitope
Subtype B
Neutralizing
Immunogen SHIV infection, vaccine
Vector/Type: peptide *Strain:* B clade BRU *HIV component:* Tat *Adjuvant:* BSA, Complete Freund's Adjuvant (CFA)
Species (Isotype) rabbit (IgG)
Ab Type N-term
References Belliard *et al.* 2003
Keywords rate of progression

- 12 rabbits were immunized with different combinations of Tat peptides. Abs raised against peptide aa 8-53 did not react with the peptide 19-53, suggesting that the N-terminal region is important. Serum from these animals was able to inhibit Tat-induced apoptosis, and Tat antibodies in humans are associated with long term survival. Belliard *et al.* [2003] (**rate of progression**)

No. 333
MAb ID B1E3
HXB2 Location Tat
Author Location Tat (44–61)
Epitope
Subtype B
Neutralizing yes
Immunogen vaccine
Strain: B clade *HIV component:* Tat
Species (Isotype) human (IgG1κ)
Ab Type Tat basic region
References Moreau *et al.* 2004
Keywords antibody binding site definition and exposure, subtype comparisons

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• B1E3: B1E3 is a MAb derived from a Tat-toxoid vaccinated uninfected volunteer. B1E3 recognized two Tat peptides, aa19-53 and aa44-61 of an unspecified HIV-1 clade B Tat protein. B1E3 demonstrates a weak binding affinity to rTAT protein in solution, suggesting that epitope recognition may be conformation dependent B1E3 did not recognize synthetic HIV-1 clade B Tat proteins Bru and HXB2, clade E (CM240), clade C (92Br), clade D (Eli) and clade A (Ug11RP). It only bound to native TAT protein, and could inhibit Tat-transactivation. Moreau *et al.* [2004] (**antibody binding site definition and exposure**, **subtype comparisons**)

No. 334
MAb ID J3B2
HXB2 Location Tat
Author Location Tat (44–61)
Epitope
Subtype B
Neutralizing yes
Immunogen vaccine
Strain: B clade *HIV component:* Tat
Species (Isotype) human (IgG1λ)
Ab Type Tat basic region
References Moreau *et al.* 2004
Keywords antibody binding site definition and exposure, subtype comparisons

• J3B2: J3B2 is a MAb derived from a Tat-toxoid vaccinated uninfected volunteer. B1E3 recognized two Tat peptides, aa33-37 and aa37-51 of an unspecified HIV-1 clade B Tat protein. J3B2 demonstrates a weak binding affinity to rTAT protein in solution, suggesting that epitope recognition may be conformation dependent, B1E3 did not recognize synthetic HIV-1 clade B Tat proteins Bru and HXB2, clade E (CM240), clade C (92Br), clade D (Eli) and clade A (Ug11RP). It only bound to native TAT protein, and could inhibit Tat-transactivation. Moreau *et al.* [2004] (**antibody binding site definition and exposure**, **subtype comparisons**)

IV-C-14 Rev Antibodies

No. 335
MAb ID 4G9
HXB2 Location Rev (5–15)
Author Location Rev (5–15)
Epitope `SGDSDEELIRT?`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Rev
Species (Isotype) mouse
References Jensen *et al.* 1997

• 4G9: Mapped binding location by protein footprinting. Jensen *et al.* [1997]

No. 336
MAb ID Ab2
HXB2 Location Rev (32–50)
Author Location Rev (32–49 BRU)
Epitope `EGTRQARRNRRRWRERQR`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Rev
Species (Isotype) (IgG1)
Research Contact Tony Lowe and Jonathan Karn, MRC Center, Cambridge
References Henderson & Percipalle 1997

• Ab2: The Ab2 binding site overlaps the nuclear localization signal – Ab2 binding to Rev was blocked by bound HIV RNA – the cellular protein importin-beta can bind in this Arg rich region – atypically, the Rev binds specifically to importin-beta, but not to the importin-beta-importin-alpha dimer. Henderson & Percipalle [1997]

No. 337
MAb ID 10.1
HXB2 Location Rev (33–48)
Author Location Rev (33–48)
Epitope `GTRQARRNRRRRWRER?`
Neutralizing
Immunogen
Species (Isotype)
References Maksiutov *et al.* 2002; Ranki *et al.* 1995; Ranki *et al.* 1994; Ovod *et al.* 1992

• 10.1: This epitope is similar to a fragment of the human protein Complement 4 (containing C4A anaphlylatoxin), GRRNRRRR. Maksiutov *et al.* [2002]
• 10.1: Binds to the RRE binding site – polyclonal anti-Rev Ab detected Rev in astrocytes in 4/5 brain autopsy samples, but only one of these was positive using 10.1, suggesting most Rev was bound to RRE. Ranki *et al.* [1995]

No. 338
MAb ID 3H6
HXB2 Location Rev (38–43)
Author Location Rev (38–44)
Epitope `RRNRRR`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Rev
Species (Isotype) mouse (IgG1κ)
References Maksiutov *et al.* 2002; Orsini *et al.* 1995

• 3H6 database comment: There is another MAb with this ID that recognizes gp41.
• 3H6: This epitope is similar to a fragment of the human protein Complement 4 (containing C4A anaphlylatoxin), GRRNRRRR. Maksiutov *et al.* [2002]
• 3H6: Directed against nucleolar localization/RRE binding domain – antigenic domain tentative, MAb failed to bind a RRNRRR Rev deletion mutant. Orsini *et al.* [1995]

No. 339
MAb ID 8E7
HXB2 Location Rev (70–84)
Author Location Rev (70–84)
Epitope `PVPLQLPPLERLTLD`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Rev
Species (Isotype) mouse (IgG2aκ)

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References Maksiutov *et al.* 2002; Boe *et al.* 1998; Jensen *et al.* 1997; Szilvay *et al.* 1995; Kalland *et al.* 1994b; Kalland *et al.* 1994a

- 8E7: This epitope is similar fragments of the human protein Epidermal growth factor receptor substrate 15, EPVPMSLPPA, and Insulin-like growth factor binding protein complex acid labile chain precursor, QPPGLERLWLEGNPWDCG. Maksiutov *et al.* [2002]
- 8E7: HIV-1 RNA and Rev localize to the same region in the nucleoplasm, but the splicing factor SC-35 localizes in different speckles with the nucleoplasm than Rev – intron containing beta-globin was distributed similarly to HIV-1, suggesting Rev and HIV-1 RNAs interact at putative sites of mRNA transcriptions and splicing. Boe *et al.* [1998]
- 8E7: Peptide interaction mapped to aa 70-84, 75-88 – protein footprint to 65-88. Jensen *et al.* [1997]
- 8E7: 8E7 worked in indirect immunofluorescence and also detected Rev in WB assays – used to detect localization of Rev in several compartments including the nucleoli, nucleoplasm, perinuclear zone, and cytoplasm – Rev co-localized with host cell factors known to assemble on nascent transcripts – Rev shuttles continuously between cytoplasmic and nucleoplasmic compartments. Kalland *et al.* [1994a,b]; Szilvay *et al.* [1995]

No. 340
MAb ID 9G2 (9G2G4D6E8)
HXB2 Location Rev (70–84)
Author Location Rev (70–84)
Epitope `PVPLQLPPLERLTLD`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Rev
Species (Isotype) mouse (IgG2aκ)
Research Contact Anne Marie Szilvay
References Maksiutov *et al.* 2002; Jensen *et al.* 1997; Kalland *et al.* 1994a

- 9G2: Called 9G2G4D6E8: UK Medical Research Council AIDS reagent: ARP3058.
- 9G2: This epitope is similar fragments of the human protein Epidermal growth factor receptor substrate 15, EPVPMSLPPA, and Insulin-like growth factor binding protein complex acid labile chain precursor, QPPGLERLWLEGNPWDCG. Maksiutov *et al.* [2002]
- 9G2: Peptide interaction mapped to aa 70-84, 75-88 – protein footprint to 65-88. Jensen *et al.* [1997]
- 9G2: Worked in indirect immunofluorescence and also detected Rev in WB assays – used to detect localization of Rev throughout the cell. Kalland *et al.* [1994a]

No. 341
MAb ID Ab4
HXB2 Location Rev (72–91)
Author Location Rev (72–91 BRU)
Epitope `PLQLPPLERLTLDCNEDCGT`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Rev
Species (Isotype) (IgG1)
Research Contact Tony Lowe and Jonathan Karn, MRC Center, Cambridge
References Maksiutov *et al.* 2002; Henderson & Percipalle 1997

- Ab4: This epitope is similar fragments of the human protein Epidermal growth factor receptor substrate 15, EPVPMSLPPA, and Insulin-like growth factor binding protein complex acid labile chain precursor, QPPGLERLWLEGNPWDCG. Maksiutov *et al.* [2002]
- Ab4: The binding site overlaps the nuclear export signal – binding was not blocked by bound HIV RNA and may be accessible for protein interaction. Henderson & Percipalle [1997]

No. 342
MAb ID 3G4
HXB2 Location Rev (90–116)
Author Location Rev (90–116)
Epitope `GTSGTQGVGSPQILVESPTVLESGTKE?`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Rev
Species (Isotype) mouse (IgG1κ)
References Orsini *et al.* 1995

- 3G4: Binds to a region that can be dispensed with and still retain Rev function. Orsini *et al.* [1995]

No. 343
MAb ID 1G10 (IG10F4)
HXB2 Location Rev (96–105)
Author Location Rev (95–105)
Epitope `GVGSPQILVE`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Rev
Species (Isotype) mouse (IgG2bκ)
Research Contact Anne Marie Szilvay
References Kanduc *et al.* 2008; Jensen *et al.* 1997; Kalland *et al.* 1994a

- 1G10: Called IG10F4: UK Medical Research Council AIDS reagent: ARP3060.
- 1G10: Similarity level of the 1G10 binding site pentapeptide SPQIL to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 1 time, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 1G10: Peptide interaction mapped to aa 91-105, 96-110 – protein footprint to aa 10-20, and 95-105. Jensen *et al.* [1997]
- 1G10: Bound Rev in indirect immunofluorescence and also detected Rev in WB – used to detect localization of Rev throughout the cell. Kalland *et al.* [1994a]

No. 344
MAb ID 1G7
HXB2 Location Rev (96–105)
Author Location Rev (95–105)
Epitope `GVGSPQILVE`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Rev
Species (Isotype) mouse (IgG2bκ)

References Jensen *et al.* 1997; Kalland *et al.* 1994a

- 1G7: Peptide interaction mapped to aa 91-105, 96-110 – protein footprint to aa 95-105. Jensen *et al.* [1997]
- 1G7: Worked in indirect immunofluorescence and also detected Rev in WB – used to detect localization of Rev throughout the cell. Kalland *et al.* [1994a]

No. 345
MAb ID Ab3
HXB2 Location Rev (102–116)
Author Location Rev (102–116 BRU)
Epitope `ILVESPTVLESDKTE`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Rev
Species (Isotype) (IgG1)
Research Contact Tony Lowe and Jonathan Karn, MRC, Cambridge
References Henderson & Percipalle 1997

- Ab3: This binding site is at the carboxy end of Rev – Ab3 binding was not blocked by bound HIV RNA. Henderson & Percipalle [1997]

No. 346
MAb ID 2G2
HXB2 Location Rev
Author Location Rev
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Rev
Species (Isotype) mouse (IgG1κ)
References Orsini *et al.* 1995

- 2G2: Does not bind to any of a set of glutathione S-transferase (GST) Rev fusion proteins, or to Rev in a RIPA buffer, suggesting a conformational epitope. Orsini *et al.* [1995]

IV-C-15 Vpu Antibodies

No. 347
MAb ID DE7
HXB2 Location Vpu (42–63)
Author Location Vpu (41–62)
Epitope `LIDRLIERAEDSGNESEGEISA`
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* Vpu
Adjuvant: BSA
Species (Isotype) mouse (IgG1)
References Gharbi-Benarous *et al.* 2004
Keywords antibody binding site definition and exposure, antibody generation

- DE7: This MAb was generated against the phosphorylated Vpu41-62 peptide. Phosphorylation of Vpu, at the Serines of the DSGXXS motif, is required for interaction of Vpu with the ubiquitin ligase that triggers CD4 degradation and infectious virion release. DE7 bound peptide conformation was analyzed using STD NMR epitope mapping, TRNOESY conformational analysis and molecular dynamics simulation, and found to adopt a compact structure with several bends, including a tight bend at DpSGNEpS. Gharbi-Benarous *et al.* [2004] (**antibody binding site definition and exposure**, **antibody generation**)

IV-C-16 gp160 Antibodies

No. 348
MAb ID M85
HXB2 Location gp160 (30–51)
Author Location gp120 (30–51 LAI)
Epitope `ATEKLWVTVYYGVPVWKEATTT`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Env
Species (Isotype) mouse (IgG1)
Ab Type gp120 C1
Research Contact Fulvia di Marzo Veronese
References Koefoed *et al.* 2005; Wyatt *et al.* 1997; Ditzel *et al.* 1997; Moore & Sodroski 1996; Moore *et al.* 1994d; Moore *et al.* 1994c; di Marzo Veronese *et al.* 1992
Keywords antibody binding site definition and exposure

- M85: IgG antibody phage display libraries were created from HIV-1 + individuals after pre-selection of PBMC with gp120, as an alternative to using bone marrow for generating libraries. M85 was among a set of Abs used for competition studies to define the binding sites of the newly isolated MAbs, and has a linear C1 epitope. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**)
- M85: Binds efficiently to sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding. Wyatt *et al.* [1997]
- M85: Binding inhibited by MAb 4D4#85, enhanced by conformationally sensitive anti-V3 MAb 5G11, and some anti-18 MAbs. Moore & Sodroski [1996]
- M85: C1 domain – mutation 40 Y/D impairs binding – the relative affinity for denatured/native gp120 is < .01, suggesting conformational component. Moore *et al.* [1994c]
- M85: Immunoblot and RIP reactive for strains IIIB, 451, MN, RF, and RUTZ – binds deglycosylated gp120. di Marzo Veronese *et al.* [1992]

No. 349
MAb ID 7E2/4
HXB2 Location gp160 (31–50)
Author Location gp120 (31–50 LAI)
Epitope `TEKLWVTVYYGVPVWKEATT`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
Research Contact S. Ranjbar, NIBSC, UK

B Cell

References Maksiutov *et al.* 2002; Moore *et al.* 1994c

- 7E2/4: UK Medical Research Council AIDS reagent: ARP3050.
- 7E2/4: This epitope has a high degree of similarity with the platelet membrane glycoprotein IIIA precursor (GLIIIA) (integrin beta- 3) (CD61): PLYKEATSTF. Maksiutov *et al.* [2002]
- 7E2/4: C1 domain – the relative affinity for denatured/native gp120 is .07, suggesting conformational component. Moore *et al.* [1994c]

No. 350
MAb ID 4D4#85
HXB2 Location gp160 (41–50)
Author Location gp120 (LAI)
Epitope GVPVWKEATT
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
Research Contact S. Nigida and L. Arthur, NCI, Frederick, MD USA
References Kanduc *et al.* 2008; Maksiutov *et al.* 2002; Binley *et al.* 1998; Wyatt *et al.* 1997; Moore & Sodroski 1996; Moore *et al.* 1994d; Moore *et al.* 1994c

- 4D4#85: Similarity level of the 4D4#85 binding site pentapeptide VPVWK to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 1 time, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 4D4#85: This epitope has a high degree of similarity with the platelet membrane glycoprotein IIIA precursor (GLIIIA) (integrin beta- 3) (CD61): PLYKEATSTF. Maksiutov *et al.* [2002]
- 4D4#85: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
- 4D4#85: Binds efficiently to sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding – does not bind to HXBc2 gp120 if the 19 C-term amino acids, in conjunction with C1 positions 31-50, are deleted. Wyatt *et al.* [1997]
- 4D4#85: Inhibits binding of C1 MAb M85, C1-C5 discontinuous epitope MAbs 181 and 212A, and CD4 binding induced MAbs 48d and 17b. Moore & Sodroski [1996]
- 4D4#85: C1 domain – the relative affinity, denatured/native gp120 is 0.1 – mutation 45 W/S impairs binding. Moore *et al.* [1994c]

No. 351
MAb ID M92
HXB2 Location gp160 (41–50)
Author Location gp120 (31–50 LAI)
Epitope GVPVWKEATT
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Env
Species (Isotype) rat (IgG1)
Ab Type gp120 C1
Research Contact Fulvia di Marzo Veronese
References Maksiutov *et al.* 2002; Moore *et al.* 1994d; Moore *et al.* 1994c; di Marzo Veronese *et al.* 1992

- M92: This epitope has a high degree of similarity with the platelet membrane glycoprotein IIIA precursor (GLIIIA) (integrin beta- 3) (CD61): PLYKEATSTF. Maksiutov *et al.* [2002]
- M92: The relative affinity for denatured/native gp120 is 1. Moore *et al.* [1994c]
- M92: Immunoblot reactive, RIP negative, but precipitates deglycosylated gp120 – reacts with strains IIIB, 451, MN, RF, and RUTZ. di Marzo Veronese *et al.* [1992]

No. 352
MAb ID M86
HXB2 Location gp160 (42–61)
Author Location gp120 (42–61 LAI)
Epitope VPVWKEATTTLFCASDAKAY
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Env
Species (Isotype) mouse (IgG1)
Ab Type gp120 C1
Research Contact Fulvia di Marzo Veronese
References Maksiutov *et al.* 2002; Moore *et al.* 1994c; di Marzo Veronese *et al.* 1992

- M86: This epitope has a high degree of similarity with the platelet membrane glycoprotein IIIA precursor (GLIIIA) (integrin beta- 3) (CD61): PLYKEATSTF. Maksiutov *et al.* [2002]
- M86: C1 domain – the relative affinity for denatured/native gp120 is 1. Moore *et al.* [1994c]
- M86: Immunoblot and RIP reactive for strains IIIB, 451, MN, RF, and RUTZ – binds deglycosylated gp120. di Marzo Veronese *et al.* [1992]

No. 353
MAb ID polyclonal
HXB2 Location gp160 (52–71)
Author Location Env (42–61 LAI)
Epitope LFCASDAKAYDTEVHNVWAT
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* Env
Species (Isotype) mouse
Ab Type gp120 C1
References Kanduc *et al.* 2008; Collado *et al.* 2000

B Cell

- Similarity level of the polyclonal Ab binding site pentapeptide KAYDT to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- Vaccinia p14 can elicit NAbs and p39 tends to be immunodominant, so these two proteins were fused to regions of HIV-1 Env – reduced glycosylation was noted when p14 or p39 was placed in the N-term region of the fusion protein – chimeric proteins shifted the Env Ab response from V3 to either a C1 or C4 domain, depending on the construct – all chimeric Env proteins: 14kEnv, 39kEnv, and Env39k elicited a strong Ab response to the C1 region of gp120 (LFCASDAKAYDTEVHNVWAT), and Env39k mounted a strong response to the C4 region (KAMYAPPISGQIRCSSNITG) Collado *et al.* [2000]

No. 354
MAb ID 133/237
HXB2 Location gp160 (61–70)
Author Location gp120 (51–70 LAI)
Epitope YDTEVHNVWA
Subtype B
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 C1
References Pantophlet *et al.* 2004; Moore *et al.* 1994d; Moore *et al.* 1994c; Niedrig *et al.* 1992b
Keywords vaccine antigen design

- 133/237: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 133/237. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- 133/237: The relative affinity, denatured/native gp120 is 1.4 – mutation of position 69 W/L impairs binding. Moore *et al.* [1994c]
- 133/237: Region of overlap for reactive peptides is WATHA – weak neutralization of lab strains. Niedrig *et al.* [1992b]

No. 355
MAb ID 133/290
HXB2 Location gp160 (61–70)
Author Location gp120 (61–70 LAI)
Epitope YDTEVHNVWA
Subtype B
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 C1
Research Contact M. Niedrig
References Pantophlet *et al.* 2003b; Yang *et al.* 2000; Binley *et al.* 1998; Wyatt *et al.* 1997; Binley *et al.* 1997a; Moore & Sodroski 1996; Wyatt *et al.* 1995; Moore *et al.* 1994d; Moore *et al.* 1994c; Thali *et al.* 1993; Niedrig *et al.* 1992b
Keywords vaccine antigen design

- 133/290: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- 133/290: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000]
- 133/290: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
- 133/290: Binds efficiently to sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding. Wyatt *et al.* [1997]
- 133/290: Reciprocal binding inhibition with the antibody 522-149, that binds to a discontinuous epitope – binding is enhanced by some C5 and C1 binding site antibodies. Moore & Sodroski [1996]
- 133/290: Used for antigen capture assay, either to bind gp120 to the ELISA plate, or to quantify bound gp120. Wyatt *et al.* [1995]
- 133/290: The relative affinity for denatured/native gp120 is 2.2 – mutation in position 69 W/L impairs binding. Moore *et al.* [1994c]
- 133/290: Region of overlap for reactive peptides is WATHA – weak neutralization of lab strains. Niedrig *et al.* [1992b]

No. 356
MAb ID 133/11
HXB2 Location gp160 (64–78)
Author Location gp120 (64–78)
Epitope EVHNVWATHACVPTD
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp120

B Cell

Species (Isotype) mouse (IgG1)
Ab Type gp120 C1
References Kanduc *et al.* 2008; Niedrig *et al.* 1992b

- 133/11: Similarity level of the 133/11 binding site pentapeptide WATHA to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 133/11: Region of overlap for reactive peptides is WATHA – weak neutralization of lab strains. Niedrig *et al.* [1992b]

No. 357
MAb ID D/3G5
HXB2 Location gp160 (73–82)
Author Location gp120 (73–82 LAI)
Epitope `ACVPTDPNPQ`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 C1
References Bristow *et al.* 1994

- D/3G5: C1 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp120 and rgp160. Bristow *et al.* [1994]

No. 358
MAb ID D/6A11
HXB2 Location gp160 (73–82)
Author Location gp120 (73–82 LAI)
Epitope `ACVPTDPNPQ`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 C1
References Kanduc *et al.* 2008; Bristow *et al.* 1994

- D/6A11: Similarity level of the D/6A11 binding site pentapeptide CVPTD to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- D/6A11: C1 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp120 and rgp160. Bristow *et al.* [1994]

No. 359
MAb ID D/5E12
HXB2 Location gp160 (73–92)
Author Location gp120 (73–92 LAI)
Epitope `ACVPTDPNPQEVVLVNVTEN`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 C1
References Bristow *et al.* 1994

- D/5E12: C1 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp120 and rgp160. Bristow *et al.* [1994]

No. 360
MAb ID L5.1
HXB2 Location gp160 (79–93)
Author Location gp120 (89–103 IIIB)
Epitope `PNPQEVVLVNVTENF`
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
References Akerblom *et al.* 1990

No. 361
MAb ID 4A7C6
HXB2 Location gp160 (81–90)
Author Location gp120 (81–90 LAI)
Epitope `PQEVVLVNVT`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
Research Contact R. Tedder
References Moore & Sodroski 1996; Moore *et al.* 1994d; Moore *et al.* 1994c; Moore & Ho 1993; Thali *et al.* 1993; Thiriart *et al.* 1989

- 4A7C6: UK Medical Research Council AIDS reagent: ARP 360.
- 4A7C6: Reciprocal binding inhibition with the antibody 133/192 – enhanced by anti-C5 antibodies, and C1 antibody 135/9. Moore & Sodroski [1996]
- 4A7C6: The relative affinity for denatured/native gp120 is 7.9 – mutation 88 N/P impairs binding. Moore *et al.* [1994c]
- 4A7C6: C1 region epitope (88 N/P substitutions abrogates binding), but substitutions 380 G/F and 420 I/R also impaired binding. Moore *et al.* [1994d]
- 4A7C6: Bound preferentially to denatured IIIB gp120. Moore & Ho [1993]

No. 362
MAb ID 1D10
HXB2 Location gp160 (81–100)
Author Location gp120 (81–100 LAI)
Epitope `PQEVVLVNVTENFDMWKNDM`
Subtype B
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp120

Species (Isotype) rat
Ab Type gp120 C1
References Moore *et al.* 1994c; Nakamura *et al.* 1992; Berman *et al.* 1991; Dowbenko *et al.* 1988

- 1D10: The relative affinity for denatured/native gp120 is 13 – mutation 88 N/P impairs binding. Moore *et al.* [1994c]
- 1D10: Cross-blocks 5B3 in IIIB-rsgp160 ELISA – type specific in rgp120 ELISA binding. Nakamura *et al.* [1992]

No. 363
MAb ID B242
HXB2 Location gp160 (83–92)
Author Location gp120 (83–92 LAI)
Epitope `EVVLVNVTEN`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43 *HIV component:* gp160
Species (Isotype) mouse (IgG1)
Ab Type gp120 C1
References Bristow *et al.* 1994

- B242: C1 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp160 IIIB:NL43, MicroGenSys. Bristow *et al.* [1994]

No. 364
MAb ID 133/192
HXB2 Location gp160 (91–100)
Author Location gp120 (91–100 LAI)
Epitope `ENFDMWKNDM`
Subtype B
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 C1
Research Contact Matthias Niedrig
References Pantophlet *et al.* 2004; Pantophlet *et al.* 2003b; Binley *et al.* 1998; Binley *et al.* 1997a; Trkola *et al.* 1996a; Moore & Sodroski 1996; Moore *et al.* 1994d; Moore *et al.* 1994c; Moore *et al.* 1993b; Niedrig *et al.* 1992b
Keywords vaccine antigen design

- 133/192: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 133/192. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- 133/192: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- 133/192: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
- 133/192: Reciprocal binding inhibition with the antibody 4A7C6 – enhanced by some anti-C5 and-C1 antibodies. Moore & Sodroski [1996]
- 133/192: Does not neutralize JR-FL nor block gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]
- 133/192: The relative affinity for denatured/native gp120 is 1.8. Moore *et al.* [1994c]
- 133/192: C1 region – substitutions 76P/Y, 113 D/A or R, 117 K/W, 420 I/R, 427 W/S impair binding, other substitutions enhanced binding. Moore *et al.* [1994d]
- 133/192: Epitope seems complex, binds multiple peptides – weak neutralization of lab strain. Niedrig *et al.* [1992b]

No. 365
MAb ID 489.1(961)
HXB2 Location gp160 (91–100)
Author Location gp120 (91–100 LAI)
Epitope `ENFDMWKNDM`
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
Research Contact C. Bruck, SKB, Belgium
References Moore *et al.* 1994c

- 489.1(961): NIH AIDS Research and Reference Reagent Program: 961.
- 489.1(961): The relative affinity for denatured/native gp120 is 1. Moore *et al.* [1994c]

No. 366
MAb ID 5B3
HXB2 Location gp160 (91–100)
Author Location gp120 (91–100 LAI)
Epitope `ENFDMWKNDM`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp160
Species (Isotype) mouse (IgG)
Ab Type gp120 C1

References Moore *et al.* 1994c; Beretta & Dalgleish 1994; Nakamura *et al.* 1992; Berman *et al.* 1991

- 5B3: The relative affinity of denatured/native gp120 is 8.3. Moore *et al.* [1994c]
- 5B3: Cross-blocks 1D10 in competitive IIIB-rsgp160 ELISA – no neutralization – blocks IIIB-gp120 sCD4 binding – localized binding to residues 72-106. Nakamura *et al.* [1992]
- 5B3: Blocks gp120 -CD4 binding. Berman *et al.* [1991]

No. 367
MAb ID B10
HXB2 Location gp160 (91–100)
Author Location gp120 (91–100 LAI)
Epitope ENFDMWKNDM
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG1)
Ab Type gp120 C1
References Moore *et al.* 1994c; Abacioglu *et al.* 1994

- B10: There is FNM/FDM polymorphism in LAI-based peptides, and N is essential (J. P. Moore, per. comm.)
- B10: C1 region – epitope boundaries mapped by peptide scanning, FNMW core. Abacioglu *et al.* [1994]
- B10: The relative affinity for denatured/native gp120 is 0.4. Moore *et al.* [1994c]

No. 368
MAb ID B2
HXB2 Location gp160 (91–100)
Author Location gp120 (91–100 LAI)
Epitope ENFDMWKNDM
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG2b)
Ab Type gp120 C1
References Binley *et al.* 1997a; Moore *et al.* 1994d; Moore *et al.* 1994c; Abacioglu *et al.* 1994; Thali *et al.* 1993

- B2: There is FNM/FDM polymorphism in LAI-based peptides, and N is essential (J. P. Moore, per. comm.)
- B2: C1 region – epitope boundaries mapped by peptide scanning, FNMW core. Abacioglu *et al.* [1994]
- B2: The relative affinity for denatured/native gp120 is 1.4. Moore *et al.* [1994c]

No. 369
MAb ID C6 (Ch6)
HXB2 Location gp160 (91–100)
Author Location gp120 (91–100 LAI)
Epitope ENFDMWKNDM
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG1)
Ab Type gp120 C1
References Pincus *et al.* 1996; Moore *et al.* 1994c; Abacioglu *et al.* 1994; Pincus & McClure 1993

- C6: There is FNM/FDM polymorphism in LAI-based peptides – N is essential (J. P. Moore, per. comm.)
- C6: NIH AIDS Research and Reference Reagent Program: 810.
- C6: Called Ch6 – binds to gp120 but not to infected cells – when linked to ricin A, the immunotoxin did not mediate cell killing – sCD4 has no effect. Pincus & McClure [1993]; Pincus *et al.* [1996]
- C6: C1 region – epitope boundaries mapped by peptide scanning, FNMW core. Abacioglu *et al.* [1994]
- C6: The relative affinity for denatured/native gp120 is 0.9. Moore *et al.* [1994c]

No. 370
MAb ID MF49.1
HXB2 Location gp160 (91–100)
Author Location gp120 (91–100 LAI)
Epitope ENFDMWKNDM
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
References Moore *et al.* 1994c; Thiriart *et al.* 1989

- MF49.1: The relative affinity of denatured/native gp120 is 3.8. Moore *et al.* [1994c]

No. 371
MAb ID T1.1
HXB2 Location gp160 (91–100)
Author Location gp120 (91–100 LAI)
Epitope ENFDMWKNDM
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* gp160
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
References Moore *et al.* 1994c; Broliden *et al.* 1990; Akerblom *et al.* 1990

- T1.1: C1 region – the relative affinity for denatured/native gp120 is 1. Moore *et al.* [1994c]
- T1.1: Also reacted in solid phase with gp120(234-248) NGTGPCTNVSTQCT. Akerblom *et al.* [1990]
- T1.1: No ADCC activity – reactive peptide: NVTENFNMWKNDMVEQ, IIIB. Broliden *et al.* [1990]

No. 372
MAb ID T7.1
HXB2 Location gp160 (91–100)
Author Location gp120 (91–100 LAI)
Epitope ENFDMWKNDM

B Cell

Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
References Moore *et al.* 1994d; Moore *et al.* 1994c; Bolmstedt *et al.* 1990; Akerblom *et al.* 1990

- T7.1: The relative affinity of denatured/native gp120 is 4.0. Moore *et al.* [1994c]

No. 373
MAb ID T9
HXB2 Location gp160 (91–100)
Author Location gp120 (91–100 LAI)
Epitope `ENFDMWKNDM`
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
Research Contact Lennart Akerblom, Britta Wahren and Jorma Hinkula
References Binley *et al.* 1997a; Moore *et al.* 1994d; Moore *et al.* 1994c; Bolmstedt *et al.* 1990; Akerblom *et al.* 1990

- T9 database comment: There are two HIV-Abs with the name T9, one binds to gp41, one to gp120.
- T9: The relative affinity of denatured/native gp120 is 7.9. Moore *et al.* [1994c]
- T9: Binds to the C1 region – 45 W/S, 88 N/P, 256 S/Y, 262 N/T, 475 M/S, 485 1.83, and 491 I/F enhanced binding, no substitution tested significantly inhibited. Moore *et al.* [1994d]

No. 374
MAb ID GV4D3
HXB2 Location gp160 (92–100)
Author Location gp120 (92–100 IIIB)
Epitope `NFNMWKNDM`
Neutralizing
Immunogen vaccine
Vector/Type: protein-Ab complex *HIV component:* gp120-Mab complex
Species (Isotype) mouse
Ab Type gp120 C1
Research Contact Patricia Earl and Christopher Broder, NIH
References Denisova *et al.* 1996

- GV4D3: When anti-V3 MAb M77 was bound to gp120 and used as an immunogen, it stimulated many MAbs to linear epitopes – MAbs GV4H4 and GV5F9 are homologous to GV4D3 and were generated in the same experiment. Denisova *et al.* [1996]

No. 375
MAb ID B27
HXB2 Location gp160 (93–96)
Author Location gp120 (94–97 BH10)
Epitope `FNMW`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43 *HIV component:* gp160
Species (Isotype) mouse (IgG1)
Ab Type gp120 C1
References Bristow *et al.* 1994; Abacioglu *et al.* 1994

- B27: C1 region – epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]
- B27: C1 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp160 IIIB:NL43, MicroGenSys. Bristow *et al.* [1994]

No. 376
MAb ID B9
HXB2 Location gp160 (93–96)
Author Location gp120 (93–96 LAI)
Epitope `FNMW`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG1)
Ab Type gp120 C1
References Abacioglu *et al.* 1994

- B9: Binds C1 region – epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

No. 377
MAb ID B35
HXB2 Location gp160 (93–98)
Author Location gp120 (94–99 BH10)
Epitope `FNMWKN`
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG1)
Ab Type gp120 C1
References Abacioglu *et al.* 1994

- B35: C1 region – epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

No. 378
MAb ID D/4B5
HXB2 Location gp160 (93–101)
Author Location gp120 (93–101 LAI)
Epitope `FNMWKNDMV`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 C1
References Kanduc *et al.* 2008; Bristow *et al.* 1994

B Cell

- D/4B5: Similarity level of the D/4B5 binding site pentapeptide WKNDM to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- D/4B5: C1 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp120 and rgp160. Bristow *et al.* [1994]

No. 379
MAb ID D/5A11
HXB2 Location gp160 (93–101)
Author Location gp120 (93–101 LAI)
Epitope FNMWKNDMV
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 C1
References Bristow *et al.* 1994

- D/5A11: C1 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp120 and rgp160. Bristow *et al.* [1994]

No. 380
MAb ID D/6B2
HXB2 Location gp160 (93–101)
Author Location gp120 (93–101 LAI)
Epitope FNMWKNDMV
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 C1
References Bristow *et al.* 1994

- D/6B2: C1 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp120 and rgp160. Bristow *et al.* [1994]

No. 381
MAb ID B18
HXB2 Location gp160 (101–110)
Author Location gp120 (101–110 LAI)
Epitope VEQMHEDIIS
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG2a)
Ab Type gp120 C1
References Kanduc *et al.* 2008; Moore *et al.* 1994c; Abacioglu *et al.* 1994

- B18: Similarity level of the B18 binding site pentapeptide VEQMH to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- B18: C1 region – epitope boundaries mapped by peptide scanning, HEDII core. Abacioglu *et al.* [1994]
- B18: The relative affinity for denatured/native gp120 is 1. Moore *et al.* [1994c]

No. 382
MAb ID B20
HXB2 Location gp160 (101–110)
Author Location gp120 (101–110 LAI)
Epitope VEQMHEDIIS
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG2a)
Ab Type gp120 C1
References Moore *et al.* 1994c; Abacioglu *et al.* 1994

- B20: C1 region – epitope boundaries mapped by peptide scanning – HEDII core. Abacioglu *et al.* [1994]
- B20: The relative affinity for denatured/native gp120 is 1. Moore *et al.* [1994c]

No. 383
MAb ID MF39.1 (39.1)
HXB2 Location gp160 (101–110)
Author Location gp120 (101–110 LAI)
Epitope VEQMHEDIIS
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
References Moore *et al.* 1994c; Cook *et al.* 1994; Thiriart *et al.* 1989

- MF39.1: Called 39.1, and is probably the same as MF39.1 – MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – MAbs against the N-terminal half of gp120 do not inhibit gp120 binding to GalCer – binding of GalCer to gp120 does not inhibit MAb binding. Cook *et al.* [1994]
- MF39.1: The relative affinity of denatured/native gp120 is 30. Moore *et al.* [1994c]

No. 384
MAb ID 187.2.1 (187.1)
HXB2 Location gp160 (101–120)
Author Location gp120 (101–120 LAI)
Epitope VEQMHEDIISLWDQSLKPCV
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Env

B Cell

Species (Isotype) mouse (IgG)
Ab Type gp120 C1
Research Contact Claudine Bruck and Clothilde Thiriart
References Moore *et al.* 1994d; Moore *et al.* 1994c; Cook *et al.* 1994; Moore & Ho 1993; Thiriart *et al.* 1989

- 187.2.1: UK Medical Research Council AIDS reagent: ARP332.
- 187.2.1: Called 187.1, and is probably the same as 187.2.1 – MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – MAbs against the N-terminal half of gp120 do not inhibit gp120 binding to GalCer – binding of GalCer to gp120 does not inhibit MAb binding. Cook *et al.* [1994]
- 187.2.1: The relative affinity for denatured/native gp120 is 7 – mutations 113 D/A (not D/R) and 117 K/W impair binding. Moore *et al.* [1994c]
- 187.2.1: Called 187.1, and is probably the same as 187.2.1 – bound preferentially to denatured IIIB gp120. Moore & Ho [1993]

No. 385
MAb ID 37.1.1(ARP 327) (37.1)
HXB2 Location gp160 (101–120)
Author Location gp120 (101–120 LAI)
Epitope VEQMHEDIISLWDQSLKPCV
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
Research Contact Claudine Bruck
References Moore *et al.* 1994c; Moore & Ho 1993; Thiriart *et al.* 1989

- 37.1.1: UK Medical Research Council AIDS reagent: ARP327.
- 37.1.1: The relative affinity for denatured/native gp120 is 8.6 – mutations 113 D/R (not D/A) and 117 K/W impair binding. Moore *et al.* [1994c]
- 37.1.1: Called 37.1 – bound preferentially to denatured IIIB gp120. Moore & Ho [1993]

No. 386
MAb ID 6D8
HXB2 Location gp160 (101–120)
Author Location gp120 (101–120 LAI)
Epitope VEQMHEDIISLWDQSLKPCV
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) rat
Ab Type gp120 C1
References Moore *et al.* 1994c; Nakamura *et al.* 1992; Dowbenko *et al.* 1988

- 6D8: The relative affinity for denatured/native gp120 is 15 – mutations 113 D/R and 113 D/A impair binding. Moore *et al.* [1994c]
- 6D8: Highly cross reactive with multiple stains by rgp120 ELISA. Nakamura *et al.* [1992]

No. 387
MAb ID M96
HXB2 Location gp160 (101–120)
Author Location gp120 (101–120 LAI)
Epitope VEQMHEDIISLWDQSLKPCV
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Env
Species (Isotype) rat (IgG2a)
Ab Type gp120 C1
Research Contact Fulvia di Marzo Veronese
References Moore *et al.* 1994d; Moore *et al.* 1994c; di Marzo Veronese *et al.* 1992

- M96: C1 region – the relative affinity for denatured/native gp120 is 6. Moore *et al.* [1994c]
- M96: Immunoblot reactive for strains IIIB, 451, MN, RF, and RUTZ. di Marzo Veronese *et al.* [1992]

No. 388
MAb ID MF119.1
HXB2 Location gp160 (101–120)
Author Location gp120 (101–120 LAI)
Epitope VEQMHEDIISLWDQSLKPCV
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
References Moore *et al.* 1994c; Thiriart *et al.* 1989

- MF119.1: The relative affinity for denatured/native gp120 is 30 – mutations 113 D/A, 113 D/R, and 117 K/W impair binding. Moore *et al.* [1994c]

No. 389
MAb ID MF4.1
HXB2 Location gp160 (101–120)
Author Location gp120 (101–120 LAI)
Epitope VEQMHEDIISLWDQSLKPCV
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
References Moore *et al.* 1994c; Thiriart *et al.* 1989

- MF4.1: The relative affinity for denatured/native gp120 is 8. Moore *et al.* [1994c]

No. 390
MAb ID MF53.1
HXB2 Location gp160 (101–120)
Author Location gp120 (101–120 LAI)
Epitope VEQMHEDIISLWDQSLKPCV
Subtype B
Neutralizing

Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
References Moore *et al.* 1994c; Thiriart *et al.* 1989

- MF53.1: The relative affinity for denatured/native gp120 is 10. Moore *et al.* [1994c]

No. 391
MAb ID MF58.1
HXB2 Location gp160 (101–120)
Author Location gp120 (101–120 LAI)
Epitope `VEQMHEDIISLWDQSLKPCV`
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
References Moore *et al.* 1994c; Thiriart *et al.* 1989

No. 392
MAb ID MF77.1
HXB2 Location gp160 (101–120)
Author Location gp120 (101–120 LAI)
Epitope `VEQMHEDIISLWDQSLKPCV`
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
References Moore *et al.* 1994c; Thiriart *et al.* 1989

- MF77.1: The relative affinity for denatured/native gp120 is 11. Moore *et al.* [1994c]

No. 393
MAb ID T2.1
HXB2 Location gp160 (101–120)
Author Location gp120 (101–120 LAI)
Epitope `VEQMHEDIISLWDQSLKPCV`
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
Research Contact Lennart Akerblom, Britta Wahren and Jorma Hinkula
References Moore *et al.* 1994d; Moore *et al.* 1994c; Bolmstedt *et al.* 1990; Akerblom *et al.* 1990

- T2.1: The relative affinity for denatured/native gp120 is .27 – mutations 113 D/R, 106 E/A, and 117 D/A impair binding. Moore *et al.* [1994c]

No. 394
MAb ID 11/65 (11/65a/5h)
HXB2 Location gp160 (102–121)
Author Location gp120 (311–321 HXB10)
Epitope `EQMHEDIISLWDQSLKPCVK`
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) rat (IgG2b)
Ab Type gp120 C1
References Peet *et al.* 1998; McKeating *et al.* 1993b; McKeating *et al.* 1992a

- 11/65: UK Medical Research Council AIDS reagent: ARP3076.
- 11/65: Called 11/65a/5h – The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind – 11/65 was not affected by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]
- 11/65: Binds only soluble gp120, not virion bound – used to quantify gp120 shedding – (numbering is incorrect in original?) McKeating *et al.* [1992a]

No. 395
MAb ID W1
HXB2 Location gp160 (102–121)
Author Location gp120 (102–121 LAI)
Epitope `EQMHEDIISLWDQSLKPCVK`
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
Research Contact D. Weiner, U. Penn.
References Moore *et al.* 1994c

- W1: The relative affinity for denatured/native gp120 is 6 – mutations 113 D/A, 113 D/R, and 117 K/W impair binding. Moore *et al.* [1994c]

No. 396
MAb ID T11
HXB2 Location gp160 (102–125)
Author Location gp120 (102–125)
Epitope `EQMHEDIISLWDQSLKPCVKLTPL`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* oligomeric gp140
Species (Isotype) mouse
Ab Type gp120 C1
Research Contact R. Doms, Univ. of Pennsylvania
References Jagodzinski *et al.* 1996; Earl *et al.* 1994

- T11: The sulfated polysaccharide, curdlan sulfate (CRDS), binds to the Envelope of T-tropic viruses and neutralizes virus – deletion of the V3 loop from gp120 results in more potent T11 inhibition by CRDS. Jagodzinski *et al.* [1996]
- T11: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

B Cell

No. 397
MAb ID GV1A8
HXB2 Location gp160 (105–113)
Author Location gp120 (105–113 IIIB)
Epitope HEDIISLWD
Neutralizing
Immunogen vaccine
Vector/Type: protein-Ab complex *HIV component:* gp120-Mab complex
Species (Isotype) mouse
Ab Type gp120 C1
References Kanduc *et al.* 2008; Denisova *et al.* 1996

- GV1A8: Similarity level of the GV1A8 binding site pentapeptide ISLWD to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 1 time, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- GV1A8: When anti-V3 MAb M77 was bound to gp120 and used as an immunogen, it stimulated many MAbs to linear epitopes – MAbs GV7A4 and GV5H5 are homologous to GV1A8 and were generated in the same experiment. Denisova *et al.* [1996]

No. 398
MAb ID CA13 (ARP3119)
HXB2 Location gp160 (106–112)
Author Location Env
Epitope EDIISLW
Subtype A
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia prime with gp120 boost *Strain:* A clade *HIV component:* Env
Species (Isotype) mouse
Ab Type gp120 C1
References Sheppard *et al.* 2007b; Holl *et al.* 2006a; Billington *et al.* 2007; Zipeto *et al.* 2005; Jeffs *et al.* 2004
Keywords dendritic cells, neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- CA13: MRC Centralized Facility for AIDS Reagents, NIBSC, UK, ARP3119.
- CA13: The MAb CA13 binds to the conserved C1 epitope EDIISLW and was used in conjunction with MAb 221, a MAb that binds to the gp120 C-terminal end, to explore the composition and stability of a highly stable trimeric rgp140 derived from a HIV-1 subtype D isolate containing intermonomer V3-derived disulfide bonds and lacking gp120/gp41 proteolytic processing. The stability of the trimer indicates it may be a good candidate for structural studies. Billington *et al.* [2007]
- CA13: This clade A derived Ab was used in the analysis of clade C gp140 (97CN54) antigenicity and was shown to recognize this molecule. Sheppard *et al.* [2007b] (**variant cross-recognition or cross-neutralization**)
- CA13: This Ab did not inhibit HIV-1 BaL replication in macrophages. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- CA13: HIV-1 fusion complexes were prepared from cell lines expressing R5 HIV-1 gp120/gp41 and CD4-CCR5. Neutralizing Abs were raised against both R5 (strain BaL) and X4 (strain 213) viruses. CA13 was used to detect gp120/gp41. Zipeto *et al.* [2005] (**vaccine antigen design**)
- CA13: A set of oligomeric envelope proteins were made from six primary isolates for potential use as vaccine antigens: 92/UG/037 (clade A), HAN2/2 (clade B), 92/BR25/025 (clade C), 92/UG/021 (clade D), 93/BR/029 (clade F) and MVP5180 (clade O). This was one of a panel of MAbs used to explore folding and exposure of well characterized epitopes. The clade C isolate BR25 is apparently misfolded, as conformation-dependent antibodies did not bind to it. CA13 is a MAb that binds to a linear epitope in the C13 region of gp120 that was raised against clade A variant 92/UG/029. C13 bound to antigens from all clades A-F, as well as group O. Polyclonal sera raised in rabbits against these antigens cross-bound the other antigens, but none of the sera had neutralizing activity. Jeffs *et al.* [2004] (**vaccine antigen design**, **subtype comparisons**)

No. 399
MAb ID 11
HXB2 Location gp160 (111–120)
Author Location gp120 (101–120 LAI)
Epitope LWDQSLKPCV
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
References Kanduc *et al.* 2008; Moore *et al.* 1994c; Thiriart *et al.* 1989

- 11: Similarity level of the 11 binding site pentapeptide WDQSL to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 11: The relative affinity for denatured/native gp120 is 7.8 – mutation 113 D/R impairs binding. Moore *et al.* [1994c]

No. 400
MAb ID 12G10
HXB2 Location gp160 (111–120)
Author Location gp120 (101–120 LAI)
Epitope LWDQSLKPCV
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
References Moore *et al.* 1994c; Thiriart *et al.* 1989

- 12G10: The relative affinity for denatured/native gp120 is 17 – mutation 117 K/W impairs binding. Moore *et al.* [1994c]

No. 401
MAb ID 135/9 (87-135/9)
HXB2 Location gp160 (111–120)

B Cell

Author Location gp120 (111–120 LAI)
Epitope LWDQSLKPCV
Subtype B
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 C1
Research Contact Matthias Niedrig
References Yang *et al.* 2000; Kropelin *et al.* 1998; Binley *et al.* 1998; Binley *et al.* 1997a; Trkola *et al.* 1996a; Moore & Sodroski 1996; Moore *et al.* 1994d; Moore *et al.* 1994c; Niedrig *et al.* 1992b

- 135/9: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000]
- 135/9: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
- 135/9: Noted to bind to C1 peptide HEDIISLWDQSLK – blocks gp120 interaction with CD4+ cells – blocking activity is additive when combined with antibodies which bind in the C4 region of gp120 (F105, 388/389, and b12) Kropelin *et al.* [1998]
- 135/9: Binding is enhanced by some anti-C1 and anti-C5 antibodies – enhances binding of some anti-V3, anti-C4 and anti-V2 MAbs – 135/9 binds to predicted alpha-helix in C1. Moore & Sodroski [1996]
- 135/9: Does not neutralize JR-FL nor block gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]
- 135/9: The relative affinity for denatured/native gp120 is 15 – mutation 113 D/R impairs binding to native and denatured, 113 D/A only to denatured. Moore *et al.* [1994c]
- 135/9: Substitutions 106 E/A, 113 D/A or R, and 117 K/W impair binding, some substitutions enhance binding. Moore *et al.* [1994d]
- 135/9: Defines the epitope as gp120(114-123) MHEDIISLWD (core LWD?) – weak neutralization of lab strain. Niedrig *et al.* [1992b]

No. 402
MAb ID 7C10
HXB2 Location gp160 (111–120)
Author Location gp120 (101–120 LAI)
Epitope LWDQSLKPCV
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
References Moore *et al.* 1994c; Thiriart *et al.* 1989

- 7C10: The relative affinity for denatured/native gp120 is 5.8 – mutation 117 K/W impairs binding. Moore *et al.* [1994c]

No. 403
MAb ID C4
HXB2 Location gp160 (111–120)
Author Location gp120 (101–120 LAI)
Epitope LWDQSLKPCV
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG1)
Ab Type gp120 C1
Research Contact George Lewis
References Moore *et al.* 1994c; Moore & Ho 1993; Abacioglu *et al.* 1994

- C4: C1 region – epitope boundaries mapped by peptide scanning, BH10 core IISLW. Abacioglu *et al.* [1994]
- C4: The relative affinity for denatured/native gp120 is 10. Moore *et al.* [1994c]
- C4: Bound preferentially to denatured IIIB gp120. Moore & Ho [1993]

No. 404
MAb ID MF46.1
HXB2 Location gp160 (111–120)
Author Location gp120 (101–120 LAI)
Epitope LWDQSLKPCV
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
References Moore *et al.* 1994c; Thiriart *et al.* 1989

- MF46.1: The relative affinity for denatured/native gp120 is 8.5. Moore *et al.* [1994c]

No. 405
MAb ID 6D5
HXB2 Location gp160 (122–141)
Author Location gp120 (122–141 LAI)
Epitope LTPLCVSLKCTDLKNDTNTN
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 V2
Research Contact S. Nigida and L. Arthur, NCI, Frederick, MD USA

B Cell

References Moore *et al.* 1994d; Moore *et al.* 1994c

- 6D5: The relative affinity for denatured/native gp120 is 15 – mutations Delta119-205 and 125 L/G impair binding. Moore *et al.* [1994c]

No. 406
MAb ID B33
HXB2 Location gp160 (123–142)
Author Location gp120 (123–142 LAI)
Epitope TPLCVSLKCTDLGNATNTNS
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43
HIV component: gp160
Species (Isotype) mouse (IgG2bκ)
Ab Type gp120 V2
Research Contact Daniels
References Bristow *et al.* 1994; Abacioglu *et al.* 1994

- B33: UK Medical Research Council AIDS reagent: ARP304, gp160/41 binding.
- B33: There are two MAbs in the literature named B33, see also gp160(727-734) Abacioglu *et al.* [1994]
- B33: Epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]
- B27: C1 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp160 IIIB:NL43, MicroGenSys. Bristow *et al.* [1994]

No. 407
MAb ID polyclonal (VEI1)
HXB2 Location gp160 (131–151)
Author Location Env (131–151)
Epitope CTDLKNDTNTNSSSGRMMMEK
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Carlos *et al.* 1999

- Antibody response to the epitopes in a vaccine construct (VEI) containing peptides from 5 hypervariable regions of gp120 was detected in the sera of HIV-1 positive subjects, including sera from 6 non-subtype B infections – serum samples from San Francisco, Canada and Puerto Rico cohort showed presence of antibodies against all five VEI hypervariable regions, but most consistently against the V3 region peptide NNNTRKSIRIGPGRAFYTTGDIGNIRQ. Carlos *et al.* [1999]

No. 408
MAb ID 35D10/D2
HXB2 Location gp160 (139–155)
Author Location gp120
Epitope NTKSSNWKEMDGEIK
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162
HIV component: gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 V1
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 35D10/D2: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yeilded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- 35D10/D2: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potently neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**)

No. 409
MAb ID 40H2/C7
HXB2 Location gp160 (139–155)
Author Location gp120
Epitope NTKSSNWKEMDGEIK
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162
HIV component: gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 V1
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 40H2/C7: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yeilded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- 40H2/C7: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potently neutralize autologous strain SF162 but

were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**)

No. 410
MAb ID 43A3/E4
HXB2 Location gp160 (139–155)
Author Location gp120
Epitope NTKSSNWKEMDGEIK
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 V1
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 43A3/E4: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yeilded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- 43A3/E4: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potently neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**)

No. 411
MAb ID 43C7/B9
HXB2 Location gp160 (139–155)
Author Location gp120
Epitope NTKSSNWKEMDGEIK
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 V1
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 43C7/B9: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yeilded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- 43C7/B9: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potently neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**)

No. 412
MAb ID 45D1/B7
HXB2 Location gp160 (139–155)
Author Location gp120
Epitope NTKSSNWKEMDGEIK
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 V1
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 45D1/B7: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yeilded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- 45D1/B7: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potently neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**)

No. 413
MAb ID 46E3/E6
HXB2 Location gp160 (139–155)
Author Location gp120

Epitope NTKSSNWKEMDGEIK
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 V1
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 46E3/E6: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yeilded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- 46E3/E6: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potently neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**)

No. 414
MAb ID 58E1/B3
HXB2 Location gp160 (139–155)
Author Location gp120
Epitope NTKSSNWKEMDGEIK
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 V1
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 58E1/B3: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yeilded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- 58E1/B3: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potently neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**)

No. 415
MAb ID 64B9/A6
HXB2 Location gp160 (139–155)
Author Location gp120
Epitope NTKSSNWKEMDGEIK
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 V1
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 64B9/A6: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yeilded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- 64B9/A6: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potently neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**)

No. 416
MAb ID 69D2/A1
HXB2 Location gp160 (139–155)
Author Location gp120
Epitope NTKSSNWKEMDGEIK
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 V1

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Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 69D2/A1: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yeilded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- 69D2/A1: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potently neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**)

No. 417
MAb ID 82D3/C3
HXB2 Location gp160 (139–155)
Author Location gp120
Epitope `NTKSSNWKEMDGEIK`
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 V1
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 82D3/C3: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yeilded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- 82D3/C3: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potently neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**)

No. 418
MAb ID P1H6
HXB2 Location gp160 (143–148)
Author Location gp120 (SF162)
Epitope `SSNWKE`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with protein boost *Strain:* B clade SF162 *HIV component:* gp140ΔV2
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 V1
Research Contact Nina Derby or Leo Stamatatos, Seattle Biomedical Research Institute, Seattle, WA, USA, leo.stamatotos@sbri.org
References Ching *et al.* 2008; Derby *et al.* 2007
Keywords antibody binding site definition and exposure, neutralization, optimal epitope

- P1H6: The study explores how the V1 loop of Env influences the neutralization susceptibilities of heterologous viruses to antibodies elicited by the SF162gp140 immunogen. When the V1 loop of the heterologous isolates was replaced by the V1 loop present on the DF162go140 immunogen, these isolates became susceptible to neutralization by p1H6. Ching *et al.* [2008] (**neutralization**)
- P1H6: Binding of P1H6 is partially dependent on the conformation of V1, while the presence of V3 is not required. P1H6 neutralized SF162 potently but it did not have any heterologous neutralizing activity. The Ab did not neutralize virus lacking V1. The SF162ΔV2 virus was significantly more susceptible to neutralization by P1H6 than the wildtype virus. Glycans at positions 154 and 195 in V1V2 were involved in regulating P1H6 neutralizing potential. Neutralization by P1H6 was also enhanced strongly by deletion of the V3 glycan at position 299, even more so by deletion at position 329, and only slightly or not at all by deletion of the glycan at position 293. Glycans present in the V4-V5 region had only modest effects on the neutralizing potential of this Ab, where their removal resulted in a more neutralization resistant virus. Derby *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **optimal epitope**)

No. 419
MAb ID 697-D (697D, 697-30D)
HXB2 Location gp160 (161–180)
Author Location gp120 (161–180 IIIB)
Epitope `ISTSIRGKVQKEYAFFYKLD`
Neutralizing P (weak)
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V2
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center) or Cellular Products Inc, Buffalo NY

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References Granados-Gonzalez *et al.* 2008; Kramer *et al.* 2007; Holl *et al.* 2006a; Selvarajah *et al.* 2005; Mc Cann *et al.* 2005; Kalia *et al.* 2005; Gorny & Zolla-Pazner 2004; He *et al.* 2002; Maksiutov *et al.* 2002; Edwards *et al.* 2002; Nyambi *et al.* 2000; Hioe *et al.* 2000; Gorny *et al.* 2000; Stamatatos & Cheng-Mayer 1998; Nyambi *et al.* 1998; Parren *et al.* 1997b; Fouts *et al.* 1997; Binley *et al.* 1997a; Trkola *et al.* 1996a; Moore & Ho 1995; Forthal *et al.* 1995; Gorny *et al.* 1994

Keywords ADCC, antibody binding site definition and exposure, binding affinity, co-receptor, dendritic cells, enhancing activity, neutralization, review, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- 697-D: The study evaluated the influence of glycosylation within the V1/V2 domain on antibody recognition. Recombinant proteins, demonstrated to be folded in native conformation, were produced following transfection of CHO cells by plasmids expressing V1/V2 domains from primary isolates of different clades. This Ab was used to validate the functional structure of the recombinant proteins produced. Granados-Gonzalez *et al.* [2008]
- 697-D: This review summarizes 697-D Ab epitope, properties and neutralization activity. Kramer *et al.* [2007] (**review**)
- 697D: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 697-30D: Point mutations in the highly conserved structural motif LLP-2 within the intracytoplasmic tail of gp41 resulted in conformational alternations of both gp41 and gp120. The alternations did not affect virus CD4 binding, coreceptor binding site exposure, or infectivity of the virus, but did result in decreased binding and neutralization by certain MAbs and human sera. 697-30D showed a decrease in binding to the LLP-2 mutant compared to the wildtype virus, indicating that its epitope was altered by the mutation. Kalia *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)
- 697-D: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **review**)
- 697-D: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. V2 MAb 697-D did not bind to mCHO and had diminished binding to GDMR, while V2 MAb 8.22.2 bound to GDMR but not mCHO. Selvarajah *et al.* [2005] (**vaccine antigen design**, **vaccine-specific epitope characteristics**)
- 697-D: In a review of Envelope binding MAbs in this database, V2-specific MAbs are noted to have some ability to neutralize HIV-1, but generally weak with limited cross-reactivity; it weakly neutralizes some primary but not TCLA strains. 697-D is the best characterized of the anti-V2 MAbs, and binds weakly and sporadically to isolates from clades A-D. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**, **subtype comparisons**)
- 697-D: Called 697D – Truncation of the gp41 cytoplasmic domain of X4, R5, and X4R5 viruses forces a conformation that more closely resembles the CD4 bound state of the external Envelope, enhancing binding of CD4i MAbs 17b and 48d and of CD4BS MAbs F105, b12, and in most cases of glycosylation site dependent MAb 2G12 and the anti-gp41 MAb 246D – in contrast, binding of the anti-V2 MAb 697D and the anti-V3 MAb 694/98D were not affected – viruses bearing the truncation were more sensitive to neutralization by MAbs 48d, b12, and 2G12 – the anti-C5 MAb 1331A was used to track levels of cell surface expression of the mutated proteins. Edwards *et al.* [2002] (**antibody binding site definition and exposure**)
- 697-D: Called 697D – Transgenic mice carrying human genes allowing production of fully human MAbs were used to rapidly create a panel of anti-HIV gp120 MAb producing hybridomas by immunization with HIV SF162 gp120 – the previously described human MAbs 5145A, 4117C and 697D were used as controls. He *et al.* [2002]
- 697-D: This epitope is similar to a fragment of the human protein macrophage colony stimulating factor I receptor SISIRLKVQK. Maksiutov *et al.* [2002]
- 697-D: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – V2 MAbs 697-D, 1357 and 1361 favored the monomer by approximately 2 fold. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)
- 697-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – CD4BS MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – V2 MAb 697-D did not effect proliferation. Hioe *et al.* [2000]
- 697-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 anti-V2 MAbs, which showed weak and sporadic binding, with the most frequent binding to C and D clades. Nyambi *et al.* [2000] (**subtype comparisons**)
- 697-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – V2 Abs 697-D, 1361, and 1357 tended to bind weakly with a similar pattern of specificity to virions, and bound well to soluble gp120: weak binding to 1/4

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B clade viruses (CA5), and weak binding to viruses from subtype A and D. Nyambi *et al.* [1998] (**subtype comparisons**)

- 697-D: Called 697-30D – deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V1 or V2 did not enable neutralization by V2 MAbs G3.4, G3.136, or 687-30D. Stamatatos & Cheng-Mayer [1998] (**variant cross-recognition or cross-neutralization**)
- 697-D: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – 697-D bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
- 697-D: Does not neutralize TCLA strains but neutralizes some primary isolates weakly. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 697-D: Partial inhibition of gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a] (**co-receptor**)
- 697-D: Not neutralizing, no ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995] (**ADCC**, **enhancing activity**)
- 697-D: Review: called 697/30D – neutralizes some primary, but not lab adapted strains. Moore & Ho [1995] (**variant cross-recognition or cross-neutralization**, **review**)
- 697-D: Conformational with weak reactivity to V2 peptide ISTSIRGKVQKEYAFFYKLD – neutralized 3/4 primary isolates, but none of 4 lab strains – V2 substitutions 176/177 FY/AT, 179/180 LD/DL, 183/184 PI/SG, and 192-194 YSL/GSS abrogate binding – anti-C4 MAbs G3-536 and G45-60 enhance binding – mild oxidation of carbohydrate moieties inhibits binding. Gorny *et al.* [1994] (**antibody binding site definition and exposure**)

No. 420
MAb ID 6C4/S
HXB2 Location gp160 (162–169)
Author Location gp120 (BH10)
Epitope STSIRGKV
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10
HIV component: gp120
Species (Isotype)
Research Contact S. Ranjbar (NIBSC, UK)
References Moore *et al.* 1993a

- 6C4/S: UK Medical Research Council AIDS reagent: ARP3049.

No. 421
MAb ID C108G (C108g)
HXB2 Location gp160 (162–169)
Author Location gp120 (162–169 HXB2)
Epitope STSIRGKV
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) chimpanzee (IgG1κ)
Ab Type gp120 V2
Research Contact S. Tilley, Public Health Research Institute, NY, NY
References Sheppard *et al.* 2007b; Honnen *et al.* 2007; Pinter *et al.* 2005; Gorny & Zolla-Pazner 2004; Alsmadi & Tilley 1998; Mondor *et al.* 1998; Ugolini *et al.* 1997; Warrier *et al.* 1996; Warrier *et al.* 1995; Wu *et al.* 1995; Warrier *et al.* 1994
Keywords ADCC, antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, review, variant cross-recognition or cross-neutralization

- C108G: Position 167 in V2 dictates the specificities of three type-specific neutralizing MAbs that bind to an otherwise relatively conserved epitope in involving V2: 2909, C108g, and 10/76b. Introduction of D167G mutation in YU2 Env resulted in significant neutralization by C108G. Removing of glycan at position N131 and V1 glycosylation site 140 resulted in increase in sensitivity to C108G. On the other hand, eliminating the glycan at position 160 in V2 in conjuction with V1 glycan and D167G mutations resulted in large decrease in sensitivity to C108, indicating that the glycan in this position is an important component of the C108G epitope. Honnen *et al.* [2007] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- C108G: This Ab was shown not to react with clade C gp140 (97CN54). Sheppard *et al.* [2007b] (**variant cross-recognition or cross-neutralization**)
- C108G: This MAb is type-specific and neutralizes BaL and HXB2. It is the most potent anti-V2 MAb, is glycan dependent, and contrary to earlier reports requires disulfide bonds. Neutralization by C108g is not mediated by CD4 or CCR5 receptor blockage on the cell surface. Binding to CD4 was inhibited by b12, but not by C108g. Binding to CCR5 was completely inhibited by two V3 MAbs, 4117C and 2219, and was substantially inihibited by 2G12, but was not inhibited by C108g.JR-FL is a neutralization resistant strain; modification of JRFL at positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potently neutralize the modified JR-FL.The MAb 10/76b, that binds to a linear V2 epitope that is unaffected by deglycosylation or reduction eliminating disulfinde bonds, could only weakly neutralize this modified JR-FL. Similarly SF162 substitutions in the neutralization sensitive virus SF162 GVK->NMK (167-169) plus the glycoslyation site at 160, created a G108g neutralization sensitive virus. In contrast, 10/76b binds to the NMK substituted variant, but addition of the glycosylation site inhibited binding. Pinter *et al.* [2005] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- C108G: This MAb is unusual among V2-directed MAbs. It is glycan dependent and can neutralize both a primary isolate (BaL and a TCLA (IIIB) strain. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure**, **review**)
- C108G: A study of 6 anti-Env MAbs and their ability to bind or direct ADCC against target cells infected with IIIB, MN, SF-2, and RF – C108G bound and directed lysis against only

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IIIB – this is first demonstration of ADCC directed by a V2 specific MAb. Alsmadi & Tilley [1998] (**ADCC**, **variant cross-recognition or cross-neutralization**)
- C108G: Inhibits HX10 binding to both CD4 positive and negative HeLa cells. Mondor *et al.* [1998]
- C108G: Viral binding inhibition by C108G was correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5) Ugolini *et al.* [1997] (**antibody binding site definition and exposure**)
- C108G: Synergistic neutralization of HIV-1 when combined with anti-V3 MAbs 0.5beta and C311E, or anti-CD4BS MAbs, 1125H and 5145A – neutralization further enhanced by presence of both 1125H and 0.5beta. Warrier *et al.* [1996] (**antibody interactions**)
- C108G: Characterization of MAb variable region. Warrier *et al.* [1995] (**antibody sequence variable domain**)
- C108G: Strain specificity: LAI, BaL, HXB2 – conformational character – glycosylation site at 160 critical – mutation of conserved glycosylation site at 156 increased epitope exposure. Wu *et al.* [1995] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- C108G: Chimps were infected with HIV-1 IIIB, and this high affinity MAb was obtained from an Epstein-Barr virus transformed B-cell line. It gave potent neutralization of HIV-1 IIIB. Binding was not affected by reduction of disulfide bonds. Binding was disrupted by removal of N-linked glycans. The peptide binds with lower affinity than glycosylated Env. Warrier *et al.* [1994] (**antibody binding site definition and exposure**, **antibody generation**)

No.	422
MAb ID	10/76b
HXB2 Location	gp160 (162–170)
Author Location	gp120 (162–171 BH10)
Epitope	STSIRGKVQ
Neutralizing	L (HXB10
Immunogen	vaccine *Vector/Type:* protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype)	rat (IgG2a)
Research Contact	Jane McKeating
References	Honnen *et al.* 2007; Pinter *et al.* 2005; McKeating *et al.* 1996; Wu *et al.* 1995; Shotton *et al.* 1995; McKeating *et al.* 1993a; McKeating *et al.* 1993b
Keywords	antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization

- 10/76b: UK Medical Research Council AIDS reagent: ARP3077.
- 10/76b: Position 167 in V2 dictates the specificities of three type-specific neutralizing MAbs that bind to an otherwise realtively conserved epitope in involving V2: 2909, C108g, and 10/76b. Introduction of D167G mutation in YU2 Env resulted in weak neutralization by 10/76b. Removing the glycan at position N131 resulted in increase in sensitivity to 10/76b while removing of V1 glycosylation site 140 had minimal effect. Eliminating the glycan at position 160 in V2 in conjuction with V1 glycan and D167G mutations resulted in an increase in sensitivity to 10/76b, indicating that the glycan in this position acts as a potent masking element for the 10/76b epitope. Honnen *et al.* [2007] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 10/76b: This study is about the MAb C108g, and 10/76b was a control. C108g is type-specific and neutralizes BaL and HXB2. It is the most potent anti-V2 MAb, and is glycan dependent and contrary to earlier reports requires disulfide bonds. Neutralization by C108g is not mediated by CD4 or CCR5 receptor blockage on the cell surface. JR-FL is a neutralization resistant strain; modification of JRFL at positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potently neutralize the modified JR-FL.The MAb 10/76b, that binds to a linear V2 epitope that is unaffected by deglycosylation or reduction eliminating disulfinde bonds, could only weakly neutralize this modified JR-FL. Similarly SF162 substitutions in the neutralization sensitive virus SF162 GVK->NMK (167-169) plus the glycoslyation site at 160, created a G108g neutralization sensitive virus. In contrast, 10/76b binds to the NMK substituted variant, but addition of the glycosylation site inhibited binding. Pinter *et al.* [2005] (**antibody binding site definition and exposure**)
- 10/76b: Neutralizes HXB2, but fails to neutralize chimeric virus with gp120 from primary isolates in an HXB2 background. McKeating *et al.* [1996]
- 10/76b: Cross-competes with MAbs 10/76b and 11/4b – HXB2 neutralization escape mutant has the substitution I/T at residue 165. Shotton *et al.* [1995] (**antibody binding site definition and exposure**)
- 10/76b: Included in cross-competition and neutralization studies. Shotton *et al.* [1995] (**antibody binding site definition and exposure**)
- 10/76b: HX10 strain specificity – binds native, deglycosylated, or denatured gp120. Wu *et al.* [1995] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 10/76b: This MAb was obtained from a hybridoma cell line. An R to L substitution abrogated binding. Human sera recognize the 10/76 epitope. McKeating *et al.* [1993b] (**antibody generation**)

No.	423
MAb ID	11/41e
HXB2 Location	gp160 (162–170)
Author Location	gp120 (162–171)
Epitope	STSIRGKVQ
Neutralizing	L (HXB10)
Immunogen	vaccine *Vector/Type:* protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype)	rat (IgG1)
References	Wu *et al.* 1995; Shotton *et al.* 1995; McKeating *et al.* 1993b

- 11/41e: Included in cross-competition and neutralization studies. Shotton *et al.* [1995]
- 11/41e: HX10 strain specificity – binds native and deglycosylated gp120. Wu *et al.* [1995]
- 11/41e: R to L abrogated binding – human sera recognize the epitope. McKeating *et al.* [1993b]

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No. 424
MAb ID 11/4b
HXB2 Location gp160 (162–170)
Author Location gp120 (162–171)
Epitope STSIRGKVQ
Neutralizing L (HXB10)
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) rat (IgG2a)
References Moore & Sodroski 1996; Wu *et al.* 1995; Shotton *et al.* 1995; McKeating *et al.* 1993b

- 11/4b: Linear V2 epitope – reciprocal binding enhancement of anti-V2 discontinuous epitope antibodies (in contrast to BAT085) and CD4 inducible antibody 48d. Reciprocal inhibits BAT085 binding – inhibits CRA-3 binding CRA-3 does not inhibit 11/4b. Moore & Sodroski [1996]
- 11/4b: Cross-competes with MAbs 10/76b and 11/4c – HXB2 neutralization escape mutant has the substitution I/T at residue 165. Shotton *et al.* [1995]
- 11/4b: HXB10 strain specificity – binds native, deglycosylated, or denatured gp120. Wu *et al.* [1995]
- 11/4b: A change from R to L abrogated binding – human sera recognize epitope. McKeating *et al.* [1993b]

No. 425
MAb ID RSD-33
HXB2 Location gp160 (162–170)
Author Location gp120 (162–171)
Epitope STSIRGKVQ
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype)
Research Contact R. Daniels (NIMR, UK)
References Moore *et al.* 1993a

No. 426
MAb ID 11/4c (11/4c/1j/4j)
HXB2 Location gp160 (162–170)
Author Location gp120 (152–181)
Epitope STSIRGKVQ
Neutralizing L (HXB2)
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) rat (IgG2a)
Ab Type gp120 V2
References Peet *et al.* 1998; Shotton *et al.* 1995; Wu *et al.* 1995; McKeating *et al.* 1993b

- 11/4c: UK Medical Research Council AIDS reagent: ARP3035.
- 11/4c: Called 11/4c/1j/4j – The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind – 11/4c was not affected by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]
- 11/4c: Cross-competes with MAbs 10/76b and 11/4b – HXB2 neutralization escape mutant has the substitution I/T at residue 165. Shotton *et al.* [1995]
- 11/4c: HX10 strain specificity – binds native, deglycosylated, or denatured gp120. Wu *et al.* [1995]
- 11/4c: R to L substitution abrogated binding – human sera recognize epitope. McKeating *et al.* [1993b]

No. 427
MAb ID 8.22.2
HXB2 Location gp160 (162–178)
Author Location gp120
Epitope TTSIRDKVQKEYALFYK
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 V2
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Granados-Gonzalez *et al.* 2008; Dhillon *et al.* 2007; Selvarajah *et al.* 2005; Pinter *et al.* 2004; Pantophlet *et al.* 2004; Gorny & Zolla-Pazner 2004; Maksiutov *et al.* 2002; He *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, neutralization, review, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- 8.22.2: The study evaluated the influence of glycosylation within the V1/V2 domain on antibody recognition. Recombinant proteins, demonstrated to be folded in native conformation, were produced following transfection of CHO cells by plasmids expressing V1/V2 domains from primary isolates of different clades. This Ab was used to validate the functional structure of the recombinant proteins produced. Granados-Gonzalez *et al.* [2008]
- 8.22.2: This Ab was used to help define the antigenic profile of envelopes used in serum depletion experiments to attempt to define the neutralizing specificities of broadly cross-reactive neutralizing serum. This Ab bound to JR-FL and JR-CSF gp120 monomers but not to core JR-CSF gp120 monomer used in the same experiments. V1, V2, and V3 specificities did not contribute to the broadly neutraling capability of sera from 3 (2 B clade ,1 A clade) HIV infected individuals. Dhillon *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**)
- 8.22.2: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs

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did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. V2 MAb 697-D did not bind to mCHO and had diminished binding to GDMR, while V2 MAb 8.22.2 bound to GDMR but not mCHO. Selvarajah *et al.* [2005] (**vaccine antigen design**, **vaccine-specific epitope characteristics**)

- 8.22.2: This broad review of anti-Envelope MAbs notes that V2 MAbs are generally weakly neutralizing at best, and somewhat strain specific. 8.22.2 weakly neutralizes SF162. Gorny & Zolla-Pazner [2004] (**review**)
- 8.22.2: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 8.22.2. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- 8.22.2: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neturalization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype.Three anti-V2 MAb were tested – 8.22.2 weakly neutralized SF162, and did not neutralize JRFL at all. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 8.22.2 : Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – 8.22.2 was the only V2-specific MAb created and it could cross-compete with MAb 697D – 8.22.2 could cross-react with BaL and JR-FL, two B clade R5 strains, but not B clade X4 or E clade viruses, and it could weakly neutralize autologous strain SF162. He *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 8.22.2: This epitope is similar to a fragment of the human protein macrophage colony stimulating factor I receptor SISIRLKVQK. Maksiutov *et al.* [2002]

No. 428
MAb ID 12b
HXB2 Location gp160 (162–181)
Author Location gp120 (162–181)
Epitope STSIRGKVQKEYAFFYKLDI
Neutralizing L (HXB10)
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) rat (IgG2a)
Ab Type gp120 V2
References Maksiutov *et al.* 2002; McKeating *et al.* 1996; Shotton *et al.* 1995

- 12b: This epitope is similar to a fragment of the human protein macrophage colony stimulating factor I receptor SISIRLKVQK. Maksiutov *et al.* [2002]
- 12b: Neutralizes HXB2, but fails to neutralize chimeric virus with gp120 from primary isolates in an HXB2 background. McKeating *et al.* [1996]
- 12b: V2 MAb neutralized HXB2 – position 179-180 LD to DL abrogates binding – competes with 60b, but not 74. Shotton *et al.* [1995]

No. 429
MAb ID G3-136 (G3.136)
HXB2 Location gp160 (170–180)
Author Location gp120 (170–180 IIIB)
Epitope QKEYAFFYKLD
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgG)
Ab Type gp120 V2
Research Contact Tanox Biosystems Inc and David Ho, ADARC, NY
References Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Ly & Stamatatos 2000; Stamatatos & Cheng-Mayer 1998; Parren *et al.* 1998a; Wyatt *et al.* 1997; Ditzel *et al.* 1997; Stamatatos *et al.* 1997; Binley *et al.* 1997a; Poignard *et al.* 1996a; Moore & Sodroski 1996; Stamatatos & Cheng-Mayer 1995; Sattentau & Moore 1995; Yoshiyama *et al.* 1994; Moore *et al.* 1993a; Moore & Ho 1993; Thali *et al.* 1993; Pirofski *et al.* 1993; Fung *et al.* 1992
Keywords antibody interactions, vaccine antigen design

- G3-136: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- G3-136: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the V2 MAb used. Zwick *et al.* [2003] (**antibody interactions**)

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- G3-136: Called G3.136 – SF162 is a neutralization-resistant HIV-1 isolate – N-linked glycosylation modifications in the V2 loop of the SF162 gp120 revealed that these sites prevent neutralization by CD4BS MAbs (IgG1b12 and IgGCD4), and protect against neutralization by V3 MAbs (447-D and 391-95D) – V2-region glycosylation site mutations did not alter neutralization resistance to V2 MAbs (G3.4 and G3.136) or CD4i MAbs (17b and 48d) – V2 glycosylation site modification allows infection of macrophages, probably due to glycosylated forms requiring fewer CCR5 molecules for viral entry. Ly & Stamatatos [2000]
- G3-136: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- G3-136: Called G3.136 – deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V1 or V2 did not enable neutralization by V2 MAbs G3.4, G3.136, or 687-30D. Stamatatos & Cheng-Mayer [1998]
- G3-136: Called G3.136 – does not mediate gp120 virion dissociation in contrast to anti-V2 MAb G3-4 – not neutralizing for SF162 or SF128A in either primary macrophages or PBMC. Stamatatos *et al.* [1997]
- G3-136: Binds both gp120 and soluble gp120+gp41 complex efficiently, suggesting its gp120 epitope is not blocked by gp41 binding. Wyatt *et al.* [1997]
- G3-136: Described epitope as STSIRGKVKEYAFFYKLDI – binds oligomer – binding of V2 MAbs G3-136, G3-4 or BAT123 did not significantly alter gp120 dissociation from virus or expose the gp41 epitope of MAb 50-69, in contrast to anti-V3 MAbs. Poignard *et al.* [1996a]
- G3-136: Bound preferentially to the monomeric rather than oligomeric form of LAI gp120 – neutralizes cell free Hx10. Sattentau & Moore [1995]
- G3-136: The binding of conformation-dependent anti-V2, anti-V3, and anti-CD4BS MAbs to monomeric and virion-associated gp120 from HIV-1 isolates with differences in cell tropism was studied – V2 loop epitopes are somewhat occluded in the oligomeric gp120 epitopes on the virion surface relative to the gp120 monomer as indicated by an increase in the half-maximal binding values to macrophage-tropic isolates SF162 and SF128a – anti-V2 MAbs G3-4 and G3.136 don't bind to T-cell tropic SF2. Stamatatos & Cheng-Mayer [1995]
- G3-136: HIV-1 RF V2 substitutions 177 Y/H and 179 L/P in the V2 loop of RF reduce affinity. Yoshiyama *et al.* [1994]
- G3-136: Conformational, does not bind well to denatured gp120 – not reactive with SF-2 gp120, and does not inhibit HIV-1 sera from binding to IIIB gp120. Moore & Ho [1993]
- G3-136: Marginal binding to peptide, binding inhibited by 183/184 PI/SG substitution. Moore *et al.* [1993a]
- G3-136: Binding enhanced by selected antibodies to C1, C4, C5, V3 and anti-CD4 binding site MAbs – enhances binding of selected V3, C4 and anti-CD4 binding site MAbs. Moore *et al.* [1993a]
- G3-136: V2 region – binds and neutralizes IIIB and RF in CEM-SS cells, but not MN – neutralization activity against a few primary isolates in PBMC – sCD4 binding inhibits binding (contrast with BAT085) – deglycosylation or reduction of gp120 by DTT diminishes reactivity. Fung *et al.* [1992]

No.	430
MAb ID	G3-4 (G3.4)
HXB2 Location	gp160 (170–180)
Author Location	gp120 (170–180 BH10)
Epitope	QKEYAFFYKLD
Neutralizing	L
Immunogen	vaccine *Vector/Type:* protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype)	mouse (IgG2bκ)
Ab Type	gp120 V2
Research Contact	Tanox Biosystems Inc and David Ho, ADARC, NY
References	Derby *et al.* 2006; Binley *et al.* 2006; Gorny *et al.* 2005; Pantophlet *et al.* 2004; McCaffrey *et al.* 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Srivastava *et al.* 2002; Ly & Stamatatos 2000; Stamatatos & Cheng-Mayer 1998; Parren *et al.* 1998a; Wyatt *et al.* 1997; Ditzel *et al.* 1997; Stamatatos *et al.* 1997; Binley *et al.* 1997a; Poignard *et al.* 1996a; Moore & Sodroski 1996; Jagodzinski *et al.* 1996; Sattentau & Moore 1995; Wu *et al.* 1995; Stamatatos & Cheng-Mayer 1995; Yoshiyama *et al.* 1994; Thali *et al.* 1994; Gorny *et al.* 1994; Moore *et al.* 1994b; Moore *et al.* 1993a; Thali *et al.* 1993; Sattentau *et al.* 1993; Sullivan *et al.* 1993; Moore & Ho 1993; McKeating *et al.* 1992a; Fung *et al.* 1992; Ho *et al.* 1992; Ho *et al.* 1991a
Keywords	antibody binding site definition and exposure, antibody interactions, binding affinity, vaccine antigen design

- G3-4: This Ab bound to Fc-gp120 construct but not to the chimeras missing the V2 loop. Binley *et al.* [2006] (**binding affinity**)
- G3.4: Macaques were immunized with SF162gp140, ΔV2gp140, ΔV2ΔV3gp140 and ΔV3gp140 constructs and their antibody responses were compared to the broadly reactive NAb responses in a macaque infected with SHIV SF162P4, and with pooled sera from humans infected with heterologous HIV-1 isolates (HIVIG). Deletion of the crown of the V2 loop reduced the binding of G3.4. This Ab also recognized ΔV3gp140 less efficiently than SF162gp140 and recognized ΔV2ΔV3gp140 less efficiently than ΔV2gp140, indicating that deletion of the V3 loop has an effect on the binding of G3.4. Derby *et al.* [2006] (**antibody binding site definition and exposure**)
- G3-4: 2909 is a human anti-Env NAb that was selected by neutralization assay and binds to the quaternary structure on the intact virion. G3-4 was used as a positive control for defining the binding properties of 2909. Gorny *et al.* [2005]

- G3-4: Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The SF2 and all five glycan mutants were resistant to G3-4. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- G3-4: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including G3-4. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- G3-4: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- G3-4: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the V2 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- G3-4: Called G3.4 – Oligomeric gp140 (o-gp140) derived from R5 primary isolate US4 was characterized for use as a vaccine reagent – antigen capture ELISA was used to compare the antigenicity of gp120 and o-gp140 using a panel of well characterized MAbs – G3.4 recognized o-gp140. Srivastava *et al.* [2002]
- G3-4: Called G3.4 – SF162 is a neutralization-resistant HIV-1 isolate – N-linked glycosylation modifications in the V2 loop of the SF162 gp120 revealed that these sites prevent neutralization by CD4BS MAbs (IgG1b12 and IgGCD4), and protect against neutralization by V3 MAbs (447-D and 391-95D) – V2-region glycosylation site mutations did not alter neutralization resistance to V2 MAbs (G3.4 and G3.136) or CD4i MAbs (17b and 48d) – V2 glycosylation site modification allows infection of macrophages, probably due to glycosylated forms requiring fewer CCR5 molecules for viral entry. Ly & Stamatatos [2000]
- G3-4: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- G3-4: Called G3.4 – Deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V1 or V2 did not enable neutralization by V2 MAbs G3.4, G3.136, or 687-30D. Stamatatos & Cheng-Mayer [1998]
- G3-4: Called G3.4 – mediates gp120 virion dissociation in contrast to anti-V2 MAb G3-136 – not neutralizing for SF162 or SF128A in either primary macrophages or PBMC. Stamatatos *et al.* [1997]
- G3-4: Binds both gp120 and soluble gp120+gp41 complex efficiently, suggesting its gp120 epitope is not blocked by gp41 binding. Wyatt *et al.* [1997]
- G3-4: The sulfated polysaccharide curdlan sulfate (CRDS) binds to the Envelope of T-tropic viruses and neutralizes virus – deletion of the V3 loop from gp120 results in more potent G3-4 binding inhibition by CRDS – G3-4 epitope described as 176-184 FYKLDIIPI and 191-193 YSL. Jagodzinski *et al.* [1996]
- G3-4: Binding enhanced by selected antibodies to C1, C4, C5, V3 and anti-CD4 binding site MAbs – enhances binding of selected V3, C4 and anti-CD4 binding site MAbs. Moore & Sodroski [1996]
- G3-4: Described epitope as STSIRGKVKEYAFFYKLDI – binds oligomer – binding of V2 MAbs G3-136, G3-4 or BAT085 did not significantly alter gp120 dissociation from virus or expose the gp41 epitope of MAb 50-69, in contrast to anti-V3 MAbs. Poignard *et al.* [1996a]
- G3-4: Bound preferentially to the monomeric rather than oligomeric form of LAI gp120 – neutralizes Hx10 cell-free virus. Sattentau & Moore [1995]
- G3-4: The binding of conformation-dependent anti-V2, anti-V3, and anti-CD4BS MAbs to monomeric and virion-associated gp120 from HIV-1 isolates with differences in cell tropism was studied – V2 loop epitopes are somewhat occluded in the oligomeric gp120 epitopes on the virion surface relative to the gp120 monomer as indicated by an increase in the half-maximal binding values to macrophage-tropic isolates SF162 and SF128a – anti-V2 MAbs G3-4 and G3.136 don't bind to T-cell tropic SF2. Stamatatos & Cheng-Mayer [1995]
- G3-4: Reactive with BH10, RF, and MN – binds native, but not denatured or deglycosylated gp120, binds to deglycosylated V1V2 fusion protein, suggesting importance of glycans outside the V1V2 region. Wu *et al.* [1995]
- G3-4: Weakly neutralizing, IC 50 = 53 mug/ml. Gorny *et al.* [1994]
- G3-4: Conformationally sensitive – sporadic cross-reactivity among, and outside, B clade gp120s. Moore *et al.* [1994b]

- G3-4: gp41 mutation (582 A/T) that reduces neutralization of anti-CD4 binding site MAbs does not alter G3-4s ability to neutralize. Thali *et al.* [1994]
- G3-4: Neutralizes RF – substitutions 177 Y/H and 179 L/P in the V2 loop of RF reduce affinity and result in neutralization escape. Yoshiyama *et al.* [1994]
- G3-4: Conformational, does not bind well to denatured gp120 – not reactive with SF-2 gp120, and does not inhibit HIV-1 sera from binding to IIIB gp120. Moore & Ho [1993]
- G3-4: V2 region, marginal binding to peptide, binding inhibited by 183/184 PI/SG substitution. Moore *et al.* [1993a]
- G3-4: Increased binding in the presence of sCD4. Sattentau *et al.* [1993]
- G3-4: Substitutions in residues 176 to 184 affect MAb recognition – substitutions in V2 can result in gp120-gp41 dissociation. Sullivan *et al.* [1993]
- G3-4: Neutralizes IIIB and RF, not MN – blocks sCD4-gp120, not as potent as MAb 15e – V2 binding MAbs BAT085 and G3-136 block G3-4 gp120 binding – sensitive to reduction of gp120 by DTT. Ho *et al.* [1992]
- G3-4: Binding is sensitive to removal of glycans by endo H – 50% neutralization of 4/9 primary isolates – has conformational features. Ho *et al.* [1991a]

No. 431
MAb ID BAT085 (BAT-085)
HXB2 Location gp160 (171–180)
Author Location gp120 (170–180 IIIB)
Epitope KEYAFFYKLD
Neutralizing L
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
Research Contact Tanox Biosystems Inc and David Ho, ADARC, NY
References Kanduc *et al.* 2008; Parren *et al.* 1998a; Ditzel *et al.* 1997; Binley *et al.* 1997a; Poignard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; Wu *et al.* 1995; Yoshiyama *et al.* 1994; Gorny *et al.* 1994; Moore *et al.* 1994d; D'Souza *et al.* 1994; Moore *et al.* 1993a; Thali *et al.* 1993; Pirofski *et al.* 1993; Moore & Ho 1993; Fung *et al.* 1992; Fung *et al.* 1987

- BAT085: Similarity level of the BAT085 binding site pentapeptide EYAFF to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- BAT085: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- BAT085: Binding is blocked by other V2 region antibodies, enhanced by several anti-C1 MAbs, and anti-V3 MAb G511 – reciprocal enhancement of CD4i MAb 48d binding. Moore & Sodroski [1996]
- BAT085: Epitope suggested to be QKEYAFFYKLD – binds oligomer – binding of V2 MAbs G3-136, G3-4 or BAT123 did not significantly alter gp120 dissociation from virus or expose the gp41 epitope of MAb 50-69, in contrast to anti-V3 MAbs. Poignard *et al.* [1996a]
- BAT085: Bound preferentially to the monomeric rather than oligomeric form of LAI gp120 – neutralizes cell free Hx10. Sattentau & Moore [1995]
- BAT085: HXB10 strain specificity – binds native, deglycosylated, or denatured gp120. Wu *et al.* [1995]
- BAT085: Multi-lab study for antibody characterization and assay comparison – did not bind MN or SF2. D'Souza *et al.* [1994]
- BAT085: Interacts with two overlapping peptides with region of overlap KEYAFFYKLD. Gorny *et al.* [1994]
- BAT085: Neutralizes RF – substitution 177 Y/H in the V2 loop of RF does not inhibit neutralization, in contrast to MAbs G3-4 and SC258. Yoshiyama *et al.* [1994]
- BAT085: Called BAT-85 – conformational, does not bind well to denatured gp120 – not reactive with SF-2 gp120, and does not inhibit HIV-1 sera from binding to IIIB gp120. Moore & Ho [1993]
- BAT085: 7/8 V2 murine MAbs required gp120 native structure to bind, but BAT085 was the exception – type-specific. Moore *et al.* [1993a]
- BAT085: Peptide affinities of G3-136 and G3-4 are 100-fold less than BAT085, but BAT085 has lower affinity for BH10 gp120 and is weaker at neutralization. Moore *et al.* [1993a]
- BAT085: V2 region – sCD4 does not block – neutralizes IIIB and some primary isolates, but not MN or RF – binds MN – deglycosylation or DDT reduction of gp120 does not diminish reactivity. Fung *et al.* [1992]

No. 432
MAb ID 60b
HXB2 Location gp160 (172–181)
Author Location gp120 (172–181 HXB2)
Epitope EYAFFYKLDI
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) rat (IgG2b)
References Shotton *et al.* 1995

- 60b: V2 MAb did not neutralize HXB2 – bound to rgp120 in ELISA – substitutions 179-180 LD/DL and 191-193 YSL/GSS abrogate binding, as do changes outside the minimum epitope – competes with 12b, but not 74. Shotton *et al.* [1995]

No. 433
MAb ID 74
HXB2 Location gp160 (172–181)
Author Location gp120 (172–181)
Epitope EYAFFYKLDI
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120

B Cell

Species (Isotype) rat (IgG1)
References Shotton *et al.* 1995

- 74: V2 MAb did not neutralize HXB2 – did not bind rgp120 ELISA – position 179-180 LD to DL abrogates binding, as do changes outside the minimum epitope – does not compete with 60b or 12b, and is enhanced by two conformation dependent MAbs. Shotton *et al.* [1995]

No. 434
MAb ID 38/12b
HXB2 Location gp160 (172–191)
Author Location gp120 (172–191 HXB2)
Epitope EYAFFYKLDIIPIDNDTTSY
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) rat
References Wu *et al.* 1995

- 38/12b: Broad specificity: HXB2, MN, SF162 – binds native and deglycosylated gp120. Wu *et al.* [1995]

No. 435
MAb ID 38/60b
HXB2 Location gp160 (172–191)
Author Location gp120 (172–191 HXB2)
Epitope EYAFFYKLDIIPIDNDTTSY
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) rat
References Wu *et al.* 1995

- 38/60b: Strain specificity: HXB2 – binds native and deglycosylated gp120. Wu *et al.* [1995]

No. 436
MAb ID polyclonal (VEI2)
HXB2 Location gp160 (176–196)
Author Location Env
Epitope FYKLDIVPIDNTTTSYRLISC
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Carlos *et al.* 1999

- Antibody response to the epitopes in a vaccine construct (VEI) containing peptides from 5 hypervariable regions of gp120 was detected in the sera of HIV-1 positive subjects, including sera from 6 non-subtype B infections – serum samples from San Francisco, Canada and Puerto Rico cohort showed presence of antibodies against all five VEI hypervariable regions, but most consistently against the V3 region peptide NNNTRKSIRIGPGRAFYTTGDIGNIRQ. Carlos *et al.* [1999]

No. 437
MAb ID 322-151
HXB2 Location gp160 (211–221)
Author Location gp120 (201–220 LAI)
Epitope EPIPIHYCAPA
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Env
Species (Isotype) mouse (IgG)
Research Contact G. Robey, Abbot Labs
References Kanduc *et al.* 2008; Moore *et al.* 1994d; Moore *et al.* 1994c

- 322-151: Similarity level of the 322-151 binding site pentapeptide IPIHY to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 322-151: The relative affinity denatured/native gp120 is 30. Moore *et al.* [1994c]

No. 438
MAb ID 3D3.B8
HXB2 Location gp160 (211–221)
Author Location gp120 (211–220 LAI)
Epitope EPIPIHYCAPA
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Env
Species (Isotype) mouse (IgG)
References Moore *et al.* 1994c; Bolmstedt *et al.* 1990

- 3D3.B8: The relative affinity denatured/native gp120 is greater than 10. Moore *et al.* [1994c]

No. 439
MAb ID 4C11.D8
HXB2 Location gp160 (211–221)
Author Location gp120 (211–220 LAI)
Epitope EPIPIHYCAPA
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Env
Species (Isotype) mouse (IgM)
References Moore *et al.* 1994c; Bolmstedt *et al.* 1990

- 4C11.D8: The relative affinity denatured/native gp120 is greater than 10. Moore *et al.* [1994c]

No. 440
MAb ID 493-156
HXB2 Location gp160 (211–230)
Author Location gp120 (211–230 LAI)
Epitope EPIPIHYCAPAGFAILKCNN
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Env
Species (Isotype) mouse (IgG)
Research Contact G. Robey, Abbot Labs
References Moore *et al.* 1994c

B Cell

- 493-156: The relative affinity denatured/native gp120 is >10. Moore *et al.* [1994c]

No. 441
MAb ID 110.1
HXB2 Location gp160 (212–221)
Author Location gp120 (200–217)
Epitope PIPIHYCAPA
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Env
Species (Isotype) human
References Valenzuela *et al.* 1998; Pincus *et al.* 1996; Pincus & McClure 1993

- 110.1 database comment: There is another antibody with this ID that binds to Env at positions 491-500 in LAI.
- 110.1: A panel of immunotoxins were generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but killing was not directly proportional to binding – 110.1-RAC did not mediate cell killing, and sCD4 has no effect. Pincus & McClure [1993]; Pincus *et al.* [1996]

No. 442
MAb ID GV4H3
HXB2 Location gp160 (219–226)
Author Location gp120 (219–226 IIIB)
Epitope APAGFAIL
Neutralizing
Immunogen vaccine
Vector/Type: protein-Ab complex *HIV component:* gp120-Mab complex
Species (Isotype) mouse
References Denisova *et al.* 1996

- GV4H3: When anti-V3 MAb M77 was bound to gp120 and used as an immunogen, it stimulated many MAbs to linear epitopes. Denisova *et al.* [1996]

No. 443
MAb ID J1
HXB2 Location gp160 (222–231)
Author Location gp120 (222–231 LAI)
Epitope GFAILKCNNK
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade LAI
Species (Isotype) mouse (IgG1)
Research Contact J. Hoxie, U. Penn.
References Kanduc *et al.* 2008; Cook *et al.* 1994; Moore *et al.* 1994d; Moore *et al.* 1994c

- J1: Similarity level of the J1 binding site pentapeptide KC-NNK to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- J1: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – MAbs against the N-terminal half of gp120 do not inhibit gp120 binding to GalCer – binding of GalCer to gp120 does not inhibit MAb binding. Cook *et al.* [1994]
- J1: The relative affinity denatured/native gp120 is 30. Moore *et al.* [1994c]

No. 444
MAb ID J3
HXB2 Location gp160 (222–231)
Author Location gp120 (222–231 LAI)
Epitope GFAILKCNNK
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade LAI
Species (Isotype) mouse (IgG1)
Research Contact J. Hoxie, U. Penn.
References Cook *et al.* 1994; Moore *et al.* 1994c

- J3: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – MAbs against the N-terminal half of gp120 do not inhibit gp120 binding to GalCer – binding of GalCer to gp120 does not inhibit MAb binding. Cook *et al.* [1994]
- J3: The relative affinity denatured/native gp120 is 30. Moore *et al.* [1994c]

No. 445
MAb ID 1006-30-D (1006-30D)
HXB2 Location gp160 (236–245)
Author Location gp120 (241–251)
Epitope KGSCKNVSTV
Neutralizing
Immunogen
Species (Isotype) human (IgG1λ)
Ab Type gp120 C2
References Visciano *et al.* 2008b; Nyambi *et al.* 2000; Hioe *et al.* 2000

- 1006-30D: gp120 in complex with 1006-30D had enhanced reactivity with anti-V3 and anti-C1 mAbs 694/98D and EH21, respectively, but had no increased reactivity with anti-V3 mAb 447. Visciano *et al.* [2008b]
- 1006-30-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – CD4BS MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – C2 MAbs 1006-30-D and 847-D did not effect proliferation. Hioe *et al.* [2000]
- 847-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including two C2 MAbs – the binding of anti-C2 MAbs was weak to isolates from clades B, C, D, E, F, G, and they did not not bind to isolates from subtypes A and H – epitope is suggested to be in a 20 amino acid peptide KGSCKNVSTVQCTHGIRPVV. Nyambi *et al.* [2000]

No. 446
MAb ID 847-D (847-30, 847)
HXB2 Location gp160 (236–245)
Author Location gp120 (241–251)

B Cell

Epitope KGSCKNVSTV
Neutralizing
Immunogen
Species (Isotype) human (IgG1λ)
Ab Type gp120 C2
References Visciano *et al.* 2008a; Kanduc *et al.* 2008; Gorny *et al.* 2006; Holl *et al.* 2006a; Nyambi *et al.* 2000; Hioe *et al.* 2000
Keywords dendritic cells, neutralization

- 847-D: Similarity level of the 847-D binding site pentapeptide KGSCK to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 1 time, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 847: A mouse CD4 T cell clone proliferated well in response to gp120 alone, and while this response was inhibited when gp120 was complexed with anti-CD4bs Abs, the addition of 847 mAb did not cause any inhibition. These results indicate that anti-CD4bs Abs, but not anti-C2 Abs, inhibit CD4 T cell responses in the murine system. Visciano *et al.* [2008a]
- 847: This MAb was used as a negative control in the neutralization assays. It did not neutralize any of the primary isolates. Gorny *et al.* [2006]
- 847-30: This Ab did not inhibit HIV-1 BaL replication in macrophages. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 847-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – CD4BS MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – C2 MAbs 1006-30-D and 847-D did not effect proliferation. Hioe *et al.* [2000]
- 847-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including two C2 MAbs – the binding of anti-C2 MAbs was weak to isolates from clades B, C, D, E, F, G, and they did not not bind to isolates from subtypes A and H – epitope is suggested to be in a 20 amino acid peptide KGSCKNVSTVQCTHGIRPVV. Nyambi *et al.* [2000]

No. 447
MAb ID MF169.1
HXB2 Location gp160 (252–261)
Author Location gp120 (242–261 LAI)
Epitope RPVVSTQLLL
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
References Moore *et al.* 1994d; Moore *et al.* 1994c; Thiriart *et al.* 1989

- MF169.1: The relative affinity denatured/native gp120 is 11 – mutations 252 R/W, 257 T/G, and 257 T/R impair binding. Moore *et al.* [1994c]

No. 448
MAb ID MF170.1
HXB2 Location gp160 (252–261)
Author Location gp120 (242–261 LAI)
Epitope RPVVSTQLLL
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
References Moore *et al.* 1994d; Moore *et al.* 1994c; Thiriart *et al.* 1989

- MF170.1: The relative affinity denatured/native gp120 is 15 – mutations 252 R/W, 257 T/G, and 257 T/R impair binding to denatured and native gp120, and 262N/T, 269 E/L and 281 A/V to only native gp120. Moore *et al.* [1994c]

No. 449
MAb ID MF87.1
HXB2 Location gp160 (252–261)
Author Location gp120 (242–261 LAI)
Epitope RPVVSTQLLL
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
References Moore *et al.* 1994c; Thiriart *et al.* 1989

- MF87.1: The relative affinity denatured/native gp120 is 10 – mutations 252 R/W, 257 T/G, and 257 T/R impair binding. Moore *et al.* [1994c]

No. 450
MAb ID 213.1
HXB2 Location gp160 (252–261)
Author Location gp120 (242–261 LAI)
Epitope RPVVSTQLLL
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Env
Species (Isotype) mouse (IgG1)
Ab Type gp120 C2
Research Contact Claudine Bruck
References Moore *et al.* 1994c; Moore & Ho 1993; Thiriart *et al.* 1989

- 213.1: UK Medical Research Council AIDS reagent: ARP334.
- 213.1: The relative affinity denatured/native gp120 is 100 – mutations 252 R/W, 257 T/G or T/R impair binding. Moore *et al.* [1994c]
- 213.1: Bound preferentially to denatured IIIB and SF2 gp120. Moore & Ho [1993]

No. 451
MAb ID B12
HXB2 Location gp160 (252–271)
Author Location gp120 (252–271 LAI)
Epitope RPVVSTQLLLNGSLAEEEVV
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160

B Cell

Species (Isotype) mouse (IgG)
Ab Type gp120 C2
References Crooks *et al.* 2007; Moore *et al.* 2006; Maksiutov *et al.* 2002; Moore *et al.* 1994c

- B12: B12 was used for probing in Western blot and SDS-PAGE assays of VLP particles containing disulfide-shackled functional Env trimers (SOS-VLPs). Crooks *et al.* [2007]
- B12: Western blots were probed with PA1 and B12 to analyze Envs derived from VLPs. Moore *et al.* [2006]
- B12: This epitope is similar to a fragment of human protein lymphatic endothelium-specific hyaluronan receptor LYVE-1, TTRLLVQGSLRAEE. Maksiutov *et al.* [2002]
- B12: C2 region – the relative affinity for denatured/native gp120 is 27 – mutations 257 T/R and 262 N/T impair binding. Moore *et al.* [1994c]

No. 452
MAb ID B13 (Bh13, Chessie B13)
HXB2 Location gp160 (252–271)
Author Location gp120 (252–271 LAI)
Epitope `RPVVSTQLLLNGSLAEEEVV`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG2a)
Ab Type gp120 C2
Research Contact George Lewis, Institute of Human Virology, Baltimore MD, USA
References Herrera *et al.* 2005; Maksiutov *et al.* 2002; Wang *et al.* 2002c; Connor *et al.* 1998; Pincus *et al.* 1996; Moore *et al.* 1994d; Abacioglu *et al.* 1994; Moore *et al.* 1994c; Moore & Ho 1993; Pincus & McClure 1993
Keywords assay standardization/improvement

- B13: DDT-induced dissociation of SOS gp140 and the estimate of amount of cleavage was scored higher when 2F5 was used as detection Ab than when B13 MAb was used. Herrera *et al.* [2005] (**assay standardization/improvement**)
- B13: This epitope is similar to a fragment of human protein lymphatic endothelium-specific hyaluronan receptor LYVE-1, TTRLLVQGSLRAEE. Maksiutov *et al.* [2002]
- B13: Called Bh13 – binds to gp120 but not to infected cells – when linked to ricin A, the immunotoxin did not mediate cell killing – sCD4 has no effect. Pincus & McClure [1993]; Pincus *et al.* [1996]
- B13: C2 region – epitope boundaries mapped by peptide scanning, core epitope: TQLLLN. Abacioglu *et al.* [1994]
- B13: The relative affinity for denatured/native gp120 is 30 – mutations 257 T/R and 269 E/L impair binding. Moore *et al.* [1994c]
- B13: Bound preferentially to denatured IIIB gp120. Moore & Ho [1993]

No. 453
MAb ID C13
HXB2 Location gp160 (252–271)
Author Location gp120 (252–271 LAI)
Epitope `RPVVSTQLLLNGSLAEEEVV`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG1)
Ab Type gp120 C2
Research Contact George Lewis
References Maksiutov *et al.* 2002; Abacioglu *et al.* 1994; Moore *et al.* 1994c; Moore & Ho 1993

- C13: NIH AIDS Research and Reference Reagent Program: 1209.
- C13: This epitope is similar to a fragment of human protein lymphatic endothelium-specific hyaluronan receptor LYVE-1, TTRLLVQGSLRAEE. Maksiutov *et al.* [2002]
- C13: Epitope boundary extended to RPVVSTQLLLNGSLAEEEVVIR, to take into account the effect of a point mutation. Abacioglu *et al.* [1994]
- C13: The relative affinity for denatured/native gp120 is 36 – mutations 257 T/R, 267 E/L, and 269 E/L impair binding. Moore *et al.* [1994c]
- C13: Bound preferentially to denatured IIIB gp120. Moore & Ho [1993]

No. 454
MAb ID M89
HXB2 Location gp160 (252–271)
Author Location gp120 (252–271 LAI)
Epitope `RPVVSTQLLLNGSLAEEEVV`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Env
Species (Isotype) mouse (IgG1)
Ab Type gp120 C2
Research Contact Fulvia di Marzo Veronese
References Maksiutov *et al.* 2002; Moore *et al.* 1994d; Moore *et al.* 1994c; di Marzo Veronese *et al.* 1992

- M89: This epitope is similar to a fragment of human protein lymphatic endothelium-specific hyaluronan receptor LYVE-1, TTRLLVQGSLRAEE. Maksiutov *et al.* [2002]
- M89: C2 region – the relative affinity for denatured/native gp120 is >30 – mutations 257 T/R and 269 E/L impair binding. Moore *et al.* [1994c]
- M89: Immunoblot reactive, RIP negative, for strains IIIB, 451, MN, RF, and RUTZ. di Marzo Veronese *et al.* [1992]

No. 455
MAb ID B21
HXB2 Location gp160 (257–262)
Author Location gp120 (257–262 BH10)
Epitope `TQLLLN`
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG1)
Ab Type gp120 C2
References Abacioglu *et al.* 1994

• B21: C2 region, epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

No. 456
MAb ID B23
HXB2 Location gp160 (257–262)
Author Location gp120 (257–262 BH10)
Epitope TQLLLN
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG2a)
Ab Type gp120 C2
References Abacioglu *et al.* 1994
• B23: C2 region, epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

No. 457
MAb ID B24
HXB2 Location gp160 (257–262)
Author Location gp120 (257–262 BH10)
Epitope TQLLLN
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG2a)
Ab Type gp120 C2
References Abacioglu *et al.* 1994
• B24: C2 region, epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

No. 458
MAb ID B25
HXB2 Location gp160 (257–262)
Author Location gp120 (257–262 BH10)
Epitope TQLLLN
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG1)
Ab Type gp120 C2
References Abacioglu *et al.* 1994
• B25: C2 region, epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

No. 459
MAb ID B3
HXB2 Location gp160 (257–262)
Author Location gp120 (257–262 BH10)
Epitope TQLLLN
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG1)
Ab Type gp120 C2
References Abacioglu *et al.* 1994
• B3: C2 region, epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

No. 460
MAb ID B26
HXB2 Location gp160 (257–263)
Author Location gp120 (257–263 BH10)
Epitope TQLLLNG
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG1)
Ab Type gp120 C2
References Abacioglu *et al.* 1994
• B26: C2 region, epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

No. 461
MAb ID B29
HXB2 Location gp160 (257–263)
Author Location gp120 (257–263 BH10)
Epitope TQLLLNG
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG2a)
Ab Type gp120 C2
References Abacioglu *et al.* 1994
• B29: C2 region, epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

No. 462
MAb ID B36
HXB2 Location gp160 (257–263)
Author Location gp120 (257–263 BH10)
Epitope TQLLLNG
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG1)
Ab Type gp120 C2
References Abacioglu *et al.* 1994
• B36: C2 region, epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

No. 463
MAb ID 110.E
HXB2 Location gp160 (262–281)
Author Location gp120 (262–281 LAI)
Epitope NGSLAEEEVVIRSVNFTDNA
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C2

B Cell

Research Contact F. Traincard
References Maksiutov *et al.* 2002; Moore *et al.* 1994d; Moore *et al.* 1994c

- 110.E: This epitope is similar to a fragment of human protein lymphatic endothelium-specific hyaluronan receptor LYVE-1, TTRLLVQGSLRAEE. Maksiutov *et al.* [2002]
- 110.E: The relative affinity for denatured/native gp120 is 7.3. Moore *et al.* [1994c]

No. 464
MAb ID 110.C
HXB2 Location gp160 (271–280)
Author Location gp120 (271–280 LAI)
Epitope `VIRSVNFTDN`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C2
Research Contact F. Traincard, Hybridolabs, Institut Pasteur
References Kanduc *et al.* 2008; Valenzuela *et al.* 1998; Moore *et al.* 1994d; Moore *et al.* 1994c

- 110.C: Similarity level of the 110.C binding site pentapeptide NFTDN to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 110.C: Only slightly reduces LAI viral binding or entry into CEM cells. Valenzuela *et al.* [1998]
- 110.C: The relative affinity for denatured/native gp120 is 1. Moore *et al.* [1994c]

No. 465
MAb ID IIIB-V3-26
HXB2 Location gp160 (291–307)
Author Location gp120 (299–304 IIIB)
Epitope `SVEINCTRPNNNTRKSI`
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB
Species (Isotype) mouse (IgG1)
Ab Type gp120 V3
References Maksiutov *et al.* 2002; Laman *et al.* 1992

- IIIB-V3-26: This epitope is similar to a fragment of the FasI receptor precursor (Apptosis-mediating surface antigen fas) (APO- 1 antigen) (CD95 antigen), VEINCTRQN. Maksiutov *et al.* [2002]
- IIIB-V3-26: Binds to the base of the V3 loop on denatured gp120. Laman *et al.* [1992]

No. 466
MAb ID IIIB-V3-21 (V3-21)
HXB2 Location gp160 (294–299)
Author Location gp120 (299–304 IIIB)
Epitope `INCTRP`
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB
Species (Isotype) mouse (IgG1)
Ab Type gp120 V3
Research Contact J. Laman
References van Montfort *et al.* 2008; van Montfort *et al.* 2007; Ling *et al.* 2004; Maksiutov *et al.* 2002; Zhang *et al.* 2002; Valenzuela *et al.* 1998; Laman *et al.* 1993; Laman *et al.* 1992
Keywords antibody binding site definition and exposure, co-receptor, dendritic cells, enhancing activity, neutralization

- IIIB-V3-21: UK Medical Research Council AIDS reagent: ARP3048.
- IIIB-V3-21: NIH AIDS Research and Reference Reagent Program: 1725.
- V3-21: Transmission of HIV-1 by immature and mature DCs to CD4+ T lymphocytes was significantly higher for CXCR4- than for CCR5-tropic strains. In addition, V3-21 inhibited transmission of CCR5-tropic viruses while transmission of V3-21-neutralized X4 variants increased, indicating that X4 HIV-1 has an advantage over R5 in transmission when neutralized with V3-21. van Montfort *et al.* [2008] (**co-receptor**, **neutralization**, **dendritic cells**)
- The role of DC-specific ICAM-grabbing nonintegrin (DC-SIGN) as a potential receptor for HIV-1 in the capture and transfer of neutralized HIV-1 to CD4 T lymphocytes was studied. The nonneutralizing V3-21 enhanced HIV-1 infection upon capture and transfer via Raji-DC-SIGN cells, whereas no infection was observed with the neutralizing b12 MAb,indicating that different Abs have variant effects on inhibiting HIV-1 transfer to CD4 T lymphocytes. van Montfort *et al.* [2007] (**enhancing activity**, **neutralization**, **dendritic cells**)
- IIIB-V3-21: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of the V3 MAbs 694-98D and 447-52D, that both bind near the tip of the loop, was decreased by both thrombin and trypsin, but anti-V3 MAb IIIB-V3-21 was not decreased in either case. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- IIIB-V3-21: This epitope is similar to a fragment of the FasI receptor precursor (Apptosis-mediating surface antigen fas) (APO- 1 antigen) (CD95 antigen), VEINCTRQN. Maksiutov *et al.* [2002]
- IIIB-V3-21: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate be-

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tween the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002]
- IIIB-V3-21: Does not block HIV-1 LAI binding or entry into CEM cells. Valenzuela *et al.* [1998]
- IIIB-V3-21: Binds to NP40 treated gp120, and epitope is probably obscured by local glycosylation. Laman *et al.* [1993]
- IIIB-V3-21: Binds to the base of the V3 loop on denatured gp120. Laman *et al.* [1992]

No. 467
MAb ID 168B8
HXB2 Location gp160 (296–317)
Author Location gp120 (BaL)
Epitope CTRPNYNKRKHIGPGRAF
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: gp120-CD4 complex *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) humanized mouse (IgG2κ)
Ab Type gp120 V3
Research Contact Abraham Pinter, Lab. of Retrovirology, Public Research Institute, pinter@phri.org
References He *et al.* 2003
Keywords antibody binding site definition and exposure, vaccine antigen design
- 168B8: Vaccination of a gp120-CD4 fusion complex in six transgenic XMG2 XenoMouse mice that produce human IgG2 with K light chain did not produce any neutralizing antibodies. 36/39 MAbs derived from one of these mice were in one of two competition groups that were conformational and specific for the complex, suggesting this chimeric vaccine may be of little value, as immunodominant responses are to epitopes unique to the complex, not present in native Env. This MAb is one of the 3/36 non-neutralizing MAbs that bound to linear epitopes on gp120. He *et al.* [2003] (**antibody binding site definition and exposure**, **vaccine antigen design**)

No. 468
MAb ID polyclonal
HXB2 Location gp160 (297–330)
Author Location Env (303–335 LAI)
Epitope TRPNNNTRKSIHIGPGRAFYATGEIIGDIRQAH
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* V3 *Adjuvant:* QS21
Species (Isotype) human (IgG)
Ab Type gp120 V3
References Pialoux *et al.* 2001
- 28 subjects were vaccinated with six HIV-1 peptides that were selected to be particularly rich in CTL epitopes, presented in lipopeptides with or without adjuvant QS21 – HIV-specific Ab responses were detected in 25/28 (89%), proliferative in 19/28 (79%), and CTL in 13/24 (54%) of testable volunteers – 14/28 had non-neutralizing Ab responses to this peptide (E), 7/24 had proliferative responses, and multiple CTL responses were detected. Pialoux *et al.* [2001]

No. 469
MAb ID MO97/V3
HXB2 Location gp160 (299–308)
Author Location gp120 (299–308 IIIB)
Epitope PNNNTRKSIR
Neutralizing no
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgM)
Ab Type gp120 V3
References Gorny & Zolla-Pazner 2004; Ohlin *et al.* 1992
Keywords review
- M097/V3: Review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains; a subset can also neutralize some primary isolates. The three IgMs, M096, M097, and M099, are non-neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
- MO97: Generated through *in vitro* stimulation of uninfected-donor lymphocytes with rpB1 (IIIB Env 286-467) Ohlin *et al.* [1992]

No. 470
MAb ID polyclonal
HXB2 Location gp160 (299–327)
Author Location gp120 (MN)
Epitope CNYNKRKRIHIGPGRAFYTTKNIIGTIC
Neutralizing L
Immunogen
Species (Isotype) rabbit (IgA, IgG)
Ab Type gp120 V3
References FitzGerald *et al.* 1998
- Polyclonal response to MN, or Thai E V3 loop inserted into Pseudomonas Exotoxin for vaccination – inserts of 14 or 26 amino acids were used from MN or a Thai E strain, constrained by disulfide bond – sera from vaccinated rabbit were reactive with strain-specific gp120 – administration to mucosal surfaces elicits IgA. FitzGerald *et al.* [1998]

No. 471
MAb ID polyclonal
HXB2 Location gp160 (299–331)
Author Location gp120 (306–338 BH10)
Epitope PNNNTRKSIRIQRGPGRAFVTIGKIGNMRQAHC
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade BH10
Species (Isotype) rabbit (IgG)
Ab Type gp120 V3
References Neurath & Strick 1990
- 21 V3 loop variant peptides spanning this region were tested and serological cross-reactivity correlated with divergence. Neurath & Strick [1990]

No. 472
MAb ID 55/11
HXB2 Location gp160 (300–315)
Author Location gp120 (300–315)

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Epitope NNNTRKRIRIQRGPGR?
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 V3
References Peet *et al.* 1998

- 55/11: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind, and anti-V3 MAb 55/11 binding was abrogated by V3 serine substitutions in the V3 loop – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]

No. 473
MAb ID 8/38c (8/38/1c, 8/38)
HXB2 Location gp160 (300–315)
Author Location gp120 (300–315 HXB10)
Epitope NNNTRKRIRIQRGPGR
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) rat (IgG2a)
Ab Type gp120 V3
Research Contact C. Dean and C. Shotton, Institute for Cancer Research, Surrey, UK
References Holl *et al.* 2006a; Peet *et al.* 1998; Parren *et al.* 1998a; Jeffs *et al.* 1996; Sattentau & Moore 1995; McKeating *et al.* 1992a
Keywords dendritic cells, neutralization

- 8/38c: UK Medical Research Council AIDS reagent: ARP3039.
- 8/38: This Ab did not inhibit HIV-1 BaL replication in macrophages. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 8/38c: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- 8/38c: Called 8/38/1c: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind, and anti-V3 MAb 8/38c binding was only diminished by V3 serine substitutions C-term to the tip of the loop – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]
- 8/38c: Deletion of the V1V2 regions did not affect anti-V3 Abs ability to bind when compared to intact rec gp120. Jeffs *et al.* [1996]
- 8/38c: Binds equally well to monomer and oligomer, less rapid association rate than other anti-V3 antibodies, and an associated less potent neutralization of lab strains. Sattentau & Moore [1995]
- 8/38c: Binds to virion gp120 and neutralizes only in the presence of sCD4. McKeating *et al.* [1992a]

No. 474
MAb ID 8/64b
HXB2 Location gp160 (300–315)
Author Location gp120 (300–315 HXB10)
Epitope NNNTRKRIRIQRGPGR
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) rat (IgM)
Ab Type gp120 V3
References Holl *et al.* 2006a; Peet *et al.* 1998; McKeating *et al.* 1992a
Keywords dendritic cells, neutralization

- 8/64b: UK Medical Research Council AIDS reagent: ARP3036.
- 8/64b: This Ab did not inhibit HIV-1 BaL replication in macrophages. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 8/64b: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind, and anti-V3 MAb 8/64b binding was abrogated by V3 serine substitutions C-term to the tip of the loop – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]
- 8/64b: Binds to virion gp120 and neutralizes only in the presence of sCD4. McKeating *et al.* [1992a]

No. 475
MAb ID polyclonal
HXB2 Location gp160 (300–321)
Author Location gp120
Epitope NYNKRKRIHIGPGRAFYTTK
Neutralizing L
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *HIV component:* V3
Species (Isotype) human
Ab Type gp120 V3
References Bartlett *et al.* 1998

- V3 peptide vaccine (MN, RF, EV91, and Can0A) with a C4 helper T cell epitope were used to vaccinate HLA-B7 HIV-infected patients – V3 Ab levels and the anti-HIV proliferative response, but no decrease in HIV-1 RNA levels or increase in CD4 levels was observed. Bartlett *et al.* [1998]

No. 476
MAb ID polyclonal
HXB2 Location gp160 (300–321)
Author Location gp120
Epitope NYNKRKRIHIGPGRAFYTTK
Neutralizing
Immunogen HIV-1 exposed seronegative
Species (Isotype) human (IgA)
Ab Type gp120 V3
References Kaul *et al.* 1999

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- HIV-1 Env-specific mucosal IgA found in genital track of 16/21 HIV-1 resistant chronically exposed Kenyan sex workers – 11/21 had detectable Th responses. Kaul *et al.* [1999]

No. 477
MAb ID polyclonal
HXB2 Location gp160 (300–322)
Author Location gp120 (IIIB)
Epitope CNNTRKSIRIQRGPGRAFVTIGK
Neutralizing L
Immunogen
Species (Isotype) guinea pig (IgG)
Ab Type gp120 V3
Research Contact D. Bolognesi and T. Matthews, Duke University
References Allaway *et al.* 1993

- Synergy with combinations of CD4-based molecules in inhibition of HIV-1 Env mediated cell fusion. Allaway *et al.* [1993]

No. 478
MAb ID polyclonal (VEI3)
HXB2 Location gp160 (300–328)
Author Location Env
Epitope NNNTRKSIRIGPGRAFYTTGDIGNIRQ
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V3
References Carlos *et al.* 1999

- Antibody response to the epitopes in a vaccine construct (VEI) containing peptides from 5 hypervariable regions of gp120 was detected in the sera of HIV-1 positive subjects, including sera from 6 non-subtype B infections – serum samples from San Francisco, Canada and Puerto Rico cohort showed presence of antibodies against all five VEI hypervariable regions, but most consistently against the V3 region peptide NNNTRKSIRIGPGRAFYTTGDIGNIRQ. Carlos *et al.* [1999]

No. 479
MAb ID 9284 (NEA 9284)
HXB2 Location gp160 (301–312)
Author Location gp120 (307–318 IIIB)
Epitope NNTRKSIRIQRG
Neutralizing L
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
Ab Type gp120 V3
Research Contact Dupont de Nemours, Les Ulis, France or Wilmington, Delaware
References Schonning *et al.* 1998; Parren *et al.* 1998a; Binley *et al.* 1997a; Cao *et al.* 1997b; Poignard *et al.* 1996a; Moore & Sodroski 1996; Fontenot *et al.* 1995; VanCott *et al.* 1995; Sattentau & Moore 1995; Sorensen *et al.* 1994; Okada *et al.* 1994; Cook *et al.* 1994; Thali *et al.* 1994; VanCott *et al.* 1994; Thali *et al.* 1993; Trujillo *et al.* 1993; Moore *et al.* 1993b; Sattentau *et al.* 1993; McKeating *et al.* 1992a; Wyatt *et al.* 1992; Sattentau & Moore 1991; Skinner *et al.* 1988a; Skinner *et al.* 1988b

- 9284: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- 9284: In a study of the influence of the glycan at position 306 of the V3 loop on MAb recognition, 9284 was found to have an inaccessible epitope on the oligomeric form of Env and anti-V3 MAbs were found to neutralize an HIV-BRU mutant virus that lacks the V3 loop glycan more efficiently than HIV-BRU. Schonning *et al.* [1998]
- 9284: Virus with the V1-V2 loop deleted was viable and more susceptible to neutralization by CD4i MAb 17b, and anti-V3 MAbs 1121, 9284, and 110.4, but not to and CD4BS MAb F105 or sCD4. Cao *et al.* [1997b]
- 9284: Binds V3 loop – anti-C1 MAbs 133/290 and 135/9 enhance binding – reciprocal binding inhibition of other anti-V3 MAbs. Moore & Sodroski [1996]
- 9284: V3 MAbs 9284, BAT123, 110.5, and 110.I could each significantly increase gp120 dissociation from virus, mimicking sCD4, and expose the gp41 epitope for MAb 50-69, in contrast to anti-V2 MAbs. Poignard *et al.* [1996a]
- 9284: Binds equally well to monomer and oligomer, rapid association and potent neutralization of lab strains – neutralizes cell-free virus Hx10. Sattentau & Moore [1995]
- 9284: Used to monitor HIV-1 Env expression in infected H9 cells, binds native and reduced gp120s similarly. VanCott *et al.* [1995]
- 9284: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – this MAb can inhibit gp120 binding to GalCer *in vitro*. Cook *et al.* [1994]
- 9284: Binding domain aa 301-310: TRKSIRIQRG – mutations in the V3 loop from basic residues can destroy virus infectivity and syncytium formation: R306T, R309T and R313G can also reduce binding of V3 MAbs with two different binding sites: 9284 and 0.5beta – called NEA9284. Okada *et al.* [1994]
- 9284: Did not neutralize infection of HIV/HTLV-I pseudotype. Sorensen *et al.* [1994]
- 9284: gp41 mutation that confers resistance to neutralization by anti-CD4 binding site antibodies does not reduce neutralizing efficiency of this V3 region MAb. Thali *et al.* [1994]
- 9284: Does not bind MN gp120, just IIIB. VanCott *et al.* [1994]
- 9284: Inhibits C4 region antibodies (G3-299, G3-519) which have conformational requirements. Moore *et al.* [1993b]
- 9284: Increased binding in the presence of sCD4. Sattentau *et al.* [1993]
- 9284: Peptide RIQRGPGRAFVTIGKIGNMRQA – Reacts with three human brain proteins of 35, 55, 110 kd – called NEA-9284. Trujillo *et al.* [1993]
- 9284: Single amino acid substitutions in the C4 region (427 W/V or W/S) or at the base of the V3 loop (298 R/G) can significantly increase binding and neutralization– position 427

B Cell

is also important for CD4 binding and anti-CD4 binding site MAbs. Wyatt *et al.* [1992]
- 9284: Two fold increase in binding to gp120 in the presence of bound sCD4. Sattentau & Moore [1991]
- 9284: IIIB type-specific binding and neutralization. Skinner *et al.* [1988b]

No. 480
MAb ID polyclonal
HXB2 Location gp160 (301–325)
Author Location gp120 (IIIB)
Epitope `NNTRKSIRIQRGPGRAFVTIGKIGN`
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *Adjuvant:* Cholera toxin (CT)
Species (Isotype) mouse (IgA)
Ab Type gp120 V3
References Bukawa *et al.* 1995
- Polyclonal secretory IgA antibody raised by mucosal immunization is able to neutralize IIIB, SF2, and MN – HIV-1 neutralization may be due to V3, CD4 or HPG30 component of the multicomponent peptide immunogen. Bukawa *et al.* [1995]

No. 481
MAb ID polyclonal
HXB2 Location gp160 (301–325)
Author Location gp120 (IIIB)
Epitope `NNTRKSIRIQRGPGRAFVTIGKIGN`
Neutralizing L
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* Env, Rev
Species (Isotype) mouse (IgA22a)
Ab Type gp120 V3
References Sasaki *et al.* 1998
- An anti-env response was sought, and co-expression of Rev was required – intramuscular versus nasal vaccination with DNA vaccine with a QS21 adjuvant was studied – QS21 enhanced the IgG2a response mediated via Th1 cytokines IFNgamma and IL-2. Sasaki *et al.* [1998]

No. 482
MAb ID polyclonal
HXB2 Location gp160 (302–317)
Author Location Env (B consensus)
Epitope `NTRKSIHIGPGRAF`
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V3
References Kanduc *et al.* 2008; Morris *et al.* 2001b
- Similarity level of the polyclonal Ab binding site pentapeptide IGPGR to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- Ab responses before HAART therapy and after one year of therapy were measured in 8 individuals that were classified HAART successes, and 10 patients who were classified as HAART failures – V3 peptide antibody binding titers to the B-consensus and MN and SF2 variants, and neutralization of HIV-1 MN and four subtype B clinical isolates were tested – subjects with strong anti-V3 and NAb humoral immune responses before starting HAART were more likely to achieve sustained viral suppression to <500 copies RNA/ml on HAART – HIV-specific Ab responses declined after 1 year of successful viral suppression on HAART. Morris *et al.* [2001b]

No. 483
MAb ID polyclonal
HXB2 Location gp160 (302–318)
Author Location Env
Epitope `NTRKSIHIGPGRAFY`
Neutralizing L P
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V3
References Bongertz *et al.* 2001
- Non-transmitting mothers had an increased frequency of high neutralizing plasma Ab titers against HIV-1 MN (1:50 dilution, >90% neutralization, 33/88 pregnant women), compared to plasma from transmitting mothers (0/8 pregnant women) – non-transmitting mothers also had more potent neutralization against primary isolates from transmitting mothers, but neutralization of autologous virus was comparable for non-transmitting (7/13) and transmitting mothers (2/4) Bongertz *et al.* [2001]

No. 484
MAb ID MAG 109
HXB2 Location gp160 (302–321)
Author Location gp120 (302–321 BH10)
Epitope `NTRKSIRIQRGPGRAFVTIG`
Neutralizing L
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 V3
References Kang *et al.* 1994
- MAG 109: Binds a V3 loop peptide – sensitive to both V3 loop mutations and a mutation at the base of the V1/V2 loop structure (120/121 VK/LE) Kang *et al.* [1994]

No. 485
MAb ID MAG 49 (#49)
HXB2 Location gp160 (302–321)
Author Location gp120 (302–321 BH10)
Epitope `NTRKSIRIQRGPGRAFVTIG`
Neutralizing L
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 V3
References Moore & Sodroski 1996; Kang *et al.* 1994

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- MAG 49: Called #49 in this text. Binding enhanced by anti-C1 MAbs 133/290, 135/9, and by many anti-CD4 binding site MAbs – reciprocal enhancement of some anti-V2 MAbs – reciprocal binding inhibition of anti-V3 MAbs. Moore & Sodroski [1996]
- MAG 49: Binds a V3 loop peptide – sensitive to both V3 loop mutations and a mutation at the base of the V1/V2 loop structure (120/121 VK/LE) Kang *et al.* [1994]

No. 486
MAb ID MAG 53
HXB2 Location gp160 (302–321)
Author Location gp120 (302–321 BH10)
Epitope NTRKSIRIQRGPGRAFVTIG
Neutralizing L
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 V3
References Kang *et al.* 1994

- MAG 53: Binds a V3 loop peptide – sensitive to both V3 loop mutations and a mutation at the base of the V1/V2 loop structure (120/121 VK/LE) Kang *et al.* [1994]

No. 487
MAb ID MAG 56
HXB2 Location gp160 (302–321)
Author Location gp120 (302–321)
Epitope NTRKSIRIQRGPGRAFVTIG
Neutralizing L
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 V3
References Kang *et al.* 1994

- MAG 56: Binds a V3 loop peptide – sensitive to both V3 loop mutations and a mutation at the base of the V1/V2 loop structure (120/121 VK/LE) Kang *et al.* [1994]

No. 488
MAb ID 1334-D (1334, 1334D)
HXB2 Location gp160 (303–307)
Author Location gp120 (HIV451)
Epitope TRTSV
Subtype CRF01_AE
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Gorny *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a
Keywords antibody binding site definition and exposure, antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 1334-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 1334-D: Called 1334. V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using HIV451 gp120. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 1334-D: Called 1334 – binds to V3 peptides from MN, SF2, NY5, RF, and CDC4 strains as well as x-reactivity with peptides from A, C, D, F, G, and H subtypes – was suggested to be IgG1lambda here – binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – V3 MAbs 447-52D, 838-D, and 1334 bound with a 7-10 fold preference for the oligomer. Gorny *et al.* [2000] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 1334-D: Called 1334D – A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 1334D showed intermediate cross-reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)
- 1334-D: This MAb was selected using oligomeric gp160 from HIV451. Zolla-Pazner *et al.* [1999a] (**antibody generation**)
- 1334-D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 1334, 419, 504, 447, 453 and 537 – the core amino acids GP tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)

No. 489
MAb ID 1324-E (1324E)
HXB2 Location gp160 (303–308)
Author Location Env (subtype CRF01)
Epitope TRTSVR
Subtype CRF01_AE
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Gorny *et al.* 1998

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Keywords antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 1324-E: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 1324-E: Called 1324E – A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 1324E showed poor cross-reactivity, and was the only MAb tested that was derived from a non-B clade infected patient, an E clade infection was the source of 1324E. Nyambi *et al.* [2000] (**subtype comparisons**)
- 1324-E: E clade stimulated MAb did not cross-react with B clade peptides nor did B clade derived peptides with an E clade V3 loop, but both E and B clade stimulated Abs can cross-react with some peptides from other clades – this Ab showed strong binding to several E, A and F peptides, one C peptide, and no reactivity with B peptides and most D peptides. Zolla-Pazner *et al.* [1999a] (**subtype comparisons**)
- 1324-E: MAb reacted with peptides from E clade, while B clade derived MAbs could not. Zolla-Pazner *et al.* [1999b] (**subtype comparisons**)
- 1324-E: A human MAb was derived from an HIV-1 E clade infection from a US service man who had served in Thailand, selected with the consensus V3 peptide from clade E – cross-reactive with V3 peptides, and gp120 from E, C and A clades, as well as cells infected with a C-clade primary isolate, but not with B and D clade V3 peptides or rgp120 – neutralizes E clade virus adapted for growth in H9 cells, but not 5 primary E clade isolates, including the autologous isolate – kinetic parameters were measured, 1324E was comparable to 447-52D. Gorny *et al.* [1998] (**antibody generation**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 490
MAb ID polyclonal
HXB2 Location gp160 (303–319)
Author Location gp120 (subtype C)
Epitope `CKRKIHIGPGQAFYT`
Subtype C
Neutralizing
Immunogen vaccine
Vector/Type: peptide in ISCOM, peptide in liposome *HIV component:* V3 *Adjuvant:* Immune stimulating complexes (ISCOM)
Species (Isotype) mouse (IgG2a, IgG2b)
Ab Type gp120 V3
References Ahluwalia *et al.* 1997

- A V3 loop peptide modified to resemble an Indian form (GPGQ) was incorporated into ISCOMS (immune stimulating complexes) or liposomes, and used to immunize mice – the IgG2a/IgG2b antibody response was enhanced by the presentation in the ISCOM suggestive of a Th1 response. Ahluwalia *et al.* [1997]

No. 491
MAb ID MO99/V3
HXB2 Location gp160 (304–308)
Author Location gp120 (304–308 IIIB)
Epitope `RKSIR`
Neutralizing no
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgM)
Ab Type gp120 V3
References Gorny & Zolla-Pazner 2004; Ohlin *et al.* 1992
Keywords antibody binding site definition and exposure, antibody generation

- M099/V3: Review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains; a subset can also neutralize some primary isolates. The three IgMs, M096, M097, and M099, are non-neutralizing. Gorny & Zolla-Pazner [2004]
- MO99: Generated through *in vitro* stimulation of uninfected-donor lymphocytes with rpB1 (IIIB Env 286-467) Ohlin *et al.* [1992] (**antibody binding site definition and exposure**, **antibody generation**)

No. 492
MAb ID C311E
HXB2 Location gp160 (304–313)
Author Location gp120 (309–316 MN)
Epitope `RKRIHIGP`
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) chimpanzee (IgG1)
Ab Type gp120 V3
References Alsmadi & Tilley 1998; Warrier *et al.* 1996

- C311E: A study of 6 anti-Env MAbs and their ability to bind or direct ADCC against target cells infected with IIIB, MN, SF-2, and RF – C311E bound and directed lysis against all four strains. Alsmadi & Tilley [1998]
- C311E: Chimps were infected with HIV-1 IIIB, and this resulting MAb gave synergistic neutralization of HIV-1 when combined with anti-V2 MAb C108G. Warrier *et al.* [1996]

No. 493
MAb ID 907
HXB2 Location gp160 (304–314)
Author Location gp120 (309–318)
Epitope `RKSIRIQRGPG`
Neutralizing L
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (Isotype) mouse (IgG1κ)
References Pincus *et al.* 1996; Pincus *et al.* 1991; Pincus *et al.* 1989; Chesebro & Wehrly 1988

- 907: A panel of immunotoxins were generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but killing was not directly proportional to binding. Pincus *et al.* [1996]
- 907: Epitope sequence is based on database count of a specified location – 924-RAC immunotoxin is IIIB strain-specific. Pincus *et al.* [1991]

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- 907: Coupled to ricin A chain (RAC), MAb 907 inhibited protein synthesis and cell growth in HIV-infected cells. Pincus *et al.* [1989]
- 907: Strain specific binding, and neutralization of only the LAV strain. Chesebro & Wehrly [1988]

No. 494
MAb ID 924
HXB2 Location gp160 (304–314)
Author Location gp120 (309–318 IIIB)
Epitope RKSIRIQRGPG
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 V3
References Pincus *et al.* 1998; Pincus *et al.* 1996; Cook *et al.* 1994; Pincus *et al.* 1993; Pincus & McClure 1993; Pincus *et al.* 1991; Chesebro & Wehrly 1988

- 924: A panel of immunotoxins were generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but killing was not directly proportional to binding. Pincus *et al.* [1996]
- 924: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – this MAb can inhibit gp120 binding to GalCer *in vitro*. Cook *et al.* [1994]
- 924: MAb was coupled to ricin A chain (RAC) – immunotoxin efficacy was not significantly decreased by sCD4, although the efficacy of gp41 MAb immunotoxins *in vitro* increased 30-fold by sCD4. Pincus & McClure [1993]
- 924: Ab response in IIIB lab workers was compared to gp160 LAI vaccine recipients – MAb 924 was used as a control – infected lab workers and a vaccinia gp160 vaccine had strong V3 MAb response, but alum absorbed rec gp160 did not generate anti-V3 response. Pincus *et al.* [1993]
- 924: Epitope sequence is based on database count of a specified location – 924-RAC immunotoxin is IIIB strain-specific. Pincus *et al.* [1991]
- 924: HIV IIIB strain specific. Chesebro & Wehrly [1988]

No. 495
MAb ID polyclonal
HXB2 Location gp160 (304–318)
Author Location gp120 (304–318 LAI)
Epitope RKSIRIQRGPGRAFV
Subtype B
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgG, IgM)
Ab Type gp120 V3
References Chin *et al.* 1995

- Mimicking the humoral immune response *in vitro* supports isotype switching – human IgG MAbs were generated from naive donors. Chin *et al.* [1995]

No. 496
MAb ID polyclonal
HXB2 Location gp160 (304–318)
Author Location gp120 (304–318 LAI)
Epitope RKSIRIQRGPGRAFV
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade LAI
Species (Isotype) human (IgG, IgM)
Ab Type gp120 V3
References Zafiropoulos *et al.* 1997

- IgG to IgM isotype switching in response to primary and secondary peptide vaccinations was studied – the immunogen contained a V3 loop fragment and a tetanus toxin helper epitope. Zafiropoulos *et al.* [1997]

No. 497
MAb ID polyclonal
HXB2 Location gp160 (304–318)
Author Location gp120 (NY5)
Epitope KKGIAIGPGRTLY
Neutralizing
Immunogen
Species (Isotype) (IgM)
Ab Type gp120 V3
References Metlas *et al.* 1999a; Metlas *et al.* 1999b

- Auto-Abs that react with the V3 loop of NY5 are present in the sera of HIV- individuals, and are predominantly IgM. Metlas *et al.* [1999b]

No. 498
MAb ID D19
HXB2 Location gp160 (304–320)
Author Location gp120 (V3) (MN)
Epitope RKRIHIGPGRAFYTT
Subtype A, B, F
Neutralizing yes
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH8 *HIV component:* gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4i, gp120 V3
Research Contact Paolo Lusso, Human Virology, San Raffaele Scientific Institute, Milan, Italy. paolo@hsr.it
References Wright *et al.* 2008; Lusso *et al.* 2005; Huang *et al.* 2005b
Keywords antibody binding site definition and exposure, antibody generation, isotype switch, mucosal immunity, neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- D19: Several IgG MAbs were isotype switched to IgA and tested for their abilities to generate immune complexes with HIV-1 and be excreted from polarized epithelial cells from the basolateral to the apical surface via polymeric Ig receptor (pIgR) binding. IgA D19 was able to excrete HIV but it had lower level of binding to the virus, and as immune complex to the pIgR, than D10 and D47 MAbs. These results show

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that IgA Abs have potential to excrete HIV from mucosal lamina propria thus decreasing the viral burden and access to susceptible cells. Wright *et al.* [2008] (**isotype switch**, **mucosal immunity**)

- D19: By isotype switching, IgG and IgA variants of D19 were produced. Both D19 IgA and IgG neutralized virus in conventional neutralization assays, however, IgA performed better. D19 IgA was also internalized into the cells by the polymeric Ig receptor (pIgR) and showed capability of intracellular neutralization of HIV-1, while D19 IgG showed no such activity. Huang *et al.* [2005b] (**isotype switch**, **neutralization**, **mucosal immunity**)
- D19: The epitope for D19 is conserved and embedded in V3. D19 is unique because for R5 viruses, it was cryptic and did not bind without exposure to sCD4, but for X4 and R5X4 isolates it was constitutively exposed. It had a similar overlapping binding region with MAbs 447-52D, B4e8, and 268-D, but different reactivity patterns and fine specificity; D19 binding to monomeric gp120 was independent of sCD4, the dependence was only seen in the context of native oligomeric Env. D19 reacted with 23/29 B clade Envs, but to only 2/14 viruses from other clades: one A and one F, but no C, D or E clade strains. D19 can neutralize X4 and R5X4 isolates, but could only neutralize R5 isolates in the presence of sCD4. The authors suggest that a more exposed V3 loop may facilitate CXCR4 coreceptor usage, but that this phenotype is limited in vivo by neutralizing antibodies until the onset of progressive disease. Lusso *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 499
MAb ID 10F10
HXB2 Location gp160 (304–320)
Author Location gp120 (MN)
Epitope RKRIHIGPGRAFYTT
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade MN *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 V3
References Duarte *et al.* 1994

- 2C4: Putative epitope lies within IHIGPGRAFYT – generated by multi-epitope polypeptide immunization – recognize MN and SC (TRSIHIGPGRAFYTT) peptides, lower affinity for SF2. Duarte *et al.* [1994]

No. 500
MAb ID 2C4
HXB2 Location gp160 (304–320)
Author Location gp120 (MN)
Epitope RKRIHIGPGRAFYTT
Neutralizing L (MN)
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade MN
Species (Isotype) mouse (IgG2a)
Ab Type gp120 V3
References Duarte *et al.* 1994

- 2C4: Putative epitope lies within IHIGPGRAFYT – neutralizes MN, not IIIB and SF2 – generated by multi-epitope polypeptide immunization – recognize MN and SC (TRSIHIGPGRAFYTT) peptides, lower affinity for SF2. Duarte *et al.* [1994]

No. 501
MAb ID 412-D (412-10D, 412, 412D)
HXB2 Location gp160 (304–320)
Author Location gp120 (MN)
Epitope RKRIHIGPGRAFYTT
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Nyambi *et al.* 1998; Gorny *et al.* 1998; Fontenot *et al.* 1995; VanCott *et al.* 1994; Spear *et al.* 1993; Gorny *et al.* 1993
Keywords antibody binding site definition and exposure, binding affinity, complement, kinetics, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- 412-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 412-D: Called 412: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 412-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 412-D showed limited reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)
- 412-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a] (**review**, **subtype comparisons**)
- 412-D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 391.5, 412 and 418, all selected with MN V3 peptide – the core amino acids HIGPGR tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 412-D: Kinetic parameters were measured, and the association rates were similar, but dissociation rate constants were quite

variable for V3 MAbs, 412-D has a relatively fast dissociation, thus low affinity among V3 MAbs. Gorny *et al.* [1998] (**kinetics**)

- 412-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – 412-D was bound only to B clade virions and to D clade MAL. Nyambi *et al.* [1998] (**subtype comparisons**)
- 412-D: Called 412 – The tip of the V3 loop was presented in a mucin backbone – higher valency correlates with higher affinity constant. Fontenot *et al.* [1995] (**vaccine antigen design**, **binding affinity**)
- 412-D: Called 412-10D – relatively rapid dissociation and weak homologous neutralization. VanCott *et al.* [1994] (**binding affinity**)
- 412-D: Neutralizes MN, does not bind SF2 or HXB2 – not reactive with hexa or heptapeptides by Pepscan. Gorny *et al.* [1993] (**variant cross-recognition or cross-neutralization**)
- 412-D: Mediated deposition of complement component C3 on HIV infected cells, enhanced by second Ab binding, rabbit anti-human IgG. Spear *et al.* [1993] (**complement**)

No. 502
MAb ID polyclonal
HXB2 Location gp160 (304–320)
Author Location gp120 (MN)
Epitope `RKRIHIGPGRAFYTT`
Neutralizing L (MN ALA-1)
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V3
References Spear *et al.* 1994

- 40% of antibody in serum that can bind to native viral proteins on MN-infected cells can be blocked by the peptide RKRIHIGPGRAFYTT, which can also block 75-95% of the complement activation on HIV infected cells. Spear *et al.* [1994]

No. 503
MAb ID CGP 47 439
HXB2 Location gp160 (304–322)
Author Location gp120
Epitope `RKRIRIQRGPGRAFVTIGK?`
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) human
Ab Type gp120 V3
References Jacobson 1998; Gauduin *et al.* 1998; Gunthard *et al.* 1994; Safrit *et al.* 1993; Liou *et al.* 1989

- CGP 47 439: Post-exposure passive transfer of murine BAT123 can confer protection to hu-PBL-SCID mice challenged with HIV-1 LAI – this protection is not elicited by CGP 47 439, suggesting that the protection is mediated by complement – the protective ability of BAT123 is lost when mice were treated with cobra venom factor, which inactivates serum complement – in this circumstance complement activation provided a protective advantage. Gauduin *et al.* [1998]
- CGP 47 439: Review of passive immunotherapy, summarizing Gunthard *et al.* [1994] in relation to other studies Jacobson [1998]. Gunthard *et al.* [1994]; Jacobson [1998]
- CGP 47 439: Phase I/IIA clinical trial studying multidose tolerability, immunogenicity and pharmacokinetic responses – GP 47 439 was well tolerated, serum t_1/2 was 8-16 days, and a virus burden reduction was noted in some patients. Gunthard *et al.* [1994]
- CGP 47 439: passive transfer to Hu-PBS-SCID mice confers protection against challenge with homologous cell-free virus – CGP 47 439 is a BAT123-human Ig chimera. Safrit *et al.* [1993]

No. 504
MAb ID polyclonal
HXB2 Location gp160 (304–322)
Author Location (MN)
Epitope `RKRIHIGPGRAFYTTKN`
Subtype multiple
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V3
References Cheingsong-Popov *et al.* 1992

- The Ab response of 829 HIV-1 infected subjects from eight geographic areas to a set of different V3 peptides was determined by ELISA and cross-inhibition studies – the Ab binding pattern was highly variable, depended on the geographic origin of the sample – 297 sera were tested in a neutralization assay – there was a correlation between Ab binding to the MN V3 loop and MN neutralizing titer, but with neutralization of IIIB or CBL-4. Cheingsong-Popov *et al.* [1992]

No. 505
MAb ID 178.1 (178.1.1)
HXB2 Location gp160 (305–309)
Author Location gp120 (305–309 BH10)
Epitope `KSiRI`
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* Env
Species (Isotype) mouse (IgG2a)
Ab Type gp120 V3
Research Contact C. Thiriart, Smith Kline and MRC AIDS reagent project
References Holl *et al.* 2006a; Cook *et al.* 1994; Moore & Ho 1993; Back *et al.* 1993; Thiriart *et al.* 1989
Keywords dendritic cells, neutralization

- 178.1: UK Medical Research Council AIDS reagent: ARP331.
- 178.1.1: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 178.1: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – this MAb can inhibit gp120 binding to GalCer *in vitro* – binding of GalCer to gp120 inhibited but did not completely block MAb binding. Cook *et al.* [1994]

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- 178.1: gp41 amino acid substitutions 668 (N/S) and 675 (I/M) in gp41 interfere with 5023s neutralization potency, region 662-675 is ELDKWANLWNWFNI. Back *et al.* [1993]
- 178.1: Called 178.1.1 – conformational, does not bind well to denatured gp120. Moore & Ho [1993]
- 178.1: Reacts to gp120 and gp160 in RIPA EIA and immunoblot. Thiriart *et al.* [1989]

No. 506
MAb ID 257-D (257, 257-2-D-IV, 257-D-IV, 257, 257-2D, 257D, ARP3023)
HXB2 Location gp160 (305–309)
Author Location gp120 (MN)
Epitope KRIHI
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Patel *et al.* 2008; Holl *et al.* 2006a; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Zhang *et al.* 2002; Vella *et al.* 2002; York *et al.* 2001; Park *et al.* 2000; Nyambi *et al.* 2000; Oggioni *et al.* 1999; Beddows *et al.* 1999; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Stamatatos & Cheng-Mayer 1998; Gorny *et al.* 1998; Yang *et al.* 1998; LaCasse *et al.* 1998; Hioe *et al.* 1997b; Hill *et al.* 1997; Stamatatos *et al.* 1997; Schutten *et al.* 1997; Schutten *et al.* 1996; Wisnewski *et al.* 1996; Fontenot *et al.* 1995; Schutten *et al.* 1995b; Schutten *et al.* 1995a; Zolla-Pazner *et al.* 1995; D'Souza *et al.* 1995; Stamatatos & Cheng-Mayer 1995; VanCott *et al.* 1994; D'Souza *et al.* 1994; Spear *et al.* 1993; Cavacini *et al.* 1993a; Gorny *et al.* 1993; Karwowska *et al.* 1992b; D'Souza *et al.* 1991; Gorny *et al.* 1991
Keywords antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, assay development, binding affinity, co-receptor, complement, dendritic cells, enhancing activity, kinetics, neutralization, review, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- 257-D: UK Medical Research Council AIDS reagent: ARP3023.
- 257-D: NIH AIDS Research and Reference Reagent Program: 1510.
- 257-DI V: To examine sequence and conformational differences between subtypes B and C, several experiments were preformed with 11 MAbs regarding binding and neutralization. Both binding and neutralization studies revealed that the 11 MAbs could be divided in three different groups, and that the most differences between the subtypes were located in the stem and turn regions of V3. 257-D belonged to the group 2 MAbs, which are able to bind subtype B but not subtype C gp120, and are able to bind both V3 peptides. 257-D was able to bind subtype B V3 in the subtype C Env backbone chimera, but not the reverse, indicating that 257-D binds to a structure created by the subtype B V3 sequence that is not impacted by the gp120 backbone. For subtype B, 257-D required an R18 residue in order to bind, but the binding was not significantly affected by the H13R change. For subtype C, Q18R mutation did not restore binding to gp120, but the R13H-Q18R double mutation did. Peptide binding was affected only by the R13H mutation, indicating that the poor binding of Q18R gp120 mutant has a structural basis. 257-D was able to neutralize SF162, and a chimeric SF162 variant with a JR-FL-like V3 sequence was hypersensitive to neutralization by this Ab. Patel *et al.* [2008] (**neutralization**, **binding affinity**, **subtype comparisons**)
- 257-D IV: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication occurs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 257-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 257-D: Called 257: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides do not show as much ability to neutralize as V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. 257 was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 257-D: Called ARP3023: Herpesvirus saimiri-immortalized CD4+ T lymphocytes (HVS T cells) were used to isolate virus and perform HIV-1 neutralization assays, and compared with a standard PBMC protocol – neutralization sensitivities to a panel of MAbs and to homologous or heterologous plasma/sera were similar for HVS T cells (CN-2 cells) and PBMCs. Vella *et al.* [2002] (**assay development**)
- 257-D: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002] (**variant cross-recognition or cross-neutralization**)
- 257-D: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and

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TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAbs alters some step after binding. York *et al.* [2001]

- 257-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 257-D showed intermediate reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)
- 257-D: Called 257D – six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000]
- 257-D: rgp120 derived from a R5X4 subtype B virus, HIV-1 W61D, was used to vaccinate healthy volunteers and the resulting sera were compared with sera from HIV-1 positive subjects and neutralizing MAbs – 257-D bound rgp120 W61D but could only neutralize the W61D isolate following T-cell line adaptation. Beddows *et al.* [1999] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **vaccine-specific epitope characteristics**)
- 257-D: Study of a live-vector mucosal vaccine that expresses HIV-1 V3 domains using the bacterium Streptococcus gordonii which can express heterologous Ag and can colonize the oral cavity and vagina of mice – 268-D and 257-D recognized S. gordonii expressing the V3 domain of MN – the vaccine stimulated V3-specific IgG2a in mice. Oggioni *et al.* [1999] (**vaccine antigen design**)
- 257-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a] (**review**, **subtype comparisons**)
- 257-D: MAb peptide reactivity pattern clustered with immunological related MAbs: 1108, 386, 268, 311, 257, 694.8 – the amino acids HI tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 257-D: Kinetic parameters were measured, and the association rates were similar, but dissociation rate constants were quite variable for V3 MAbs, 257-D has a slow dissociation, thus the highest affinity among V3 MAbs. Gorny *et al.* [1998] (**kinetics**, **binding affinity**)
- 257-D: A T-cell line-adapted (TCLA) derivative of SI primary isolate 168P acquired the ability to be neutralized by anti-V3 MAbs – the primary isolate could use either CCR5 or CXCR4, and was not neutralized when infection was directed via either pathway, however the TCLA derivative uses CXCR4 only and is neutralized. LaCasse *et al.* [1998] (**co-receptor**, **variant cross-recognition or cross-neutralization**)
- 257-D: Called 257D – deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V1 or V2 did not enable neutralization by V3 MAbs 391-95D or 257D. Stamatatos & Cheng-Mayer [1998] (**vaccine antigen design**, **subtype comparisons**)
- 257-D: A neutralization assay was developed based on hemi-nested PCR amplification of the LTR (HNPCR) – LTR-HNPCR consistently revealed HIV DNA and was shown to be a rapid, specific and reliable neutralization assay based on tests with 6 MAbs and 5 isolates. Yang *et al.* [1998] (**assay development**)
- 257-D: Called 257 – gp120 can inhibit MIP-1alpha from binding to CCR5, but this inhibitory effect is blocked by pre-incubation of gp120 with three anti-V3 MAbs: 447, 257, 1027 – MAb 670 which binds in the C5 region had no effect. Hill *et al.* [1997] (**antibody binding site definition and exposure**, **co-receptor**)
- 257-D: Neutralized (>90%) an SI-env chimeric virus and enhanced (>200%) an NSI-env chimeric virus. Schutten *et al.* [1997] (**enhancing activity**, **variant cross-recognition or cross-neutralization**)
- 257-D: Binds less extensively than MAb 391-95D on the surface of HIV-1 isolates SF162 and SF128A – neutralizes less potently than 391-95D – stronger neutralization of primary macrophage targets than PBMC. Stamatatos *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- 257-D: IIIB neutralizing MAbs *in vitro* fail to neutralize in a mouse model *in vivo*. Schutten *et al.* [1996]
- 257-D: 257-D is V H5 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996] (**antibody sequence variable domain**)
- 257-D: Called 257-D-IV – could neutralize MN and closely related JRCSF, but not 2 B subtype and 1 D subtype primary isolates in a multi-laboratory study involving 11 labs. D'Souza *et al.* [1995] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 257-D: Only inhibition of SI phenotype virus, and strong enhancement of NSI phenotype chimeric viruses, that incorporated different envs from the same donor. Schutten *et al.* [1995a] (**enhancing activity**, **variant cross-recognition or cross-neutralization**)
- 257-D: Comparable affinity for SI and NSI viruses, in contrast to MAb MN215. Schutten *et al.* [1995b] (**variant cross-recognition or cross-neutralization**)
- 257-D: The binding of conformation-dependent anti-V2, anti-V3, and anti-CD4BS MAbs to monomeric and virion-associated gp120 from HIV-1 isolates with differences in cell tropism was studied – V3 loop epitopes were less accessible to Ab binding on the virion surface than in the gp120 monomer, particularly for macrophage-tropic isolates SF162 and SF128a, relative to T-cell tropic SF2 – sCD4 association with gp120 better revealed this V3 epitope on TCLA SF2 and dual tropic (MU3) viruses than on macrophage tropic isolates. Stamatatos & Cheng-Mayer [1995] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 257-D: In serotyping study using flow-cytometry, bound only to virus with KRIHI. Zolla-Pazner *et al.* [1995] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)

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- 257-D: Included a multi-lab study for antibody characterization and assay comparison – best NAb against MN, but not IIIB. D'Souza *et al.* [1994] (**variant cross-recognition or cross-neutralization**)
- 257-D: Potent MN neutralization, slow dissociation constant. VanCott *et al.* [1994] (**binding affinity**)
- 257-D: Additive MN or SF2 neutralization when combined with CD4 binding site MAb F105 – does not neutralize RF. Cavacini *et al.* [1993a] (**antibody interactions**, **variant cross-recognition or cross-neutralization**)
- 257-D: Neutralizes MN – binds SF2: epitope KSIYI – specificity: MN, SF2, NY5, RF. Gorny *et al.* [1993] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 257-D: Mediated deposition of complement component C3 on HIV infected cells, enhanced by second Ab binding, rabbit anti-human IgG – complement mediated virolysis of MN, but not in the presence of sCD4. Spear *et al.* [1993] (**complement**)
- 257-D: Reacts with MN, NY5, CDC4 and SF2, does not cross-react with RF, WM52, or HXB2. Karwowska *et al.* [1992b] (**variant cross-recognition or cross-neutralization**)
- 257-D: Called 257-2-D-IV – potent neutralizing MAb. D'Souza *et al.* [1991]

No.	507
MAb ID	311-11-D (311-11D, 311, 311D, 311-D)
HXB2 Location	gp160 (305–313)
Author Location	gp120 (MN)
Epitope	KRIHIGP
Subtype	B
Neutralizing	L
Immunogen	HIV-1 infection
Species (Isotype)	human (IgG1λ)
Ab Type	gp120 V3
Research Contact	Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References	Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Gorny *et al.* 1998; Spear *et al.* 1993; Gorny *et al.* 1993; Gorny *et al.* 1991
Keywords	antibody binding site definition and exposure, antibody generation, complement, review, subtype comparisons

- 311-11-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 311-11-D: Called 311: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides do not neutralize as well as V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. 311 was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 311-11-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 311-11-D showed weak reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)
- 311-11-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a] (**review**, **subtype comparisons**)
- 311-11-D: MAb peptide reactivity pattern clustered with immunological related MAbs: 1108, 386, 268, 311, 257, 694.8 – the amino acids HI tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 311-11-D: Neutralizes MN – binds SF2: KSIYIGP. Gorny *et al.* [1993] (**antibody binding site definition and exposure**, **antibody generation**)
- 311-11-D: Mediated deposition of complement component C3 on HIV infected cells, enhanced by second Ab binding, rabbit anti-human IgG. Spear *et al.* [1993] (**complement**)

No.	508
MAb ID	41148D
HXB2 Location	gp160 (305–313)
Author Location	gp120 (MN)
Epitope	KRIHIGP
Neutralizing	L
Immunogen	HIV-1 infection
Species (Isotype)	human (IgG1)
Ab Type	gp120 V3
References	Kanduc *et al.* 2008; Gorny & Zolla-Pazner 2004; Alsmadi & Tilley 1998; Pinter *et al.* 1993b
Keywords	ADCC, review, variant cross-recognition or cross-neutralization

- 41148D: Similarity level of the 41148D binding site pentapeptide IHIGP to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 1 time, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 41148D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. 4117C and 41148D are anti-V3 MAbs that neutralize TCLA strains. Gorny & Zolla-Pazner [2004] (**review**)
- 41148D: A study of 6 anti-Env MAbs and their ability to bind or direct ADCC against target cells infected with IIIB, MN, SF-2, and RF – bound and directed lysis against strains IIIB, MN, SF-2, comparable to 4117C, however 41148D is 10x less efficient at neutralization, showing ADCC and neutralization don't always correlate. Alsmadi & Tilley [1998] (**ADCC**)
- 41148D: Neutralizes less potently than 4117C, reacts with MN, IIIB, SF2. Pinter *et al.* [1993b] (**variant cross-recognition or cross-neutralization**)

No.	509
MAb ID	391/95-D (391-95D, 391.5, 391/95D, 391/95)

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HXB2 Location gp160 (305–318)
Author Location gp120 (MN)
Epitope KRIHIGPGRAFY
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Srivastava *et al.* 2008; Holl *et al.* 2006a; McCaffrey *et al.* 2004; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Zhang *et al.* 2002; Lawson *et al.* 2002; Guillon *et al.* 2002b; Park *et al.* 2000; Ly & Stamatatos 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Stamatatos & Cheng-Mayer 1998; Stamatatos *et al.* 1997; Seligman *et al.* 1996; Stamatatos & Cheng-Mayer 1995; Fontenot *et al.* 1995; Gorny *et al.* 1993; Gorny *et al.* 1991
Keywords acute/early infection, antibody binding site definition and exposure, binding affinity, co-receptor, dendritic cells, enhancing activity, neutralization, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- 391-95d: Trimeric envelope glycoproteins with a partial deletion of the V2 loop derived from subtype B SF162 and subtype C TV1 were compared. 391-95d recognized both B and C trimers with similar efficiency, indicating that the conformational epitope recognized by this Ab is exposed and preserved in the subtype C trimers. Subtype C trimer had many biophysical, biochemical, and immunological characteristics similar to subtype B trimer, except for a difference in the three binding sites for CD4, which showed cooperativity of CD4 binding in subtype C but not in subtype B. Srivastava *et al.* [2008] (**binding affinity**, **subtype comparisons**)
- 391-D: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 391/95-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 391/95-D: Called 391/95: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides do not show as much ability to neutralize as V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. 391/95 was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 391/95-D: Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The loss of any of the five glycans, within the V3 loop (GM299 V3), C2 (GM292 C2), C3 (GM329 C3), C4 (GM438 C4), or V5 (GM454 V5) made SF162 become sensitive to 391/95-D; SF162 is resistant to 391/95-D neutralization. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- 391/95-D: The affect of Ab binding on infectivity was studied by pseudotyping three related envs with different phenotypes – R5 viruses were preferentially enhanced, not X4 – the V3 region was the main determinant of Ab-mediated enhancement and modulation of the interaction between CCR5 and gp120 is critical – tests with MAbs anti-V3 391/95-D and CD4BS-specific GP68 indicate that Ab specificity did not determine whether or not infectivity was enhanced or neutralized, rather the phenotype was determined by Env conformation. Guillon *et al.* [2002b] (**co-receptor**, **enhancing activity**)
- 391/95-D: The phenotype and genotype of viral env sequences were studied over a period of seroconversion in one individual – Env trans-complementation demonstrated infectivity of clones derived pre-seroconversion were not influenced by MAb 391/95-D, but post-seroconversion clones were enhanced in the presence of 391/95-D, although the V3 binding region was unchanged – a change in the CD4-binding site was observed (NL43 427 Glu–>Lys) to be present in the post-seroconversion 391/95-D enhanced clone (see Guillon *et al.* [2002b]) Lawson *et al.* [2002]. Guillon *et al.* [2002b]; Lawson *et al.* [2002] (**enhancing activity**, **acute/early infection**)
- 391/95-D: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 391/95-D: Called 391-95D – SF162 is a neutralization-resistant HIV-1 isolate – N-linked glycosylation modifications in the V2 loop of the SF162 gp120 revealed that these sites prevent neutralization by CD4BS MAbs (IgG1b12 and IgGCD4), and protect against neutralization by V3 MAbs (447-D and 391-95D) – V2-region glycosylation site mutations did not alter neutralization resistance to V2 MAbs (G3.4 and G3.136) or CD4i MAbs (17b and 48d) – V2 glycosylation site modification allows infection of macrophages, probably due to glycosylated forms requiring fewer CCR5 molecules for viral entry. Ly & Stamatatos [2000] (**antibody binding site definition and exposure**)
- 391/95-D: Called 391/95D – six mutations in MN change the virus from a high-infectivity neutralization resistant pheno-

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type to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000] (**antibody binding site definition and exposure**)
- 391/95-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a] (**review**, **subtype comparisons**)
- 391/95-D: Called 391.5 – MAb peptide-reactivity pattern clustered with immunological related MAbs: 391.5, 412 and 418, all selected with MN V3 peptide – the core amino acids HIGPGR tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 391/95-D: Called 391-95D – deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V1 or V2 did not enable neutralization by V3 MAbs 391-95D or 257D. Stamatatos & Cheng-Mayer [1998] (**antibody binding site definition and exposure**, **subtype comparisons**)
- 391/95-D: Called 391-95D – binds more extensively than MAb 257-D on the surface of HIV-1 isolates SF162 and SF128A – neutralizes more potently than 257-D – stronger neutralization of primary macrophage targets than PBMC – binding post-gp120-sCD4 association related to anti-V3 Abs neutralizing capacity. Stamatatos *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- 391/95-D: Competition ELISAs with serial deletions estimated the epitope to be KRIHIGPGRAFY – unconstrained peptide had higher affinity than cyclic. Seligman *et al.* [1996] (**antibody binding site definition and exposure**)
- 391/95-D: The binding of conformation-dependent anti-V2, anti-V3, and anti-CD4BS MAbs to monomeric and virion-associated gp120 from HIV-1 isolates with differences in cell tropism was studied – V3 loop epitopes were less accessible to Ab binding on the virion surface than in the gp120 monomer, particularly for macrophage-tropic isolates SF162 and SF128a, relative to T-cell tropic SF2 – sCD4 association with gp120 better revealed this V3 epitope on macrophage tropic and dual tropic (MU3) viruses, but not in TCLA SF2. Stamatatos & Cheng-Mayer [1995] (**antibody binding site definition and exposure**)
- 391/95-D: Neutralizes MN – binds to SF2, not IIIB. Gorny *et al.* [1993]

No. 510
MAb ID Aw
HXB2 Location gp160 (305–320)
Author Location gp120 (Gun-1wt)
Epitope `KSITIGPGRAFHAI`
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* Gun-1 *HIV component:* V3
Species (Isotype) rat
Ab Type gp120 V3
References McKnight *et al.* 1995
- Aw: Rat antibodies were raised against V3 peptides that represent either the wildtype (wt), or brain-cell tropic variant (v) of the isolate Gun-1 – Aw gives weak neutralization of both wildtype and v strains. McKnight *et al.* [1995]

No. 511
MAb ID Bw
HXB2 Location gp160 (305–320)
Author Location gp120 (Gun-1wt)
Epitope `KSITIGPGRAFHAI`
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* Gun-1 *HIV component:* V3
Species (Isotype) rat
Ab Type gp120 V3
References McKnight *et al.* 1995
- Bw: Rat antibodies were raised against V3 peptides that represent either the wildtype (wt), or brain-cell tropic variant (v) of the isolate Gun-1 – Bw gives weak neutralization of only the wildtype strain, does not bind to variant. McKnight *et al.* [1995]

No. 512
MAb ID DO142-10 (DO 142-10)
HXB2 Location gp160 (305–320)
Author Location gp120 (MN)
Epitope `KRIHIGPGRAFYTT`
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
Ab Type gp120 V3
References Kramer *et al.* 2007; Mc Cann *et al.* 2005; Gorny & Zolla-Pazner 2004; Kwong *et al.* 2002; Sullivan *et al.* 1998a; Parren *et al.* 1998a; Parren & Burton 1997; Parren *et al.* 1997b; Ditzel *et al.* 1997; Seligman *et al.* 1996
Keywords antibody binding site definition and exposure, antibody generation, binding affinity, enhancing activity, review, variant cross-recognition or cross-neutralization
- DO142-10: This review summarizes DO142-10 Ab epitope, properties and neutralization activity. Kramer *et al.* [2007] (**review**)
- DO142-10: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **review**)

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- DO124-10: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. DO124-10 neutralizes some TCLA strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- D0124-10: Called D0124. Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-2999) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- DO142-10: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different that Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**variant cross-recognition or cross-neutralization**, **binding affinity**)
- DO124-10: The HIV-1 virus YU2 entry can be enhanced by MAbs binding to the CD4BS, V3 loop, and CD4i epitopes – the activation for this enhanced entry state could be conferred on HxB2 by introducing the YU2 V3 loop, or the YU2 V3 and V1/V2 loops – a similar effect is observed by subneutralizing concentrations of sCD4 and the effect is dependent of CCR5 – Fab Ab fragment DO124-10 also enhances YU2 entry, ruling out Fc interactions or Env cross-linking as a mechanism – while DO124-10 enhances YU2 entry 6-fold, it neutralizes HXBc2 under identical conditions. Sullivan *et al.* [1998a] (**enhancing activity**, **variant cross-recognition or cross-neutralization**)
- DO142-10: Phage expression libraries panned against MN peptide were used to select Fab DO142-10 – Fab binds MN gp120, but not a primary isolate rec gp120. Ditzel *et al.* [1997] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- DO142-10: Neutralizes TCLA strains but not primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- DO142-10: Binds to gp120 MN and an MN V3 peptide with equal affinity, but binds a consensus B peptide and JRCSF less well, and to IIIB gp120 not at all. Parren & Burton [1997] (**variant cross-recognition or cross-neutralization**, **binding affinity**)
- DO142-10: Fab fragment – competition ELISAs with serial deletions defined the epitope KRIHIGPGRAFYTT. Seligman *et al.* [1996] (**antibody binding site definition and exposure**, **antibody generation**)

No. 513
MAb ID Dv
HXB2 Location gp160 (305–320)
Author Location gp120 (Gun-1v)
Epitope KSITIGSGRAFHAI
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* Gun-1 *HIV component:* V3
Species (Isotype) rat
Ab Type gp120 V3
References McKnight *et al.* 1995

- Dv: Rat antibodies were raised against V3 peptides that represent either the wildtype (wt), or brain-cell tropic variant (v) of the isolate Gun-1 – neutralization of only the variant strain, does not bind to wildtype. McKnight *et al.* [1995]

No. 514
MAb ID Fv
HXB2 Location gp160 (305–320)
Author Location gp120 (Gun-1v)
Epitope KSITIGSGRAFHAI
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* Gun-1 *HIV component:* V3
Species (Isotype) rat
Ab Type gp120 V3
References McKnight *et al.* 1995

- Fv: Rat antibodies were raised against V3 peptides that represent either the wildtype (wt), or brain-cell tropic variant (v) of the isolate Gun-1 – neutralization of only the variant strain, does not bind to wildtype. McKnight *et al.* [1995]

No. 515
MAb ID Gv
HXB2 Location gp160 (305–320)
Author Location gp120 (Gun-1v)
Epitope KSITIGSGRAFHAI
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* Gun-1 *HIV component:* V3
Species (Isotype) rat
Ab Type gp120 V3
References McKnight *et al.* 1995

- Gv: Rat antibodies were raised against V3 peptides that represent either the wildtype (wt), or brain-cell tropic variant (v) of the isolate Gun-1 – neutralization of only the variant strain, does not bind to wildtype. McKnight *et al.* [1995]

No. 516
MAb ID Hv
HXB2 Location gp160 (305–320)
Author Location gp120 (Gun-1v)
Epitope KSITIGSGRAFHAI
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* Gun-1 *HIV component:* V3
Species (Isotype) rat
Ab Type gp120 V3
References McKnight *et al.* 1995

- Hv: Rat antibodies were raised against V3 peptides that represent either the wildtype (wt), or brain-cell tropic variant (v) of the isolate Gun-1 – neutralization of only the variant strain, does not bind to wildtype. McKnight *et al.* [1995]

No. 517
MAb ID polyclonal
HXB2 Location gp160 (305–322)
Author Location gp140 (SF162)
Epitope KSITIGPGRAFYATGD
Neutralizing yes
Immunogen vaccine
Vector/Type: DNA with CMV promotor *Strain:* B clade SF162 *HIV component:* gp140 *Adjuvant:* MF59
Species (Isotype) macaque, rabbit (IgG)
Ab Type gp120 V3
References Barnett *et al.* 2001

- SF162ΔV2 is a virus that has a 30 amino acids deletion in the V2 loop that does not abrogate its infectivity but renders it highly susceptible to neutralization – when incorporated into a codon-optimized DNA vaccine with a CMV promoter, delivered by gene gun, SF162Δ2 gave higher neutralizing Ab titers against SF162 than did SF162 itself, and Abs that cross-neutralized non-homologous primary isolates were obtained only when SF162ΔV2, but not intactSF162, was used as the immunogen – NAbs titers specific for SF162 increased with multiple immunizations, while titers for non-homologous isolates decreased, but anti-V3 peptide binding Abs were not likely the source of this distinction because anti-V3 titers were much lower than those against the entire envelope, and the second booster immunization did not increase the titer of anti-V3 loop Abs. Barnett *et al.* [2001]

No. 518
MAb ID 50.1 (R/V3-50.1, Fab 50.1)
HXB2 Location gp160 (306–310)
Author Location gp120 (MN)
Epitope RIHIG
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade MN *HIV component:* V3
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 V3
Research Contact Mary White-Scharf, Repligen Corporation, Cambridge, MA
References Pantophlet *et al.* 2008; Sirois *et al.* 2007; Stanfield & Wilson 2005; Huang *et al.* 2005a; Zhang *et al.* 2002; York *et al.* 2001; Park *et al.* 2000; Hoffman *et al.* 1999; Stanfield *et al.* 1999; LaCasse *et al.* 1998; Berman *et al.* 1997; Seligman *et al.* 1996; Fontenot *et al.* 1995; VanCott *et al.* 1995; Moore *et al.* 1994b; Robert-Guroff *et al.* 1994; VanCott *et al.* 1994; Bou-Habib *et al.* 1994; Rini *et al.* 1993; Ghiara *et al.* 1993; Potts *et al.* 1993; White-Scharf *et al.* 1993; D'Souza *et al.* 1991
Keywords antibody binding site definition and exposure, review, structure

- 50.1: NIH AIDS Research and Reference Reagent Program: 1289.
- 50.1: Angle of interaction between 50.1 and V3 was shown by superimposing the Fab fragment of the Ab with V3. Pantophlet *et al.* [2008] (**antibody binding site definition and exposure**, **structure**)
- 50.1: Data is summarized on the X-ray crystal structures resolution and NMR studies of 50.1. Sirois *et al.* [2007] (**review**, **structure**)
- 50.1: The crystal structure of V3-reactive antibody-peptide complexes were examined. 50.1 completely surrounded V3, suggesting a high degree of accessibility for generating an immune response. Accessibility of V3 to this MAb is shown in a 3D figure. Huang *et al.* [2005a] (**antibody binding site definition and exposure**, **structure**)
- 50.1: This review summarizes data on crystallographic structures of 50.1 binding to its V3 peptide antigens. Conformation of the V3 peptide bound to 50.1 is very similar to its conformation when bound to 447-52D. Stanfield & Wilson [2005] (**antibody binding site definition and exposure**, **review**, **structure**)
- 50.1: Called R/V3-50.1 – A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002]
- 50.1: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAbs alters some step after binding

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– the dissociation constant, Kd of 50.1 for the cell associated primary and TCLA Envs was equal, 7nM. York *et al.* [2001]

- 50.1: Called R/V3-50.1 – six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes – 50.1 could only neutralize the sensitive form. Park *et al.* [2000]
- 50.1: The crystal structure of V3 loop peptides bound to Fabs was obtained – conformational changes in the tip of the V3 loop (GPGR) were observed when different Fabs were bound. Stanfield *et al.* [1999]
- 50.1: A T-cell line-adapted (TCLA) derivative of SI primary isolate 168P acquired the ability to be neutralized by anti-V3 MAbs – the primary isolate could use either CCR5 or CXCR4, and was not neutralized when infection was directed via either pathway, however the TCLA derivative uses CXCR4 only and is neutralized. LaCasse *et al.* [1998]
- 50.1: Binds to 6/7 isolates from breakthrough cases from a MN gp120 vaccine trial. Berman *et al.* [1997]
- 50.1: Competition ELISAs with serial deletions produced comparable estimate of epitope length to crystal structure and alanine substitution – KRIHIGP. Seligman *et al.* [1996]
- 50.1: Used to monitor HIV-1 Env expression in infected H9 cells. VanCott *et al.* [1995]
- 50.1: No neutralization of primary isolate JR-CSF – greater affinity for and neutralization of T cell tropic strain T-CSF, derived from JR-CSF. Bou-Habib *et al.* [1994]
- 50.1: Shows modest cross-reactivity among B clade gp120s, little outside B clade. Moore *et al.* [1994b]
- 50.1: Chimeric MN V3 loop in an HXB2 background allows increased FACS signal, Ab affinity, and viral neutralization. Robert-Guroff *et al.* [1994]
- 50.1: Potent MN neutralization, slow dissociation rate. VanCott *et al.* [1994]
- 50.1: Crystal structure of a 24 amino acid peptide from the V3 loop bound to 59.1 and 50.1 Fab fragments – epitope KRIHIGP. Ghiara *et al.* [1993]
- 50.1: No synergistic neutralization of MN when combined with CD4BS MAb F105 – isotype stated to be IgG2a. Potts *et al.* [1993]
- 50.1: Crystal structure of V3 loop bound to 50.1 – light chain binds just to the left of GPG, heavy chain binds further to the left. Rini *et al.* [1993]
- 50.1: Epitope defined by peptide reactivity and changes affinity with amino acid substitutions – epitope RIHIGP. White-Scharf *et al.* [1993]
- 50.1: Called R/V3-50.1 – potent neutralizing of lab strains. D'Souza *et al.* [1991]

No. 519
MAb ID
HXB2 Location gp160 (306–322)
Author Location gp160
Epitope RIRPGRAFVTIGK
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: influenza *Strain:* B clade IIIB *HIV component:* V3
Species (Isotype) human (IgA, IgG)
Ab Type gp120 V3
References Garulli *et al.* 2004
Keywords mucosal immunity

- Progesterone-treated BALB/c mice were intravaginally infected with recombinant influenza A virus (Flu/P18IIIB), expressing the immunodominant CTL epitope (P18IIIB, RIRPGRAFVTIGK, H-2Dd). A second immunization administered 2 weeks after the first doubled serum IgG levels and enabled detection of vaginal IgG. Low levels of vaginal IgA were detected in some animals. Garulli *et al.* [2004] (**mucosal immunity**)

No. 520
MAb ID BAT123 (BAT-123, CGP 47 439)
HXB2 Location gp160 (306–322)
Author Location gp120 (308–322 HXB2)
Epitope RIRIQRGPGRAFVTIGK
Subtype B
Neutralizing L
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 V3
Research Contact Tanox Biosystems Inc and David Ho, ADARC, NY
References Gauduin *et al.* 1998; Parren *et al.* 1998a; Andrus *et al.* 1998; Poignard *et al.* 1996a; Sattentau & Moore 1995; Gauduin *et al.* 1995; Pirofski *et al.* 1993; Thali *et al.* 1993; Safrit *et al.* 1993; Moore & Ho 1993; Fung *et al.* 1990; Liou *et al.* 1989; Fung *et al.* 1987

- BAT123: Post-exposure prophylaxis was effective when MAb 694/98-D was delivered 15 min post-exposure to HIV-1 LAI in hu-PBL-SCID mice, but declined to 50% if delivered 60 min post-exposure, and similar time constraints have been observed for HIVIG, 2F5 and 2G12, in contrast to MAb BAT123 that could protect delivered 4 hours post infection. Andrus *et al.* [1998]
- BAT123: Post-exposure passive transfer of murine BAT123 can confer protection to hu-PBL-SCID mice challenged with HIV-1 LAI – this protection is not elicited by CGP 47 439, a BAT123 chimera that has a human IgG1 Fc domain, suggesting that the protection is mediated by complement – the protective ability of BAT123 is lost when mice were treated with cobra venom factor, which inactivates serum complement – IgG1 does not fix complement efficiently so an IgG2 MAb might perform better. Gauduin *et al.* [1998]
- BAT123: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- BAT123: Epitope described as RGPGRAFVTIGK – V3 MAbs 9284, BAT123, 110.5, and 110.I could each significantly increase gp120 dissociation from virus (BAT123 less so

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than the others), mimicking sCD4, and expose the gp41 epitope for MAb 50-69, in contrast to anti-V2 MAbs. Poignard *et al.* [1996a]

- BAT123: Passive transfer of BAT123 to hu-PBL-SCID mice 1 hour prior to inoculation with HIV-1 LAI, or up to four hours post-exposure, could protect mice from infection – the protection, like the MAb, was specific for the viral strain LAI. Gauduin *et al.* [1995]
- BAT123: Binds with high affinity to monomer and oligomer, rapid association and potent neutralization of lab strain. Sattentau & Moore [1995]
- BAT123: Called BAT-123 – conformational, does not bind well to denatured gp120 – not reactive with SF-2 gp120 – does not inhibit HIV-1 sera from binding to IIIB gp120. Moore & Ho [1993]
- BAT123: Variable region sequenced – heavy chain: V 3660-SB32, D unknown, J H3 – light chain: V kappa21, J kappa2. Pirofski *et al.* [1993]
- BAT123: Passive transfer to Hu-PBS-SCID mice confers protection against challenge with homologous cell-free virus. Safrit *et al.* [1993]
- BAT123: Anti-idiotypic MAb, AB19-4i, stimulates anti-anti-ID which neutralizes MN and IIIB. Fung *et al.* [1990]
- BAT123: CGP 47 439 is a BAT123 chimera that has a human IgG1 Fc domain. Liou *et al.* [1989]

No. 521
MAb ID 838-D (838)
HXB2 Location gp160 (307–311)
Author Location Env (RF)
Epitope KSITK
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Zhang *et al.* 2002; He *et al.* 2002; Nyambi *et al.* 2000; Gorny *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Nyambi *et al.* 1998; Hioe *et al.* 1997b; Gorny *et al.* 1997
Keywords antibody binding site definition and exposure, antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 838-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- 838-D: Called 838: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 838-D: Called 838 – Transgenic mice carrying human genes allowing production of fully human MAbs were used to rapidly create a panel of anti-HIV gp120 MAb producing hybridomas by immunization with HIV SF162 gp120 – the previously described human MAbs 5145A(CD4BS) , 4117C (plus others, V3) and 697D (and SC258, V2) were used as controls. He *et al.* [2002]
- 838-D: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002]
- 838-D: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – V3 MAbs 447-52D, 838-D, and 1334 bound with a 7-10 fold preference for the oligomer. Gorny *et al.* [2000] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 838-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 838-D showed intermediate reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)
- 838-D: Review of clade specificity and anti-V3 HIV-1-Abs – this Ab showed strong binding to many A, B, C and F peptides, poor binding to D and E. Zolla-Pazner *et al.* [1999a] (**review**, **subtype comparisons**)
- 838-D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 838, 782, 1027, 908, and 1006, all selected with RF V3 peptide – the core amino acids KSITK tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 838-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – 838-D bound B clade virions but had limited cross-reactivity with other clades, with low levels of binding to A and D virions. Nyambi *et al.* [1998] (**subtype comparisons**)
- 838-D: Five human MAbs against were derived from HIV-infected North American subjects after selection by the V3 RF peptide – 838-D was cross-reactive with V3 peptides from clade A and C, and could bind to 5/8 B clade V3 peptides – 50% neutralization of RF was obtained. Gorny *et al.* [1997] (**antibody generation**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

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- 838-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D)and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)

No. 522
MAb ID 1006-15D (1006)
HXB2 Location gp160 (307–312)
Author Location gp120 (RF)
Epitope KSITKG
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Eda *et al.* 2006b; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; He *et al.* 2002; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Gorny *et al.* 1997
Keywords antibody binding site definition and exposure, antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 1006-15D: The neutralization potency of this Ab against 7 HIV-1 primary isolates was compared to the neutralization potency of the Ab KD-247. The same Ab concentrations were needed for neutralization of the N-NIID and 92TH022 isolates, while higher concentrations of 1006-15D were needed for the neutralization of the rest of the HIV-1 isolates suggesting 1006-15D has lower neutralization potency. Eda *et al.* [2006b] (**variant cross-recognition or cross-neutralization**)
- 1006-15D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 1006-15D: Called 1006-15: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 1006-15D: Called 1006 – Transgenic mice carrying human genes allowing production of fully human MAbs were used to rapidly create a panel of anti-HIV gp120 MAb producing hybridomas by immunization with HIV SF162 gp120 – the previously described human MAbs 5145A(CD4BS) , 4117C (plus others, V3) and 697D (and SC258, V2) were used as controls. He *et al.* [2002]
- 1006-15D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 1006-15D showed strong cross-reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)
- 1006-15D: Review of clade specificity and anti-V3 HIV-1-Abs – this Ab showed strong binding to several B and F peptides, one C peptide, and some reactivity with A peptides – no binding was observed with D and E peptides. Zolla-Pazner *et al.* [1999a] (**review**, **subtype comparisons**)
- 1006-15D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 838, 782, 1027, 908, and 1006, all selected with RF V3 peptide – the core amino acids KSITK tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 1006-15D: Five human MAbs against were derived from HIV-infected North American subjects after selection by the V3 RF peptide – was somewhat cross-reactive with V3 peptides from clade A, C and other B clade V3 peptides, but not E clade. Gorny *et al.* [1997] (**antibody generation**, **subtype comparisons**)

No. 523
MAb ID 782-D (782)
HXB2 Location gp160 (307–312)
Author Location Env (RF)
Epitope KSITKG
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Hioe *et al.* 1997b; Gorny *et al.* 1997
Keywords antibody binding site definition and exposure, antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 782-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- 782-D: Called 782: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This

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MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)

- 782-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 782-D showed intermediate reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)
- 782-D: Review of clade specificity and anti-V3 HIV-1-Abs – this Ab showed strong binding to several B and F peptides, one C peptide, and some reactivity with A and D peptides. Zolla-Pazner *et al.* [1999a] (**variant cross-recognition or cross-neutralization**, **review**, **subtype comparisons**)
- 782-D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 838, 782, 1027, 908, and 1006, all selected with RF V3 peptide – the core amino acids KSITK tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 782-D: Five human MAbs against were derived from HIV-infected North American subjects after selection by the V3 RF peptide – 782-D was not cross-reactive with V3 peptides from clade A or E, but could bind to 3/8 B clade V3 peptides, and 1/2 C clade V3 peptides – 50% neutralization of RF was obtained. Gorny *et al.* [1997] (**antibody generation**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 782-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D)and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)

No. 524
MAb ID 908-D (908, 908-12D)
HXB2 Location gp160 (307–312)
Author Location gp120 (RF)
Epitope `KSITKG`
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Gorny *et al.* 1997
Keywords antibody binding site definition and exposure, antibody generation, review, subtype comparisons

- 908-D:This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 908-D: Called 908: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 908-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross -reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 908-D showed strong cross-reactivity, but achieved only 50% neutralization on 2/5 isolates tested. Nyambi *et al.* [2000] (**subtype comparisons**)
- 908-D: Review of clade specificity and anti-V3 HIV-1-Abs – this Ab showed strong binding to several A, B, C and F peptides, and poor binding to E and D peptides. Zolla-Pazner *et al.* [1999a] (**review**, **subtype comparisons**)
- 908-D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 838, 782, 1027, 908, and 1006, all selected with RF V3 peptide – the core amino acids KSITK tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 908-D: Five human MAbs against were derived from HIV-infected North American subjects after selection by the V3 RF peptide – 908-D was not cross-reactive with V3 peptides from clade E, but could bind to 6/8 B clade V3 peptides, 2/4 A clade, and 1/2 C clade – 50% neutralization of RF was obtained. Gorny *et al.* [1997] (**antibody binding site definition and exposure**, **antibody generation**, **subtype comparisons**)

No. 525
MAb ID 1027-15D (1027, 1027-D, 1027D, 1027-15)
HXB2 Location gp160 (307–313)
Author Location Env (RF)
Epitope `KSITKGP`
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Zhang *et al.* 2002; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Gorny *et al.* 1997

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Keywords antibody binding site definition and exposure, antibody generation, review, subtype comparisons

- 1027-15D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 1027-15S: Called 1027-15: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 1027-15D: Called 1027-D – A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002] (**antibody binding site definition and exposure**)
- 1027-15D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 1027-15D showed strong cross-reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)
- 1027-15D: Review of clade specificity and anti-V3 HIV-1-Abs – this Ab showed moderate binding to several B and F peptides, one C peptide, and was not reactivity with A, D and E peptides. Zolla-Pazner *et al.* [1999a] (**review**, **subtype comparisons**)
- 1027-15D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 838, 782, 1027, 908, and 1006, all selected with RF V3 peptide – the core amino acids KSITK tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 1027-15D: Five human MAbs against were derived from HIV-infected North American subjects after selection by the V3 RF peptide – 1027-15D was not cross-reactive with V3 peptides from clade A or E, but could bind to 3/8 B clade V3 peptides, and 1/2 C clade V3 peptides. Gorny *et al.* [1997] (**antibody binding site definition and exposure**, **antibody generation**, **subtype comparisons**)

No. 526
MAb ID V3-13
HXB2 Location gp160 (307–315)
Author Location gp120 (V3)
Epitope `IRIQRGPGR`
Neutralizing
Immunogen
Species (Isotype)
Research Contact National Institute for Biological Standards and Control
References van Montfort *et al.* 2008
Keywords co-receptor, dendritic cells, neutralization

- V3-13: Transmission of HIV-1 by immature and mature DCs to CD4+ T lymphocytes was significantly higher for CXCR4- than for CCR5-tropic strains. In addition, V3-13 inhibited transmission of CCR5-tropic viruses while transmission of V3-13-neutralized X4 variants increased, indicating that X4 HIV-1 has an advantage over R5 in transmission when neutralized with V3-13. van Montfort *et al.* [2008] (**co-receptor**, **neutralization**, **dendritic cells**)

No. 527
MAb ID F19.26-4
HXB2 Location gp160 (307–319)
Author Location gp120 (312–324 LAI)
Epitope `IRIQRGPGRAFVT`
Subtype B
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgG2aκ)
Ab Type gp120 V3
References Boudet *et al.* 1994

- F19.26-4: Strain specific – used to raise anti-idiotype antibodies. Boudet *et al.* [1994]

No. 528
MAb ID F19.48-3
HXB2 Location gp160 (307–319)
Author Location gp120 (312–324 LAI)
Epitope `IRIQRGPGRAFVT`
Subtype B
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgG2aκ)
Ab Type gp120 V3
References Boudet *et al.* 1994

- F19.48-3: Strain specific – used to raise anti-idiotype antibodies. Boudet *et al.* [1994]

No. 529
MAb ID F19.57-11
HXB2 Location gp160 (307–319)
Author Location gp120 (312–324 LAI)
Epitope `IRIQRGPGRAFVT`
Subtype B
Neutralizing L (LAI)
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 V3

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References Boudet *et al.* 1995; Boudet *et al.* 1994; Boudet *et al.* 1991

- F19.57-11: Anti-anti-idiotypic antibodies (Ab3) were raised in BALBc mice that had greater breadth of reactivity than the original F19.57-11 (Ab3 could also recognize 1282 and SF2, with aa TRK(R or S)IYIGPGRA(WY or FH)T) Boudet *et al.* [1995]
- F19.57-11: MAb F19.57-11 is strain specific for LAI – used to raise anti-idiotype rabbit antibodies (called 57-B Ab2) Boudet *et al.* [1994]

No. 530
MAb ID 13105100
HXB2 Location gp160 (307–320)
Author Location gp120 (HXB2)
Epitope IRIQRGPGRAFVTI
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* V3
Species (Isotype) mouse (IgG1)
Ab Type gp120 V3
Research Contact ABI, Columbia, MD
References Dairou *et al.* 2004
Keywords antibody binding site definition and exposure

- 13105100: This MAb was raised against the peptide IRIQRGPGRAFVTI, located within the V3 loop flanking the GPGR apical motif. Two MAbs were used to determine the photodamage location in HIV-1 Env induced by sulfonated anionic porphyrins. The negatively charged porphyrins interact with positive charge in the V3 loop. When light activated, they damage amino acid side chains in the C5 region of Env, as evidenced by inhibition of binding of C5 MAb 9201, but not V3 MAb 13105100. Anionic porphyrins could be used in targeted photodynamic decontamination of biological fluids, such as blood, killing HIV without disabling the function of desirable transfusion products. Dairou *et al.* [2004] (**antibody binding site definition and exposure**)

No. 531
MAb ID M77
HXB2 Location gp160 (307–320)
Author Location gp120 (IIIB)
Epitope IRIQRGPGRAFVTI
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 V3
Research Contact Advanced BioScience Laboratories, Rockville, MD, commercial
References Gorny & Zolla-Pazner 2004; Finnegan *et al.* 2002; Denisova *et al.* 2000; Watkins *et al.* 1996; Denisova *et al.* 1996; Denisova *et al.* 1995; DeVico *et al.* 1995; Cook *et al.* 1994; Watkins *et al.* 1993; di Marzo Veronese *et al.* 1993; di Marzo Veronese *et al.* 1992; Pal *et al.* 1992
Keywords antibody binding site definition and exposure, escape, review, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- M77: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. M77 neutralizes some TCLA strains. Gorny & Zolla-Pazner [2004] (**review**)
- M77: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I and Cluster II MAbs required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor, binding to a fusion intermediate. Cluster I and II MAbs bound to gp120/gp41 complexes at the cell-to-cell contact interface, in contrast to M77 which bound to gp120 that was evenly dispersed over the target cell surface. Finnegan *et al.* [2002]
- M77: M77 is highly strain specific for IIIB, but anti-idiotypic Abs directed against M77 can in turn elicit an Ab response with expanded HIV cross-reactivity – this mechanism may serve to prolong the primary response and to counter-balance viral immune evasion by mutation. Denisova *et al.* [2000] (**variant cross-recognition or cross-neutralization**)
- M77: Used M77 bound to gp120 as an immunogen – analysis of polyclonal and monoclonal (62 MAbs were generated) response suggests the M77-gp120 immunogen generated MAbs to more linear epitopes than gp120 alone or gp120 bound to CD4. Denisova *et al.* [1996] (**vaccine-specific epitope characteristics**)
- M77: Native M77 is highly strain specific, and V3 binding is primarily dependent on its heavy chain – a light chain switched Fab version of M77 could recognize HIV-1 strains that had substitutions on the left side of the V3 loop – R in GPGR is likely to be critical for binding. Watkins *et al.* [1996] (**variant cross-recognition or cross-neutralization**)
- M77: Reacted with both reduced and non-reduced covalently cross-linked gp120-CD4 complex. DeVico *et al.* [1995] (**antibody binding site definition and exposure**)
- M77: Conformational rearrangements upon binding of M77 to gp120 generates novel epitopes called metatopes. Denisova *et al.* [1995]
- M77: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – this MAb can inhibit gp120 binding to GalCer *in vitro*. Cook *et al.* [1994]
- M77: Stated to be a murine MAb – a neutralization escape mutant (HXB2 A281V) was selected by growth of HXB2 in the presence of broadly neutralizing sera – M77 neutralization was only slightly reduced by this mutation. Watkins *et al.* [1993] (**escape**)
- M77: Antibody binding to viral isolates from IIIB infected lab worker followed through time – A to T substitution resulted in the loss of neutralization and native gp120 binding, but not peptide binding. di Marzo Veronese *et al.* [1993] (**escape**)
- M77: IIIB-specific MAb, immunoprecipitates deglycosylated form. di Marzo Veronese *et al.* [1992] (**variant cross-recognition or cross-neutralization**)

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MAb ID polyclonal
HXB2 Location gp160 (307–321)
Author Location gp120 (307–321)
Epitope IRIQRGPGRAFVTIG
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) chimpanzee
Ab Type gp120 V3
References Goudsmit *et al.* 1988
Keywords antibody binding site definition and exposure, autologous responses, variant cross-recognition or cross-neutralization

- By three months post infection, chimpanzees infected with four strains of HIV-1 developed perisistant Ab responses. The V3 loop was a critical binding domain for strain-specific NAbs in sera from the infected chimpanzees. Goudsmit *et al.* [1988] (**antibody binding site definition and exposure**, **autologous responses**, **variant cross-recognition or cross-neutralization**)

No. 533
MAb ID SP.BAL114
HXB2 Location gp160 (308–317)
Author Location gp120 (BAL)
Epitope SIHIGPGRAF
Neutralizing L
Immunogen
Species (Isotype) mouse (IgG2aκ)
Ab Type gp120 V3
References Kanduc *et al.* 2008; Arendrup *et al.* 1995

- SP.BAL114: Similarity level of the SP.BAL114 binding site pentapeptide IHIGP to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- Authors suggest that during *in vivo* immunoselection of escape virus, the V3 domain gains increasing resemblance to that of lab strains. Arendrup *et al.* [1995]

No. 534
MAb ID SP.SF2:104
HXB2 Location gp160 (308–317)
Author Location gp120 (SF2)
Epitope SIYIGPGRAF
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) (IgG2aκ)
Ab Type gp120 V3
References Arendrup *et al.* 1995; Arendrup *et al.* 1993

- SP.SF2:104: Authors suggest that during *in vivo* immunoselection of escape virus, the V3 domain gains increasing resemblance to lab strains. Arendrup *et al.* [1995]
- SP.SF2:104: Anti-V3 antibody that could neutralize primary virus isolated from a time point of neutralization resistance of autologous virus. Arendrup *et al.* [1993]

No. 535
MAb ID polyclonal
HXB2 Location gp160 (308–319)
Author Location gp120 (304–318 LAI)
Epitope RIHIGPGRAFYT
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG, IgM)
Ab Type gp120 V3
References Langedijk *et al.* 1995

- Polylconal sera from six individuals tested for reactivity against a panel of peptides based on autologous sequences provide evidence for immunological escape mutations in the tip of the V3 loop. Langedijk *et al.* [1995]

No. 536
MAb ID loop 2 (Loop 2, IgG1 Loop 2, loop2)
HXB2 Location gp160 (308–321)
Author Location gp120
Epitope SISGPGRAFYTG
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V3
Research Contact D. Burton, Scripps Research Institute, La Jolla, CA
References Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Sullivan *et al.* 1998a; Parren *et al.* 1998a; Mondor *et al.* 1998; Parren & Burton 1997; Parren *et al.* 1997b; Ugolini *et al.* 1997; Ditzel *et al.* 1997; Wu *et al.* 1996; Moore *et al.* 1994b; Barbas III *et al.* 1993
Keywords antibody generation, antibody interactions, antibody sequence variable domain, binding affinity, co-receptor, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- loop 2 database comment: Also known as Loop 2, IgG1 Loop 2 was a obtained by engineering Fab loop2 into an IgG1 molecule. (**antibody generation**)
- loop 2: Called loop2. This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. loop 2 neutralizes some TCLA strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- loop 2: This paper attempts to engineer a gp120 molecule that would focus the immune response onto the IgG1b12 epitope. Adding a glycosylation sequon (P313N) to the V3 loop knocked out binding to anti-V3 MAbs loop 2, 19b and 447-52-D. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- loop 2: Called loop2. scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that

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the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the V3 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)

- loop 2: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope – binding affinity of divalent IgG1 loop 2 is only 2-fold greater than monovalent Fab loop 2, suggesting the IgG1 form may bind with only one arm. Parren *et al.* [1998a] (**binding affinity**)
- loop 2: The HIV-1 virus YU2 entry can be enhanced by MAbs binding to the CD4BS, V3 loop, and CD4i epitopes – the activation for this enhanced entry state could be conferred on HxB2 by introducing the YU2 V3 loop, or the YU2 V3 and V1/V2 loops – a similar effect is observed by sub-neutralizing concentrations of sCD4 and the effect is dependent of CCR5 – loop 2 enhances YU2 at concentrations up to 20 ug/ml. Sullivan *et al.* [1998a]
- loop 2: Binds to gp120 from MN and SF2 but not LAI. Ditzel *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- loop 2: Epitope is suggested to be GPGRAF – binds to 10/17 US clade B monomeric gp120s – IgG1 form can neutralize MN and 2 primary isolates tested. Parren & Burton [1997]
- loop 2: Neutralizes TCLA strains but not primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- loop 2: Viral binding inhibition by loop 2 MAb or Fab was correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5) Ugolini *et al.* [1997]
- loop 2: MIP-1alpha binding to CCR-5 expressing cells can be inhibited by gp120-sCD4 – binding of loop 2 blocks this inhibition. Wu *et al.* [1996] (**co-receptor**)
- loop 2: Called Loop 2 – shows modest cross-reactivity among B clade gp120s, little outside B clade. Moore *et al.* [1994b] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- loop 2: Sequences of the heavy and light chain Fab variable regions were generated. Barbas III *et al.* [1993] (**antibody sequence variable domain**)

No. 537
MAb ID 4G10
HXB2 Location gp160 (308–322)
Author Location gp120 (308–322 LAI)
Epitope RIQRGPGRAFVTGK
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: HBcAg fusion *HIV component:* V3
Species (Isotype) mouse
Ab Type gp120 V3
Research Contact Dr. Albrecht von Brunn, Max-von-Pettenkofer-Institut, Ludwig-Maximilians-Universitat Munchen, Germany
References Holl *et al.* 2006a; von Brunn *et al.* 1993
Keywords dendritic cells, neutralization

- 4G10: NIH AIDS Research and Reference Reagent Program: 2534.
- 4G10: This Ab did not inhibit HIV-1 BaL replication in macrophages. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 4G10: A 25 amino acid V3-loop sequence fused to HBcAg enhanced V3 immunogenicity. von Brunn *et al.* [1993]

No. 538
MAb ID 5F7
HXB2 Location gp160 (308–322)
Author Location gp120 (308–322 LAI)
Epitope RIQRGPGRAFVTGK
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: HBcAg fusion *HIV component:* V3
Species (Isotype) mouse
Ab Type gp120 V3
Research Contact Dr. Albrecht von Brunn, Max-von-Pettenkofer-Institut, Ludwig-Maximilians-Universitat Munchen, Germany
References von Brunn *et al.* 1993

- 5F7: NIH AIDS Research and Reference Reagent Program: 2533.
- 5F7: A 25 amino acid V3-loop sequence fused to HBcAg enhanced V3 immunogenicity. von Brunn *et al.* [1993]

No. 539
MAb ID G3-523
HXB2 Location gp160 (308–322)
Author Location gp120 (308–322)
Epitope RIQRGPGRAFVTIGK
Neutralizing
Immunogen
Species (Isotype) mouse
Ab Type gp120 V3
References Jagodzinski *et al.* 1996; Matsushita *et al.* 1988

- G3-523: The sulfated polysaccharide curdlan sulfate (CRDS) binds to the Envelope of T-tropic viruses and neutralizes virus – CRDS inhibits G3-523 binding. Jagodzinski *et al.* [1996]

No. 540
MAb ID MN215
HXB2 Location gp160 (308–322)
Author Location gp120 (MN)
Epitope RIHIGPGRAFYTTKN
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
Ab Type gp120 V3

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References Martin *et al.* 2008; Holl *et al.* 2006a; Zipeto *et al.* 2005; Gorny & Zolla-Pazner 2004; Schutten *et al.* 1995b
Keywords antibody binding site definition and exposure, assay development, binding affinity, dendritic cells, neutralization, review, vaccine antigen design, variant cross-recognition or cross-neutralization

- MN215: MRC Centralized Facility for AIDS Reagents, NIBSC, UK, EVA3056
- MN215: A new purification method was developed using a high affinity peptide mimicking CD4 as a ligand in affinity chromatography. This allowed the separation in one step of HIV envelope monomer from cell supernatant and capture of pre-purified trimer. gp140DF162ΔV2 was purified by the miniCD4 method to asses its ability to capture gp140 trimers. Binding of MN215 to gp140DF162ΔV2 purified by the miniCD4 affinity chromatography and a multi-step method was comparable, suggesting that the SF162 trimer antigenicity was preserved. Martin *et al.* [2008] (**assay development**, **binding affinity**)
- MN215: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication occurs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- MN215: HIV-1 fusion complexes were prepared from cell lines expressing R5 HIV-1 gp120/gp41 and CD4-CCR5. Neutralizing Abs were raised against both R5 (strain BaL) and X4 (strain 213) viruses. MN215 was used to detect gp120/gp41. Zipeto *et al.* [2005] (**vaccine antigen design**)
- MN215: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. MN215 neutralizes some TCLA strains. Gorny & Zolla-Pazner [2004] (**review**)
- MN215: Minimum epitope for MAB using the Dutch consensus is AFYTTGE, different than defined for MN – generated by EBV transformation of PBMC – displayed higher affinity for NSI than for SI glycoproteins – amino acids HIGP were essential for binding. Schutten *et al.* [1995b] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)

No. 541
MAb ID Nea 9301
HXB2 Location gp160 (308–323)
Author Location gp120 (IIIB)
Epitope RIQRGPGRAFVTIGKI
Neutralizing
Immunogen
Species (Isotype) mouse
Ab Type gp120 V3
Research Contact Dupont, commercial
References Wagner *et al.* 1996

No. 542
MAb ID 4117C (4117c)
HXB2 Location gp160 (309–315)
Author Location gp120
Epitope IXIGPGR
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
Research Contact Abraham Pinter, Public Health Research Institute, Newark, NJ, 07103. pinter@phri.org.
References Krachmarov *et al.* 2006; Pinter *et al.* 2005; Krachmarov *et al.* 2005; Pinter *et al.* 2004; Gorny & Zolla-Pazner 2004; He *et al.* 2002; Alsmadi & Tilley 1998; Pinter *et al.* 1993b; Pinter *et al.* 1993a; di Marzo Veronese *et al.* 1993; Tilley *et al.* 1992; Tilley *et al.* 1991a
Keywords ADCC, antibody binding site definition and exposure, antibody interactions, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 4117C: This Ab was shown to neutralize SF162 and the neutralization sensitivity increased in the SF162 variant with a JR-FL V3 loop, SF162(JR-FL V3). In contrast, a great reduction in sensitivity to neutralization was observed in the SF162(JR-FL V1/V2) variant and was somewhat restored in the SF162(JR-FL V1/V2/V3) variant, indicating that the masking of the V1/V2 loop plays a much greater role in restricting neutralization sensitivity than the variations in V3. This Ab was shown to neutralize viruses with V3 sequences from several different subtypes (B, F, A1 and H) except subtypes C, CRF01_AE and CRF02_AG. This Ab failed to neutralize SF162(JR-FL V1/V2) with V3 derived from different HIV-1 clades indicating effective V1/V2-mediated masking of several HIV-1 clades. The effect on the neutralization sensitivity of the residue at the crown of the V3 loop (position 18) was shown to be low for this Ab. Krachmarov *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 4117c: Sera from subtype A infected individuals from Cameroon have antibodies that react strongly with subtype A and subtype B V3 loops in fusion proteins, and neutralize SF162 pseudotypes, while sera from subtype B infected individuals reacted only with subtype B. Sera from Cameroon did not neutralize primary A or B isolates, due to indirect masking by the V1/V2 domain rather than due to loss of the target epitope. Neutralization by anti-V3 B clade specific MAbs 447-52D and 4117C was fully blocked by a clade V3 loop fusion protein, but not an A clade fusion protein, while Cameroonian sera neutralization was fully blocked by both A and B clade fusion proteins. Krachmarov *et al.* [2005] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 4117c: This study is about the MAb C108g, and 4117C was a control. 4117C is a linear V3 epitope unaffected by reduction, whereas C108g, contrary to earlier reports, requires disulfide bonds. C108G is type-specific and neutralizes BaL and HXB2. JR-FL is a neutralization resistant strain; modification of JRFL at V2 positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potently neutralize the modified JR-FL. The modification in V2 also increased neutralization sensitivity to V3 MABs 4117c, 2219, 2191, and 447-52D,

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but only had minor effects on neutralization by CD4BS MAb 5145A, and broadly neutralizing MAbs IgG1b12, 2G12, and 2F5. Binding to CCR5 was completely inhibited by two V3 MAbs, 4117C and 2219, and was substantially inhibited by 2G12, but was not inhibited by C108g. Pinter *et al.* [2005] (**antibody binding site definition and exposure**)

- 4117c: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. 4117C and 4118D are anti-V3 MAbs that neutralize TCLA strains. Gorny & Zolla-Pazner [2004] (**review**)
- 4117c: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neturalization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12 which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. 5/6 anti-V3 MAbs, including 4117c, had similar binding affinity to soluble SF162 and JR-FL rgp120s, although the V3 loop differs at three positions (HigpgrafyTtgE for JR-FL and TigpgrafyAtgD for SF162). Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 4117C: Transgenic mice carrying human genes allowing production of fully human MAbs were used to rapidly create a panel of anti-HIV gp120 MAb producing hybridomas by immunization with HIV SF162 gp120 – the previously described human MAbs 5145A(CD4BS) , 4117C (plus others, V3) and 697D (and SC258, V2) were used as controls. He *et al.* [2002]
- 4117C: A study of 6 anti-Env MAbs and their ability to bind or direct ADCC against target cells infected with IIIB, MN, SF-2, and RF – bound and directed lysis against MN and SF2, but not IIIB and RF. Alsmadi & Tilley [1998] (**ADCC**, **variant cross-recognition or cross-neutralization**)
- 4117C: Neutralizes SF2 and MN synergistically combined with anti-CD4 binding site discontinuous MAb. Pinter *et al.* [1993a]; Tilley *et al.* [1992] (**antibody interactions**, **variant cross-recognition or cross-neutralization**)
- 4117C: Binds V3 loop – does not immunoprecipitate soluble gp120, does react with gp120 on intact virions. Pinter *et al.* [1993b] (**antibody binding site definition and exposure**)
- 4117C: Potent neutralizing activity against MN, SF-2, and NY-5 – synergy with CD4BS MAb 1125H. Tilley *et al.* [1991a] (**antibody binding site definition and exposure**, **antibody interactions**, **variant cross-recognition or cross-neutralization**)

No. 543
MAb ID 419-D (419, 419D)
HXB2 Location gp160 (309–315)
Author Location gp120 (MN)
Epitope IHIGPGR
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; He *et al.* 2002; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Nyambi *et al.* 1998; Hioe *et al.* 1997b; Fontenot *et al.* 1995; Spear *et al.* 1993; Gorny *et al.* 1993; Karwowska *et al.* 1992b
Keywords antibody binding site definition and exposure, complement, mimotopes, review, subtype comparisons, superinfection, variant cross-recognition or cross-neutralization

- 419-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 419-D: Called 419: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**mimotopes**, **superinfection**)
- 419-D: Called 419 – Transgenic mice carrying human genes allowing production of fully human MAbs were used to rapidly create a panel of anti-HIV gp120 MAb producing hybridomas by immunization with HIV SF162 gp120 – the previously described human MAbs 5145A(CD4BS) , 4117C (plus others, V3) and 697D (and SC258, V2) were used as controls. He *et al.* [2002]
- 419-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 419-D showed intermediate reactivity, and no neutralization when tested against five strains – discrepancy between the epitope as described in earlier papers and as described here, KRIHIGP. Nyambi *et al.* [2000] (**subtype comparisons**)
- 419-D: Review of clade specificity and anti-V3 HIV-1-Abs – epitope is described as KRIHIGP. Zolla-Pazner *et al.* [1999a] (**antibody binding site definition and exposure**, **review**)
- 419-D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 1334, 419, 504, 447, 453 and 537 – the core amino acids GP tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 419-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – 419-D bound to 3/4 B clade virions, and to D clade MAL. Nyambi *et al.* [1998] (**subtype comparisons**)
- 419-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera

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and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D)and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)

- 419-D: Neutralizes MN – binds SF2: IYIGPGR. Gorny *et al.* [1993] (**variant cross-recognition or cross-neutralization**)
- 419-D: Mediated deposition of complement component C3 on HIV infected cells, enhanced by second Ab binding, rabbit anti-human IgG. Spear *et al.* [1993] (**complement**)
- 419-D: MN, NY5 and SF2 strain specific, does not cross-react with RF, CDC4, WM52 or HXB2. Karwowska *et al.* [1992b] (**variant cross-recognition or cross-neutralization**)

No. 544
MAb ID 453-D (453)
HXB2 Location gp160 (309–315)
Author Location gp120 (MN)
Epitope IHIGPGR
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Fontenot *et al.* 1995; VanCott *et al.* 1994; Gorny *et al.* 1993; Gorny *et al.* 1991
Keywords antibody binding site definition and exposure, binding affinity, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- 453-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**)
- 453-D: Called 453: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 453-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 453-D showed intermediate reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)
- 453-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a] (**review**, **subtype comparisons**)
- 453-D : MAb peptide-reactivity pattern clustered with immunological related MAbs: 1334, 419, 504, 447, 453 and 537 – the core amino acids GP tended to be critical for reactivity in this group – MAb 268, with a previously defined core epitope identical to 453 (HIGPGR), was not part of this reactivity group, illustrating that context can be critical. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 453-D : Called 453, epitope described as KRIHIGPGR – the tip of the V3 loop was presented in a mucin backbone – higher valency correlates with stronger affinity constant. Fontenot *et al.* [1995] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- 453-D: Moderate homologous neutralization, moderately slow dissociation rate. VanCott *et al.* [1994] (**binding affinity**)
- 453-D: Neutralizes MN – binds SF2: IYIGPGR – specificity: MN, SF2, NY5, RF. Gorny *et al.* [1993] (**antibody binding site definition and exposure**)

No. 545
MAb ID 504-D (504, 504-10D)
HXB2 Location gp160 (309–315)
Author Location gp120 (MN)
Epitope IHIGPGR
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Gorny *et al.* 1993
Keywords antibody binding site definition and exposure, review, subtype comparisons

- 504-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 504-D: Called 504: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 504-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to

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E, F, G, and H – 504-D showed weak reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)

- 504-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a] (**review**)
- 504-D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 1334, 419, 504, 447, 453 and 537 – the core amino acids GP tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 504-D – Neutralizes MN – binds SF2: IYIGPGR. Gorny *et al.* [1993] (**antibody binding site definition and exposure**)

No. 546
MAb ID 83.1 (MAb 83.1)
HXB2 Location gp160 (309–315)
Author Location gp120 (SF2)
Epitope IYIGPGR
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade MN *HIV component:* V3
Species (Isotype) mouse (IgG1)
Ab Type gp120 V3
Research Contact Mary White-Scharf, Repligen Corporation, Cambridge, MA
References Pantophlet *et al.* 2008; Sirois *et al.* 2007; Stanfield & Wilson 2005; Huang *et al.* 2005a; Binley *et al.* 1999; Keller & Arora 1999; Jelonek *et al.* 1999; Potts *et al.* 1993; White-Scharf *et al.* 1993
Keywords antibody binding site definition and exposure, review, structure

- 83.1: Angle of interaction between 83.1 and V3 was shown by superimposing the Fab fragment of the Ab with V3. Pantophlet *et al.* [2008] (**antibody binding site definition and exposure**, **structure**)
- 83.1: Data is summarized on the X-ray crystal structures resolution and NMR studies of 83.1. Sirois *et al.* [2007] (**review**, **structure**)
- 83.1: The crystal structure of V3-reactive antibody-peptide complexes were examined. 83.1 completely surrounded V3, suggesting a high degree of accessibility for generating an immune response. Accessibility of V3 to this MAb is shown in a 3D figure. Huang *et al.* [2005a] (**antibody binding site definition and exposure**, **structure**)
- 83.1: This review summarizes data on crystallographic structures of 83.1 binding to its V3 peptide antigens. Conformation of the V3 peptide bound to 83.1 is very similar to its conformation when bound to 447-52D. Stanfield & Wilson [2005] (**antibody binding site definition and exposure**, **review**, **structure**)
- 83.1: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999]
- 83.1: Maternally transferred anti-V3 loop MAb selectively inhibits the anti-V3 loop Ab component of the IgG response to rgp120 SF2 in 21 day old BALBc mice. Jelonek *et al.* [1999]
- 83.1: 19 day old mice injected with 83.1 have a shift in IgG1 response away from the V3 loop upon vaccination, without decreasing the total IgG anti-gp120 response, suggesting that prior treatment with a MAb can mask immunogenic sites and shift the immune response to vaccination. Keller & Arora [1999]
- 83.1: Study of synergism of neutralization and binding comparing F105 and sCD4 with the V3 MAbs: 50.1, 59.1, 83.1, and 58.2 – synergy was observed, and the data suggest that binding of one ligand (F105) can increase the binding of the second (e. g. V3 loop MAbs) due to conformational changes. Potts *et al.* [1993]
- 83.1: Neutralizes SF2. White-Scharf *et al.* [1993]

No. 547
MAb ID 5023B
HXB2 Location gp160 (309–316)
Author Location gp120 (309–316 BH10)
Epitope IQRGPGra
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade BH10 *HIV component:* V3
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
References Langedijk *et al.* 1991

- 5023B: Generation and fine mapping of murine MAbs. Langedijk *et al.* [1991]

No. 548
MAb ID F58/D1 (F58)
HXB2 Location gp160 (309–316)
Author Location gp120 (IIIB)
Epitope IxxGPGRA
Neutralizing L
Immunogen vaccine
Vector/Type: virus derived protein *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 V3
References Heap *et al.* 2005b; Jackson *et al.* 1999; Millar *et al.* 1998; Moore *et al.* 1993b; Levi *et al.* 1993; Broliden *et al.* 1991; Akerblom *et al.* 1990
Keywords antibody binding site definition and exposure, antibody sequence variable domain, structure

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- F58/D1: Called F58. A 17 amino acid peptide from the CDR-H3 region of F58 retained specificity for gp120 and could neutralize IIIB, although less efficiently than the intact antibody. The F58 MicroAb has a 3-fold faster association rate and a 37.5-fold more rapid dissociation rate than the intact antibody. Such Ab binding site fragments, that retain binding specificity, are called microantibodies. Alanine-substitutions in F58 MicroAb at three positions significantly compromised neutralization but did not reduce binding to soluble gp120, while substitutions at three other positions abrogated both binding and neutralization. The microAb forms a conformationally constrained beta sheet. Heap *et al.* [2005b] (**antibody binding site definition and exposure**, **antibody sequence variable domain**, **structure**)
- F58/D1: A 17 amino acid MicroAB was made from the third complementarity-determining region of the heavy chain of MAb – F58 neutralized 5x's more efficiently in terms of mass than the original MAb, 32-fold less on a molar basis – neutralization does not involve initial attachment, but fusion and events in early infection. Jackson *et al.* [1999]
- F58/D1: The interaction of a 17-amino-acid neutralizing microantibody (MicroAB) based on F58 and HIV-1 env was studied by electrospray ionization mass spectrometry. Millar *et al.* [1998]
- F58/D1: Called F58. The complementarity-determining region of F58 was used to create a miniantibody that could neutralize both HIV-1 IIIB and SF2 in vitro. Levi *et al.* [1993] (**antibody binding site definition and exposure**, **antibody sequence variable domain**)
- F58/D1: Binding to native gp120 1-3 fold greater than to denatured – 314G/W substitution abolishes binding, changes outside the loop have little effect. Moore *et al.* [1993b]

No. 549
MAb ID P1/D12
HXB2 Location gp160 (309–316)
Author Location gp120
Epitope IxxGPGRA
Neutralizing L
Immunogen vaccine
Vector/Type: virus derived protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
References Moore *et al.* 1993b; Akerblom *et al.* 1990

- P1/D12: Binding to native gp120 1-3 fold greater than to denatured – 314G/W substitution abolishes binding, changes outside the loop have little effect. Moore *et al.* [1993b]

No. 550
MAb ID P4/D10 (P4D10)
HXB2 Location gp160 (309–316)
Author Location gp120
Epitope IxxGPGRA
Neutralizing L
Immunogen vaccine
Vector/Type: virus derived protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 V3
References Schonning *et al.* 1999; Schonning *et al.* 1998; Jacobson 1998; Hinkula *et al.* 1994; Arendrup *et al.* 1993; Moore *et al.* 1993b; Marks *et al.* 1992; Broliden *et al.* 1991; Broliden *et al.* 1990; Akerblom *et al.* 1990

- P4/D10: Called P4D10 – the stoichiometry of MAb neutralization was tested and the data indicated that binding for neutralization was was incremental not all or none, i.e., each envelope oligomer binds a single MAb and each Env oligomer bound reduces the chances of infection – MAb BC1071 was used for virion quantification – P4D10 binds only to Env with a glycosylation site mutation at the base of the V3 loop A308T. Schonning *et al.* [1999]
- P4/D10: Review of passive immunotherapy, summarizing Hinkula *et al.* [1994] in relation to other studies Jacobson [1998]. Hinkula *et al.* [1994]; Jacobson [1998]
- P4/D10: Called P4D10 – In a study of the influence of the glycan at position 306 of the V3 loop on MAb recognition, anti-V3 MAbs were found to neutralize an HIV-BRU mutant virus that lacks the V3 loop glycan more efficiently than HIV-BRU – Ab binding site was suggested to be 314-323 of BRU. Schonning *et al.* [1998]
- P4/D10: Used for passive immunotherapy in four late-stage HIV-infected patients – the serum level of p24 did not decrease in any of these four – see also MAb F58/H3. Hinkula *et al.* [1994]
- P4/D10: Primary isolates from different time points from one individual were not susceptible to neutralization by P4/D10. Arendrup *et al.* [1993]
- P4/D10: Binding to native gp120 3 fold greater than to denatured – 314G/W substitution abolishes binding, changes outside the loop have little effect. Moore *et al.* [1993b]
- P4/D10: Variable domain sequenced and is identical to F58/H3. Marks *et al.* [1992]
- P4/D10: Neutralizing and ADCC activity. Broliden *et al.* [1990]

No. 551
MAb ID IIIB-13 V3 (1044-13 IIIB-V3-13 1727)
HXB2 Location gp160 (309–317)
Author Location gp120 (308–316 IIIB)
Epitope IQRGPGRAF
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB
Species (Isotype) mouse (IgG1)
Ab Type gp120 V3
References Holl *et al.* 2006a; Zhang *et al.* 2002; Chakrabarti *et al.* 2002; Watkins *et al.* 1993; D'Souza *et al.* 1994; Laman *et al.* 1993; Laman *et al.* 1992
Keywords dendritic cells, neutralization

- IIIB-13 V3: Also known as 1044-13 and as IIIB-V3-13 (J. P. Moore, per. comm.)
- IIIB-13 V3: UK Medical Research Council AIDS reagent: ARP3046.
- IIIB-13 V3: NIH AIDS Research and Reference Reagent Program: 1727.

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- IIIB-V3 13: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication occurs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- IIIB-13 V3: Called 1727: Used as a standard for comparing immune responses to modified gp140 (gp140deltaCFI), with C-term mutations intended to mimic a fusion intermediate and stabilize trimer formation – experiment showed enhanced humoral immunity without diminishing the CTL response in mice injected with a DNA vaccine. Chakrabarti *et al.* [2002]
- IIIB-13 V3: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002]
- IIIB-13 V3: Included in a panel of antibodies used in a multilab study for antibody characterization and assay comparison, some neutralization of strains other than IIIB. D'Souza *et al.* [1994]
- IIIB-13 V3: Called IIIB-V3-13 – a neutralization escape mutant (HXB2 A281V) was selected by growth of HXB2 in the presence of broadly neutralizing sera – IIIB-V3-13 neutralization was only slightly reduced by this mutation. Watkins *et al.* [1993]
- IIIB-13 V3: Neutralizes IIIB but not MN. Laman *et al.* [1992]

No. 552
MAb ID IIIB-34 V3 (IIIB-V3-34)
HXB2 Location gp160 (309–317)
Author Location gp120 (308–316 IIIB)
Epitope IQRGPGRAF
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB
Species (Isotype) mouse (IgG1)
Ab Type gp120 V3
References Laman *et al.* 1993; Laman *et al.* 1992

- IIIB-34 V3: UK Medical Research Council AIDS reagent: ARP3047.
- IIIB-34 V3: Called IIIB-V3-34 – IIIB strain specific neutralization – binding is reduced somewhat by DTT or SDS-DTT, enhanced by NP40, but binds to native and denatured gp120. Laman *et al.* [1993]
- IIIB-34 V3: Neutralizes IIIB but not MN – QXGPG are critical amino acids for binding by Pepscan analysis. Laman *et al.* [1992]

No. 553
MAb ID A47/B1
HXB2 Location gp160 (309–318)
Author Location gp120 (307–316 IIIB)
Epitope IQRGPGRAFV
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB
HIV component: gp120
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
References Akerblom *et al.* 1990

No. 554
MAb ID D59/A2
HXB2 Location gp160 (309–318)
Author Location gp120 (307–316 IIIB)
Epitope IQRGPGRAFV
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB
HIV component: gp120
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
References Akerblom *et al.* 1990

No. 555
MAb ID G44/H7
HXB2 Location gp160 (309–318)
Author Location gp120 (307–316 IIIB)
Epitope IQRGPGRAFV
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB
HIV component: gp120
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
References Akerblom *et al.* 1990

No. 556
MAb ID MO96/V3 (M096, M096/V3)
HXB2 Location gp160 (309–318)
Author Location gp120 (309–318)
Epitope IQRGPGRAFV+AHCNISRAKW
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgM)
Ab Type gp120 V3
References Gorny & Zolla-Pazner 2004; Ohlin *et al.* 1992
Keywords antibody binding site definition and exposure, antibody generation, review

- M093/V3: Review. provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains; a subset can also neutralize some primary isolates. The three IgMs, M096, M097, and M099, are non-neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
- M096/V3: Generated in response to IIIB Env 286-467 upon *in vitro* stimulation of uninfected-donor lymphocytes, and binds to two peptides: 309-318 + 329-338. Ohlin *et al.* [1992] (**antibody binding site definition and exposure**, **antibody generation**)

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MAb ID µ5.5 (5.5, µ5.5, Rµ5.5)
HXB2 Location gp160 (309–319)
Author Location gp120 (MN)
Epitope IHIGPGRAFYT
Neutralizing L P
Immunogen
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 V3
References Eda *et al.* 2006b; Matsushita *et al.* 2005; Okamoto *et al.* 1998; Maeda *et al.* 1992
Keywords antibody binding site definition and exposure, binding affinity, neutralization, variant cross-recognition or cross-neutralization

- µ5.5: This Ab was shown not to neutralize HIV-1 MNp in spite of the fact that HIV-1 MNp V3 tip sequence is identical to the V3 sequence of this Ab's epitope, suggesting that the neutralization epitope of HIV-1 MNp may be narrower than that of the V3 epitope of Rµ5.5. Rµ5.5 also did not neutralize HIV-1 AD8, SHIV 89.6 and SHIV C2/1. The affinity of this Ab was tested for HIV-1 MN. Eda *et al.* [2006b] (**neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**)
- Rµ5.5: This MAb was used as a positive control in KD-247 studies. HIV-1 plasma and PBMC clone sequences from two patients were used for prediction of the effect of KD-247 against patient's primary isolates. In patient 1 all clones matched epitope sequence recognized by KD-247 while 5 out of 7 plasma, and 2 out of 22 PBMC sequences matched the sequence recognized by Rµ5.5. In the second patient only a small portion of the quasi-species was recognized by Rµ5.5. Matsushita *et al.* [2005] (**antibody binding site definition and exposure**)
- µ5.5: Rµ5.5 is a humanized antibody of mouse MAb m5.5 – neutralized primary isolates with similar V3 loops – passive transfer of MAb to SCID-hu or hu-PBL-SCID mice conferred protection. Okamoto *et al.* [1998]
- mu5.5: sCD4 causes loss of IIIB type-specificity for MAb 0.5beta, allowing binding and neutralization of MN, in contrast to MAb µ5.5. Maeda *et al.* [1992]

No. 558
MAb ID µ5.5 (5.5, mu5.5, Rmu5.5)
HXB2 Location gp160 (309–319)
Author Location gp120 (MN)
Epitope IHIGPGRAFYT
Neutralizing L P
Immunogen
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 V3
References Okamoto *et al.* 1998; Maeda *et al.* 1992

- mu5.5: Rmu5.5 is a humanized antibody of mouse MAb m5.5 – neutralized primary isolates with similar V3 loops – passive transfer of MAb to SCID-hu or hu-PBL-SCID mice conferred protection. Okamoto *et al.* [1998]
- mu5.5: sCD4 causes loss of IIIB type-specificity for MAb 0.5beta, allowing binding and neutralization of MN, in contrast to MAb mu5.5. Maeda *et al.* [1992]

No. 559
MAb ID 19b
HXB2 Location gp160 (309–320)
Author Location gp120
Epitope -I----G--FY-T
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
Ab Type gp120 V3
Research Contact James Robinson, University of Connecticut, Storrs
References Patel *et al.* 2008; Pantophlet *et al.* 2008; Sheppard *et al.* 2007b; Kanduc *et al.* 2008; Kramer *et al.* 2007; Gao *et al.* 2007; Cham *et al.* 2006; Liao *et al.* 2006; Srivastava *et al.* 2005; Selvarajah *et al.* 2005; Mc Cann *et al.* 2005; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Poignard *et al.* 2003; Kwong *et al.* 2002; Zhang *et al.* 2002; Schulke *et al.* 2002; Kolchinsky *et al.* 2001; Park *et al.* 2000; Binley *et al.* 1999; Trkola *et al.* 1998; Parren *et al.* 1998a; Mondor *et al.* 1998; Parren *et al.* 1997b; Boots *et al.* 1997; Ugolini *et al.* 1997; Fouts *et al.* 1997; Binley *et al.* 1997a; D'Souza *et al.* 1997; Trkola *et al.* 1996a; Wu *et al.* 1996; Gauduin *et al.* 1996; Sattentau *et al.* 1995; Moore & Ho 1995; Moore *et al.* 1995a; Moore *et al.* 1995b; Sattentau 1995; Moore *et al.* 1994a; Moore *et al.* 1994b; Scott *et al.* 1990
Keywords antibody binding site definition and exposure, antibody interactions, binding affinity, neutralization, review, structure, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- 19b: Similarity level of the 19b binding site pentapeptide -I—-G–FY-T to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 4 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 19b: 19b neutralized two of the 15 subtype B isolates tested, 5768-p27 and 92BR020c. Binding affinity of MAb 19b to gp120 was strongly reduced (>10-fold) upon substitutions of Arg304, Ile307, Pro313, Arg315, Phe317, or Tyr318 to Ala. The affinity was moderately reduced (∼4-fold) upon substitution of Lys305. Thr320 was not important for 19b binding. Substituting Asp325 with Ala increased the binding affinity of 19b by 2-fold, suggesting that Ala at this position prevents formation of a salt bridge thus allowing for a better presentation of 19b epitope. 19b neutralized 5768-p27 more potently than 92BR020c although the viruses have same V3 residues important for 19b binding. 5768-p27 has a Met at position 309 and 92BR020c has Ile, indicating that 19b requires an aliphatic side chain at position 309. The inability of 19b to neutralize 6 of the 15 viruses tested could be explained by substitutions at important contact residues, while its inability to neutralize the remaining 6 viruses could not be explained by this. The fine specificity of 19b was mapped onto V3 in the structural

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context of gp120. Binding site was formed by Arg304 in the N-terminal V3 stem, and Arg315, Phe317, and Tyr318 were in the C-terminal half of the V3 tip. The presence of Pro313 and Arg315 is required to form the V3 tip hairpin turn and juxtapose the true contact residues. Thus, 19b may need to interact with V3 from an angle, which does not permit access to V3 on many different primary viruses. Pantophlet *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **structure**)

- 19b: To examine sequence and conformational differences between subtypes B and C, several experiments were preformed with 11 MAbs regarding binding and neutralization. Both binding and neutralization studies revealed that the 11 MAbs could be divided in three different groups, and that the most differences between the subtypes were located in the stem and turn regions of V3. 19b belonged to the group 1 MAbs, which are able to bind both subtype B and C gp120 proteins and peptides. 19b bound to B gp120 and C gp120 with low avidity. Furthermore, 19b was able to bind both subtype C V3 in the subtype B Env backbone chimera, and reverse, indicating that 19b binds to V3 in a way that is not affected by the gp120 backbone. For subtype B, changes in the position 13 (H13R) and/or position 18 (R18Q) showed no difference of 19b binding compared to wildtype. For subtype C, H13 residue enhanced binding of 19b, but the R18 mutation reduced binding, indicating that R18 affects the conformation of V3 subtype C. Although 19b bound to JR-FL V3, this isolate was resistant to neutralization by 19b, as was SF162. However, a chimeric SF162 variant with a JR-FL-like V3 sequence was hypersensitive to neutralization by 19b, suggesting an important role of one or more of the three V3 amino acids that differ between these two isolates in defining the epitope and/or structure of the protein. Patel *et al.* [2008] (**neutralization**, **binding affinity**, **subtype comparisons**)
- 19b: This review summarizes data on the development of HIV-1 centralized genes (consensus and ancestral) for induction of neutralizing antibody responses. Functionality and conformation of native epitopes in proteins based on the centralized genes was tested and confirmed by binding to 19b and other MAbs. Gao *et al.* [2007] (**antibody binding site definition and exposure**, **review**)
- 19b: This review summarizes 19b Ab epitope, properties and neutralization activity. Kramer *et al.* [2007] (**review**)
- 19b: This Ab was used in the analysis of clade C gp140 (97CN54) antigenicity and was shown to bind with relatively high avidity. Sheppard *et al.* [2007b] (**variant cross-recognition or cross-neutralization**)
- 19b: This Ab was shown to infrequently neutralize cloned Envs (clades A, B, C, D, F1, CRF01_AE, CRF02_AG, CRF06_cpx and CRF11_cpx) derived from donors with and without broadly cross-reactive neutralizing antibodies. Cham *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 19b: The gp140δCFI protein of CON-S M group consensus protein and gp140CFI and gp140CF proteins of CON6 and WT viruses from HIV-1 subtypes A, B and C were expressed in recombinant vaccinia viruses and tested as immunogens in guinea pigs. 19b was shown to bind specifically to all the recombinant proteins as well as to the gp120 from two subtype B isolates. The specific binding of his Ab to CON-S indicated that its conformational epitope was intact. Liao *et al.* [2006] (**antibody binding site definition and exposure**, **vaccine antigen design**, **subtype comparisons**)
- 19b: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **review**)
- 19b: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. V3 MAbs (447-52D, 19b, F245-B4e8 and 39F) bound to the GDMR antigen, but either did not bind or had diminished binding to mCHO. Selvarajah *et al.* [2005] (**vaccine antigen design**, **vaccine-specific epitope characteristics**)
- 19b: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**neutralization**, **variant cross-recognition or cross-neutralization**, **review**, **subtype comparisons**)
- 19b: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 19b: This paper attempts to engineer a gp120 molecule that would focus the immune response onto the IgG1b12 epitope. Adding a glycosylation sequon (P313N) to the V3 loop knocked out binding to anti-V3 MAbs loop 2, 19b and 447-52-D. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- 19b: Virion capture assays are not a good predictor of neutralization, and the presentation of epitopes using this assay seems to be different from that of functional Envelope spikes on primary isolates – F105 and b6 could efficiently block the b12-mediated capture of infectious virions in a virus capture, but did not inhibit b12 neutralization – while b12 was potent at neutralizing the three primary virions JR-CSF, A DA, and 89.6, the Abs F105, 19b, and Fab b6 were overall very poor neutralizers. Poignard *et al.* [2003]
- 19b: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4)

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region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the V3 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)

- 19b: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-2999) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- 19b: Ab binding characteristics of SOS gp140 were tested using SPR and RIPA – SOS gp140 is gp120-gp41 bound by a disulfide bond – NAbs 2G12, 2F5, IgG1b12, CD4 inducible 17b, and 19b bound to SOS gp140 better than uncleaved gp140 (gp140unc) and gp120 – non-neutralizing MAbs 2.2B (binds to gp41 in gp140unc) and 23A (binds gp120) did not bind SOS gp140. Schulke *et al.* [2002]
- 19b: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002]
- 19b: Mutations in two glycosylation sites in the V2 region of HIV-1 ADA at positions 190 and 197 (187 DNTSYRLINCNTS 199) cause the virus to become CD4-independent and able to enter cells through CCR5 alone – these same mutations tended to increase the neutralization sensitivity of the virus, including to 19b. Kolchinsky *et al.* [2001]
- 19b: Six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form but 19b was an exception and required around 950 ng/ml to neutralize either form. Park *et al.* [2000]
- 19b: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999]
- 19b: Used as a control in this Hx10 binding and neutralizing MAb study because 19b does not bind to Hx10. Mondor *et al.* [1998]
- 19b: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- 19b: No detectable neutralizing activity among primary isolates with different co-receptor usage – some neutralization of TCLA strains. Trkola *et al.* [1998]
- 19b: Abs that recognize discontinuous epitopes can identify mimotopes from a phage peptide display library – 19b has an epitope involving the tip of the V3 loop, with 5 or 6 essential amino acids distributed within a 12 amino acid stretch – the previously determined binding site was confirmed -I—-G–FY-T and some tolerated variants described, the I can be I, V, or L, the Y can be Y, F, or W – probably a beta-turn is required for FY or FF binding, but WY in can bind with out the context of the turn. Boots *et al.* [1997]
- 19b: In a multilaboratory blinded study, failed to consistently neutralize any of nine B clade primary isolates – there were four sequences with variations in the defined epitope among the 9 isolates tested. D'Souza *et al.* [1997]
- 19b: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – 19b bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997]
- 19b: Neutralizes TCLA strains but not primary isolates. Parren *et al.* [1997b]
- 19b: Viral binding inhibition by 19b was weakly correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5) Ugolini *et al.* [1997]
- 19b: Not as effective as IgG1b12 at neutralization *ex vivo* of virus direct from plasma of HIV-1 infected individuals. Gauduin *et al.* [1996]

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- 19b: Inhibits gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]
- 19b: MIP-1alpha binding to CCR-5 expressing cells can be inhibited by gp120-sCD4 – binding of 19b blocks this inhibition. Wu *et al.* [1996]
- 19b: Binds to some gp120s from clades A,B,C,E, and F – weakly neutralized some B and one C clade virus. Moore *et al.* [1995b]
- 19b: Despite broad gp120 binding reactivity, not broadly neutralizing. Moore *et al.* [1995a]
- 19b: Review: more broadly cross-reactive than anti-V3 tip MAb 447-D. Moore & Ho [1995]
- 19b: Formalin inactivation of virus at 0.1% formalin for 10 hours at 4 degrees was optimal for inactivation of virus while maintaining epitope integrity. Sattentau *et al.* [1995]
- 19b: V3 loop binding MAb that is more broadly clade cross-reactive than most (binds to 19/29 clade B and 10/12 clade E gp120s) Moore *et al.* [1994b]
- 19b: Competition studies with human sera from seroconverting individuals showed that anti-CD4 BS antibodies can arise very early in infection, comparable or prior to anti-V3 antibodies. Moore *et al.* [1994a]

No. 560
MAb ID 268-D (268-11-D-IV, 268D, 268, 268-11D, 268-10D, MAb 268, 268-10-D, ARP)
HXB2 Location gp160 (310–315)
Author Location gp120 (MN)
Epitope HIGPGR
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Patel *et al.* 2008; Holl *et al.* 2006a; Lusso *et al.* 2005; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Zhang *et al.* 2002; Vella *et al.* 2002; York *et al.* 2001; Park *et al.* 2000; Nyambi *et al.* 2000; Hioe *et al.* 2000; Laisney & Strosberg 1999; Oggioni *et al.* 1999; Beddows *et al.* 1999; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; LaCasse *et al.* 1998; Stamatatos *et al.* 1997; Hioe *et al.* 1997b; Wisnewski *et al.* 1996; McKeating *et al.* 1996; Fontenot *et al.* 1995; Zolla-Pazner *et al.* 1995; Stamatatos & Cheng-Mayer 1995; VanCott *et al.* 1994; Spear *et al.* 1993; Gorny *et al.* 1993; Karwowska *et al.* 1992b; D'Souza *et al.* 1991; Gorny *et al.* 1991
Keywords antibody binding site definition and exposure, binding affinity, dendritic cells, neutralization, review, subtype comparisons

- 268-D: UK Medical Research Council AIDS reagent: ARP3024.
- 268-D: NIH AIDS Research and Reference Reagent Program: 1511.
- 268-DI V: To examine sequence and conformational differences between subtypes B and C, several experiments were preformed with 11 MAbs regarding binding and neutralization. Both binding and neutralization studies revealed that the 11 MAbs could be divided in three different groups, and that the most differences between the subtypes were located in the stem and turn regions of V3. 268-DI V belonged to the group 3 MAbs, which are able to bind subtype B but not subtype C gp120 and V3 peptide. 268-DI V was able to bind subtype B V3 in the subtype C Env backbone chimera, but not the reverse, indicating that 268-DI V binds to a structure created by the subtype B V3 sequence that is not impacted by the gp120 backbone. For both subtypes B and C, 268-DI V required H13 and R18 residues in order to bind, indicating that these residues likely define key aspects of the Ab epitope. 268-DI V was not able to neutralize JR-FL or SF162 isolates, but a chimeric SF162 variant with a JR-FL-like V3 sequence was hypersensitive to neutralization by this Ab. Patel *et al.* [2008] (**neutralization**, **binding affinity**, **subtype comparisons**)
- 268-D IV: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication occurs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 268-D: The epitope for the MAb D19 is conserved and embedded in V3. D19 is unique in that for R5 viruses, it was cryptic and did not bind without exposure to sCD4, and for X4 and R5X4 isolates it was constitutively exposed. It had an overlapping binding region with MAbs 447-52D, B4e8, and 268-D, but different reactivity patterns and fine specificity. Lusso *et al.* [2005]
- 268-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, while many neutralize some TCLA strains, a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 268-D: Called 268: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4 induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides do not show as much ability to neutralize as V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. 268 was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 268-D: Called ARP3024: Herpesvirus saimiri-immortalized CD4+ T lymphocytes (HVS T cells) were used to isolate virus and perform HIV-1 neutralization assays, and compared with a standard PBMC protocol – neutralization sensitivities to a panel of MAbs and to homologous or heterologous plasma/sera were similar for HVS T cells (CN-2 cells) and PBMCs. Vella *et al.* [2002]
- 268-D: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera—2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5—thus multiple epi-

topes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002]

- 268-D: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAbs alters some step after binding – one of the TCLA V3 viruses 320SI-C3.3 shows reduced binding with this MAb, the sequence of the epitope in 320SI is HIGPGR and in 320SI-C3.3 is RIGPGR. York *et al.* [2001]
- 268-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – CD4BS MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – V3 MAbs 447-52-D and 268-10-D did not effect proliferation. Hioe *et al.* [2000]
- 268-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 268-D showed weak reactivity. Nyambi *et al.* [2000]
- 268-D: Called 268D – six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000]
- 268-D: rgp120 derived from a R5X4 subtype B virus, HIV-1 W61D, was used to vaccinate healthy volunteers and the resulting sera were compared with sera from HIV-1 positive subjects and neutralizing MAbs – 268-D bound rgp120 W61D but could only neutralize the W61D isolate following T-cell line adaptation. Beddows *et al.* [1999]
- 268-D: Called MAb 268 – To identify potential mimotopes of V3, a hexapeptide phage library was screened with MAb 268 – two hexamers were identified, HLGPGR or KAIHRI that bind to 268 with the same binding site as the V3 loop and inhibit 268 MN gp120 – KLH conjugated hexamer KAIHRI stimulates Abs in rabbits that cross-react with ML gp120. Laisney & Strosberg [1999]
- 268-D: Called 268-11D – Study of a live-vector mucosal vaccine that expresses HIV-1 V3 domains using the bacterium Streptococcus gordonii which can express heterologous Ag and can colonize the oral cavity and vagina of mice – 268-D and 257-D recognized S. gordonii expressing the V3 domain of MN – the vaccine stimulated V3-specific IgG2a in mice. Oggioni *et al.* [1999]
- 268-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a]
- 268-D: Peptide reactivity pattern clustered with immunological related MAbs: 1108, 386, 268, 311, 257, 694.8 – the amino acids HI tended to be critical for reactivity in this group – MAb 453, with an identical core epitope to 268 based on prior experiments (HIGPGR), was not part of this reactivity group, illustrating that context can be critical. Zolla-Pazner *et al.* [1999b]
- 268-D: A T-cell line-adapted (TCLA) derivative of SI primary isolate 168P acquired the ability to be neutralized by anti-V3 MAbs – the primary isolate could use either CCR5 or CXCR4, and was not neutralized when infection was directed via either pathway, however the TCLA derivative uses CXCR4 only and is neutralized. LaCasse *et al.* [1998]
- 268-D: Poor reactivity against HIV-1 isolates SF162 and SF128A and no neutralization, in contrast to MAbs 391/95-D and 257-D. Stamatatos *et al.* [1997]
- 268-D: Failed to neutralize HXB2 and chimeric virus with gp120 from primary isolates in an HXB2 background. McKeating *et al.* [1996]
- 268-D: 268-D is V H4 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996]
- 268-D: The binding of conformation-dependent anti-V2, anti-V3, and anti-CD4BS MAbs to monomeric and virion-associated gp120 from HIV-1 isolates with differences in cell tropism was studied – V3 loop epitopes were less accessible to Ab binding on the virion surface than in the gp120 monomer, particularly for macrophage-tropic isolates SF162 and SF128a, relative to T-cell tropic SF2 – sCD4 association with gp120 did not influence the binding of 268-D to virion-associated gp120, although sCD4 binding did alter epitope exposure for other anti-V3 MAbs. Stamatatos & Cheng-Mayer [1995]
- 268-D: Serotyping study using flow-cytometry, if H of HIGPGR was substituted in virus, 268-D did not bind. Zolla-Pazner *et al.* [1995]
- 268-D: Moderate dissociation rate and homologous neutralization titer. VanCott *et al.* [1994]
- 268-D: Neutralizes MN – binds SF2: YIGPGR – specificity: MN, SF2, NY5, RF, CDC4. Gorny *et al.* [1993]
- 268-D: Mediated deposition of complement component C3 on HIV infected cells, but not in the presence of sCD4. Spear *et al.* [1993]
- 268-D: Reacts with MN, NY5, CDC4, RF and SF2, does not cross-react with WM52 or HXB2. Karwowska *et al.* [1992b]
- 268-D: Called 268-11-D-IV – strain specific weakly neutralizing. D'Souza *et al.* [1991]

No.	561
MAb ID	386-D (386, 386-10D, 386D)
HXB2 Location	gp160 (310–315)
Author Location	gp120 (MN)
Epitope	HIGPGR
Subtype	B
Neutralizing	L
Immunogen	HIV-1 infection
Species (Isotype)	human (IgG1λ)
Ab Type	gp120 V3

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Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Fontenot *et al.* 1995; VanCott *et al.* 1994; Gorny *et al.* 1993; Karwowska *et al.* 1992b
Keywords antibody binding site definition and exposure, binding affinity, isotype switch, review, subtype comparisons

- 386-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 386-D: Called 386: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides do not show as much ability to neutralize as V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. 386 was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 386-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 386-D showed intermediate reactivity. Nyambi *et al.* [2000] (**isotype switch**, **subtype comparisons**)
- 386-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a] (**review**, **subtype comparisons**)
- 386-D: Peptide reactivity pattern clustered with immunological related MAbs: 1108, 386, 268, 311, 257, 694.8 – the amino acids HI tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 386-D: Slow dissociation rate, potent homologous neutralization. VanCott *et al.* [1994] (**binding affinity**)
- 386-D: Neutralizes MN – binds SF2: YIGPGR – specificity: MN, SF2, NY5, RF, CDC4. Gorny *et al.* [1993] (**antibody binding site definition and exposure**)

No. 562
MAb ID 5042A
HXB2 Location gp160 (310–315)
Author Location gp120 (310–315 BH10)
Epitope `QrGPGR`
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade BH10 *HIV component:* V3
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
References Gorny *et al.* 1991; Langedijk *et al.* 1991

- 5042A: Generation and fine mapping of murine MAbs. Langedijk *et al.* [1991]

No. 563
MAb ID 5042B
HXB2 Location gp160 (310–315)
Author Location gp120 (310–315 BH10)
Epitope `QRGPGr`
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade BH10 *HIV component:* V3
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
References Langedijk *et al.* 1991

- 5042B: Generation and fine mapping of murine MAbs. Langedijk *et al.* [1991]

No. 564
MAb ID 418-D (418, 418D)
HXB2 Location gp160 (310–316)
Author Location gp120 (MN)
Epitope `HIGPGRA`
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Zhang *et al.* 2002; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Gorny *et al.* 1993; Karwowska *et al.* 1992b
Keywords antibody binding site definition and exposure, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 418-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 418-D: Called 418: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. 418 was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 418-D: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002]

B Cell

- 418-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 418-D showed intermediate reactivity. Nyambi *et al.* [2000] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 418-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a] (**review**, **subtype comparisons**)
- 418-D: Called 418 – MAb peptide-reactivity pattern clustered with immunological related MAbs: 391.5, 412 and 418, all selected with MN V3 peptide – the core amino acids HIGPGR tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 418-D: Neutralizes MN, does not bind to SF2 or HXB2. Gorny *et al.* [1993] (**variant cross-recognition or cross-neutralization**)
- 418-D: MN strain specific, does not cross-react with SF2, NY5, RF, CDC4 WM52 or HXB2. Karwowska *et al.* [1992b] (**variant cross-recognition or cross-neutralization**)

No. 565
MAb ID 5021
HXB2 Location gp160 (310–316)
Author Location gp120
Epitope QrGPGRa
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade BH10 *HIV component:* V3
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
References Moore *et al.* 1993b; Langedijk *et al.* 1991; Durda *et al.* 1990; Durda *et al.* 1988

- 5021: Binding to native gp120 100-300 fold greater than to denatured – 314G/W substitution abolishes binding, changes outside the loop have little effect. Moore *et al.* [1993b]
- 5021: Generation and fine mapping of murine MAbs. Langedijk *et al.* [1991]

No. 566
MAb ID 5025B
HXB2 Location gp160 (310–316)
Author Location gp120 (310–316 BH10)
Epitope QRGPGra
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade BH10 *HIV component:* V3
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
References Langedijk *et al.* 1991

- 5025B: Generation and fine mapping of murine MAbs. Langedijk *et al.* [1991]

No. 567
MAb ID 5042
HXB2 Location gp160 (310–316)
Author Location gp120
Epitope QRGPGRA
Neutralizing L
Immunogen vaccine
Vector/Type: peptide
Species (Isotype) mouse
Ab Type gp120 V3
References Moore *et al.* 1993b; Durda *et al.* 1990; Durda *et al.* 1988

- 5042: Binding to native gp120 100-300 fold greater than to denatured – 314G/W substitution abolishes binding, changes outside the loop have little effect. Moore *et al.* [1993b]

No. 568
MAb ID 110.3
HXB2 Location gp160 (310–317)
Author Location gp120 (308–328 BRU)
Epitope QRGPGRAF
Neutralizing L
Immunogen vaccine
Vector/Type: HIV infected-cell lysate *Strain:* B clade BRU *HIV component:* HIV-1
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 V3
References Connelly *et al.* 1994; Pirofski *et al.* 1993; Langedijk *et al.* 1992; Evans *et al.* 1989; Thomas *et al.* 1988

- 110.3: An anti-idiotypic MAb generated against 110.3 both mimics and binds to V3, suggesting that the V3 loop may associated with itself. Connelly *et al.* [1994]
- 110.3: MAb variable region sequenced – heavy chain: V 7138(40), D deletion, J H4 – light chain: V kappa21(47), J kappa2. Pirofski *et al.* [1993]
- 110.3: Included as a control. Evans *et al.* [1989]

No. 569
MAb ID 110.4
HXB2 Location gp160 (310–317)
Author Location gp120 (308–328 BRU)
Epitope QRGPGRAF
Neutralizing L
Immunogen vaccine
Vector/Type: HIV infected-cell lysate *Strain:* B clade BRU *HIV component:* HIV-1
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 V3
Research Contact Genetic Systems Corp, Seattle WA, E. Kinney-Thomas
References Guillerm *et al.* 1998; Cao *et al.* 1997b; Valenzuela *et al.* 1998; McDougal *et al.* 1996; Connelly *et al.* 1994; Boudet *et al.* 1994; Thali *et al.* 1994; Arendrup *et al.* 1993; Pirofski *et al.* 1993; Thali *et al.* 1993; Langedijk *et al.* 1992; Thali *et al.* 1992b; Callahan *et al.* 1991; Thomas *et al.* 1988
Keywords anti-idiotype, antibody binding site definition and exposure, antibody sequence variable domain, escape

B Cell

- 110.4: Used for flow cytometry in a study of the anti-CD4, CDR3 loop MAb called 13B8.2, in a study of HIV-1 induced programmed cell death. Guillerm *et al.* [1998]
- 110.4: Neutralization of LAI in CEM cells by anti-V3 MAbs 110.4 and N11-20 is through inhibition of viral binding to the cell. Valenzuela *et al.* [1998]
- 110.4: Virus with the V1-V2 loop deleted was viable and more susceptible to neutralization by CD4i MAb 17b, and anti-V3 MAbs 1121, 9284, and 110.4, but not to and CD4BS MAb F105 or sCD4. Cao *et al.* [1997b] (**antibody binding site definition and exposure**)
- 110.4: Neutralizes HIV-1 LAI. McDougal *et al.* [1996]
- 110.4: An anti-idiotypic MAb generated against 110.3 also blocks binding of 110.4. Connelly *et al.* [1994] (**anti-idiotype**)
- 110.4: gp41 mutation that confers resistance to neutralization by anti-CD4 binding site antibodies does not reduce neutralizing efficiency of this V3 region MAb. Thali *et al.* [1994] (**antibody binding site definition and exposure**)
- 110.4: Primary isolates from different time points from one individual were not susceptible to neutralization by 110.4. Arendrup *et al.* [1993]
- 110.4: MAb variable region sequenced – heavy chain: V 3660-SB32, D closest to DSP2.3, 2.4 and .6, J H2 – light chain: V kappa21, J kappa2. Pirofski *et al.* [1993] (**antibody sequence variable domain**)
- 110.4: 313 P/S substitution in the V3 region disrupts binding. Thali *et al.* [1992b] (**antibody binding site definition and exposure**, **escape**)
- 110.4: Polyanionic polysaccharides were proposed to inhibit viral functions such as binding and syncytia formation through interations mediated through the local high positive charge density in the V3 loop. The binding of this anti-V3 antibody is inhibited by dextransulfate. Callahan *et al.* [1991]

No. 570
MAb ID 110.5
HXB2 Location gp160 (310–317)
Author Location gp120 (308–328 BRU)
Epitope QRGPGRAF
Neutralizing L
Immunogen vaccine
Vector/Type: HIV infected-cell lysate *Strain:* B clade BRU *HIV component:* HIV-1
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 V3
Research Contact E. Kinney-Thomas or Genetic Systems, Seattle WA
References Parren *et al.* 1998a; Ugolini *et al.* 1997; Binley *et al.* 1997a; Jeffs *et al.* 1996; McDougal *et al.* 1996; Poignard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; Sattentau *et al.* 1995; Klasse *et al.* 1993a; Thali *et al.* 1993; Moore *et al.* 1993b; Pirofski *et al.* 1993; McKeating *et al.* 1992a; Langedijk *et al.* 1992; Sattentau & Moore 1991; Cordell *et al.* 1991; Moore *et al.* 1990; Thomas *et al.* 1988; Reitz *et al.* 1988

- 110.5: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- 110.5: Viral binding inhibition by 110.5 was correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5) Ugolini *et al.* [1997]
- 110.5: Deletion of the V1V2 regions did not affect anti-V3 Abs ability to bind when compared to intact rec gp120. Jeffs *et al.* [1996]
- 110.5: Neutralizes HIV-1 LAI. McDougal *et al.* [1996]
- 110.5: Reciprocal binding inhibition with other anti-V3 MAbs – enhances binding of some anti-V2 MAbs – binding enhanced by some CD4 binding site MAbs. Moore & Sodroski [1996]
- 110.5: Did not induce dissociation of gp120, as sCD4 did – discrepancy with Poignard *et al.* [1996a], that was suggested to be due to MAb interference with detection, as the gp120-MAb complex was denatured in the Poignard study Moore *et al.* [1990]. Moore *et al.* [1990]; Poignard *et al.* [1996a]
- 110.5: V3 MAbs 9284, BAT123, 110.5, and 110.I could each significantly increase gp120 dissociation from virus, mimicking sCD4, and expose the gp41 epitope for MAb 50-69, in contrast to anti-V2 MAbs. Poignard *et al.* [1996a]
- 110.5: Pretreatment of HX10-infected H9 cells with sCD4 decreases signal from 110.5 at 37 degrees due to dissociation of gp120-gp41. Sattentau *et al.* [1995]
- 110.5: Binds with high affinity to monomer and oligomer, rapid association and potent neutralization of lab strains – neutralizes cell-free Hx10. Sattentau & Moore [1995]
- 110.5: The gp41 mutation 582(Ala to Thr) results in conformational changes in gp120 that confer neutralization resistance to conformationally sensitive neutralizing MAbs – neutralization efficiency of 110.5 is not affected. Klasse *et al.* [1993a]; Reitz *et al.* [1988]
- 110.5: Thrombin cleavage of V3 loop between R-315 and A-316 abrogates binding – can inhibit C4 region antibody which has conformational requirements (G3-299) – binding to native gp120 100-300 fold greater than to denatured. Moore *et al.* [1993b]
- 110.5: Variable region sequenced – heavy chain: V 3660-SB32, D closest to DSP2.3, 2.4 and .6, J H2 – light chain: V kappa21, J kappa2. Pirofski *et al.* [1993]
- 110.5: Binding insensitive to gp120 reduction. Cordell *et al.* [1991]
- 110.5: Two fold increase in binding to gp120 in the presence of bound sCD4. Sattentau & Moore [1991]

No. 571
MAb ID 58.2
HXB2 Location gp160 (310–317)
Author Location gp120 (MN)
Epitope HIGPGRAF
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade MN *HIV component:* V3
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 V3

B Cell

Research Contact Repligen Corp.
References Pantophlet *et al.* 2008; Sirois *et al.* 2007; Stanfield & Wilson 2005; Huang *et al.* 2005a; Binley *et al.* 2004; York *et al.* 2001; Stanfield *et al.* 1999; Seligman *et al.* 1996; Moore *et al.* 1994b; Potts *et al.* 1993; White-Scharf *et al.* 1993
Keywords antibody binding site definition and exposure, neutralization, review, structure, subtype comparisons, variant cross-recognition or cross-neutralization

- 58.2: 58.2 neutralized 5 of the 15 subtype B isolates tested, of which 4 were resistant to neutralization by MAbs 19b, 39F, CO11, F2A3, F530, LA21 and LE311. Angle of interaction between 58.2 and V3 was shown by superimposing the Fab fragment of the Ab with V3. 58.2 was shown to interact with V3 from a nearly identical angle as MAb 447D. Pantophlet *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**, **structure**)
- 58.2: Data is summarized on the X-ray crystal structures resolution and NMR studies of 58.2. Sirois *et al.* [2007] (**review**, **structure**)
- 58.2: The crystal structure of V3-reactive antibody-peptide complexes were examined. 58.2 completely surrounded V3, suggesting a high degree of accessibility for generating an immune response. Accessibility of V3 to this MAb is shown in a 3D figure. Huang *et al.* [2005a] (**antibody binding site definition and exposure**, **structure**)
- 58.2: This review summarizes data on crystallographic structures of 58.2 binding to its V3 peptide antigens. Stanfield & Wilson [2005] (**antibody binding site definition and exposure**, **review**, **structure**)
- 58.2: 93 viruses from different clades were tested for their neutralization cross-reactivity using a panel of HIV antibodies. 58.2 could only neutralize B subtype viruses, and seemed to have a minimal epitope of (H/T)IGPGR(A/T)(F/L). Binley *et al.* [2004] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 58.2: 58.2's epitope was noted to be IGPGRAF – Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAbs alters some step after binding. York *et al.* [2001]
- 58.2: The crystal structure of Fab 58.2 bound to V3 loop peptides was obtained – conformational changes in the tip of the V3 loop (GPGR) were observed when different MAbs were bound – 58.2's epitope was defined as KRKRIHIGPGRAFY. Stanfield *et al.* [1999]
- 58.2: Competition ELISAs with serial deletions produced longer estimates of epitope length, RIHIGPGRAFY, than Alanine substitution, suggesting significance of non-contact residues. Seligman *et al.* [1996]
- 58.2: Modest cross-reactivity among B clade gp120s, little outside B clade – core epitope as I-IHIG. Moore *et al.* [1994b]
- 58.2: Did not synergistically neutralize MN in combination with MAb F105 – there was synergistic neutralization when combined with sCD4. Potts *et al.* [1993]
- 58.2: Epitope defined by peptide reactivity and changes in affinity with amino acid substitutions – 4/7 primarily isolates were neutralized. White-Scharf *et al.* [1993]

No. 572
MAb ID polyclonal
HXB2 Location gp160 (310–318)
Author Location gp120
Epitope QRGPGRAFV?
Neutralizing L
Immunogen vaccine
Vector/Type: peptide keyhole limpet hemocyanin (KLH) conjugate, peptide Brucella abortus (Ba) conjugate, peptide lipopolysaccharide (LPS) conjugate *Strain:* B clade MN *HIV component:* V3
Species (Isotype) mouse (IgA, IgG1, IgG2a)
References Golding *et al.* 2002a

- Internasal (i.n.) immunization with V3-Ba induced mucosal anti-V3 NAbs and IFN-gamma secreting T cells – V3-Ba, V3-KLH and V3-LPS could each induce serum and mucosal IgA and IgG in BALB/c mice – i.n. plus i.p. immunizations gave higher titers than i.n. alone – the response to V3-KLH was mainly restricted to IgG1, and to V3-Ba, IgG2a – class II KO mice (CD4+-deficient) did not respond to V3-KLH, but did respond to V3-Ba, suggesting that V3-Ba may be effective in eliciting Ab responses in HIV-1 infected individuals that have impaired CD4+ T cell function. Golding *et al.* [2002a]

No. 573
MAb ID KD-247
HXB2 Location gp160 (311–315)
Author Location (MOKW)
Epitope IGPGR
Subtype B
Neutralizing P
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade, B clade MN, B clade RF, Other *HIV component:* V3 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) humanized mouse (IgG)
Ab Type gp120 V3
Research Contact Shuzo Matsushita, Kumamoto University, Japan shuzo@kaiju.medic.kumamoto-u.ac.jp
References Yoshimura *et al.* 2006; Shibata *et al.* 2007; Eda *et al.* 2006b; Eda *et al.* 2006a; Matsushita *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, binding affinity, escape, immunoprophylaxis, neutralization, optimal epitope, variant cross-recognition or cross-neutralization

B Cell

- KD-247: Escape variants were induced by exposing the HIV-1 strain MOKW to different concentrations of KD-247 in vitro. In the presence of relatively low concentrations of the Ab, viral variants with V2 mutations R166K and D167N were found with partial resistance against KD-247. In the presence of high concentrations of KD-247, in addition to the V2 mutations, a V3 tip mutation (P313L) induced complete resistance to KD-247. V2 P175L substitution conferred high resistance to KD-247, however, additional KN susbstitutions in positions 166 and 167 resulted in a less resistant virus with a replication advantage. Shibata *et al.* [2007] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **escape**, **binding affinity**)
- KD-247: A new humanize MAb recognizing the V3 tip sequence was generated by transferring the genes of the complementary determining region of the mouse NAb C25 into genes of a human V region. C25 was raised by serial vaccinations of a mouse with distinctive six B clade V3 loop peptides. KD-247 was shown to neutralize laboratory and primary isolates of CXCR4 and CCR5 viruses that possess a GPGR sequence in the Env V3 tip region more effectively than any of the reference Abs used in the study. KD-247 was shown to recognize the narrow V3 tip sequence with high affinity. Eda *et al.* [2006b] (**antibody binding site definition and exposure**, **antibody generation**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **antibody sequence variable domain**)
- KD-247: This Ab was shown to efficiently neutralize clade B and B' CXCR4 and CCR5 HIV-1 primary isolates with matching V3 sequence motifs while it did not neutralize sequence-mismatched clade B and E isolates. It was also shown to provide sterile protection against SHIV challenge when passively transfered to monkeys in a single high dose. Lower doses provided partial protection. Eda *et al.* [2006a] (**immunoprophylaxis**, **variant cross-recognition or cross-neutralization**)
- KD-247: An escape variant highly resistant to KD-247 was induced with a mutation G314E in the V3 tip of gp120. This mutant virus was shown to be sensitive to CCR5 inhibitors, RANTES, rsCD4 and an anti-CCR5 MAb, but resistant to an anti-CD4 MAb. Combinations of this Ab and CCR5 inhibitors were found to be highly synergistic. Yoshimura *et al.* [2006] (**escape**)
- KD-247: The epitope recognized by this MAb was mapped to IGPGRA. The arginine (R) could not be replaced by any other amino acid, while the amino acids in the flanking sequence, IG, could be substituted without loss of KD-247 binding. The neutralizing sensitivity of clade B SF162, 89.6 and JR-FL to this Ab varied although they share the IGPGRA sequence. At high concentrations, KD-247 was able to suppress replication of viruses derived from patients. At lower concentrations of the MAb, viral replication continued and neutralization escape variants emerged. The escaped viruses had either igpgGa or igpgSa sequences at the tip of the V3 loop. Matsushita *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **optimal epitope**, **escape**)

No. 574
MAb ID 537-D (537)
HXB2 Location gp160 (311–315)
Author Location gp120 (MN)
Epitope IGPGR
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Kanduc *et al.* 2008; Gorny *et al.* 2004; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Fontenot *et al.* 1995; VanCott *et al.* 1994; Gorny *et al.* 1993; Gorny *et al.* 1992; Karwowska *et al.* 1992b
Keywords antibody binding site definition and exposure

- 537-D: Similarity level of the 537-D binding site pentapeptide IGPGR to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 537-D: Called 537: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 537-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 537-D showed weak reactivity. Nyambi *et al.* [2000]
- 537-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a]
- 537-D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 1334, 419, 504, 447, 453 and 537 – the core amino acids GP tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b]
- 537-D: Moderate homologous neutralization, relatively rapid dissociation constant. VanCott *et al.* [1994]
- 537-D: MN type specific neutralization observed – binds SF2, also IGPGR. Gorny *et al.* [1992, 1993]
- 537-D: Reacts with MN, NY5, CDC4, RF, WM52 and SF2, but does not cross-react with HXB2. Karwowska *et al.* [1992b]

No. 575
MAb ID 5020
HXB2 Location gp160 (311–316)
Author Location gp120 (311–316 BH10)
Epitope RGPGRA
Neutralizing no
Immunogen vaccine

B Cell

Vector/Type: peptide *Strain:* B clade BH10 *HIV component:* V3
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
References Langedijk *et al.* 1991

- 5020: Generation and fine mapping of murine MAbs. Langedijk *et al.* [1991]

No. 576
MAb ID RC25
HXB2 Location gp160 (311–316)
Author Location gp120 (JRFL)
Epitope IGPGRA
Subtype B
Neutralizing L
Immunogen
Species (Isotype) humanized mouse
Ab Type gp120 V3
References Kaizu *et al.* 2003; Kimura *et al.* 2002
Keywords co-receptor, HAART, ART

- RC25: MD14 is a R5X4 SHIV with a B clade Env; the V3 loop of an E-clade Env was inserted into MD14 to create SHIV-TH09V3, an R5 virus. SHIV-TH09V3 could infect both cynomolgous and pig-tailed macaques, and the R5 co-receptor usage was maintained after passage through macaques. The MAb RC25 recognized B clade V3 loops, and reacted with SHIV-MD14. Rabbit anti-sera raised against a NSI Clade E consensus preferentially recognized SHIV-TH09V3. Kaizu *et al.* [2003] (**co-receptor**)
- RC25: RC25 is a humanized MAb that recognizes the epitope IGPGRA – it has strong neutralizing activity against JRFL (R5 virus) and weak against NL4-3 (X4 virus) and is used as a control in a study of NAb activity in patients undergoing HAART. Kimura *et al.* [2002] (**HAART, ART**)

No. 577
MAb ID P3E1
HXB2 Location gp160 (311–317)
Author Location gp41 (SF162)
Epitope IGPGRAF
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp140
Species (Isotype) mouse (IgG2aκ)
Ab Type gp120 V3
Research Contact Nina Derby or Leo Stamatatos, Seattle Biomedical Research Institute, Seattle, WA, USA, leo.stamatotos@sbri.org
References Ching *et al.* 2008; Derby *et al.* 2007; Kraft *et al.* 2007; Derby *et al.* 2006
Keywords antibody binding site definition and exposure, escape, kinetics, neutralization, optimal epitope, variant cross-recognition or cross-neutralization

- P3E1: The study explores how the V1 loop of Env influences the neutralization susceptibilities of heterologous viruses to antibodies elicited by the SF162gp140 immunogen. When the V1 loop of the heterologous isolates was replaced by the V1 loop present on the DF162go140 immunogen, these isolates became susceptible to neutralization by anti-V3 MAb P3E1, indicating that the V1 loop plays an important role in the resistance of heterologous viruses to neutralization. Ching *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**)
- P3E1: The minimal epitope for this Ab is most probably located within the V3 crown IGPGRAF. The presence of F and R was important for P3E1 binding. Binding did not depend on the oligomerization state of Env. P3E1 neutralized SF162 and also exhibited cross-neutralizing activity with 89.6, SS1196.1 and 6535.3. On other primary isolates, V1 loop masked the exposure of the P3E1 epitope in V3 and affected neutralization. The SF162ΔV2 virus was significantly more susceptible to neutralization by P3E1 than the wildtype virus, while ΔV1 virus was neutralized with reduced potency. Glycans at positions 154 and 195 in V1V2 enhanced P3E1 neutralizing potency. Neutralization by P3E1 was also enhanced strongly by deletion of the V3 glycan at position 299, somewhat less by deletion at position 329, and not at all by deletion of the glycan at position 293. Glycans present in the V4-V5 region had only modest effects on the neutralizing potential of this Ab, where their removal resulted in a more neutralization resistant virus. Derby *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **optimal epitope**, **variant cross-recognition or cross-neutralization**, **kinetics**)
- P3E1: This is a new anti-V3 loop Ab isolated from mice immunized with SF162-derived gp140 proteins. Viruses from early and late infection of a macaque with SHIV SF162P4 were resistant to contemporaneous serum that had broadly reactive NAbs. SF162 was highly susceptible to neutralization by anti-V3 MAbs 447D and P3E1, as well as anti-V1 MAb P3C8, while envelopes cloned from this animal at 304 days and at 643 days (time of death) post infection had developed resistance to all three of these antibodies. Kraft *et al.* [2007] (**neutralization**, **escape**)
- P3E1: Macaques were immunized with SF162gp140, ΔV2gp140, ΔV2ΔV3gp140 and ΔV3gp140 constructs and their antibody responses were compared to the broadly reactive NAb responses in a macaque infected with SHIV SF162P4, and with pooled sera from humans infected with heterologous HIV-1 isolates (HIVIG). P3E1 recognized SF162gp140 and ΔV2gp140 equally and failed to recognize ΔV2ΔV3gp140 and ΔV3gp140. P3E1 neutralized SF162 efficiently while its neutralization potential was reduced by 93% in the presence of V3 peptides. 6% reduction in neutralization by P3E1 was observed by the presence of a scrambled V3 peptide used as a control for nonspecific binding by sera, although the scrambled peptide was not recognized by P3E1 in epitope mapping studies. Derby *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**)

No. 578
MAb ID 5023A (5023, NEA-9205, NEA 9205)
HXB2 Location gp160 (311–317)
Author Location gp120 (311–317 BH10)

B Cell

Epitope RgPGRAF
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade BH10 *HIV component:* V3
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
Research Contact Paul Durda, Du Pont de Nemours and Co
References Schonning *et al.* 1998; Rovinski *et al.* 1995; Back *et al.* 1993; D'Souza *et al.* 1991; Langedijk *et al.* 1991

- 5023A: Called NEA-9205 – The N306 glycan of the V3 loop makes the tip of the V3 loop inaccessible to this MAb in oligomeric Env, loss of this glycan enhances neutralization sensitivity. Schonning *et al.* [1998]
- 5023A: Called 5023 in this paper – Used to precipitate gp160 in immunoblots in a study examining the feasibility of using unprocessed gp160 glycoprotein as an immunogen. Rovinski *et al.* [1995]
- 5023A: Called 5023 – Langedijk also has an MAb called 5023B – gp41 amino acid substitutions 668 (N/S) and 675 (I/M) in gp41 interfere with 5023s neutralization potency, region 662-675 is ELDKWANLWNWFNI. Back *et al.* [1993]
- 5023A: Called 5023 – Langedijk also has an MAb called 5023B – strong cross-reactive neutralizing MAb. D'Souza *et al.* [1991]
- 5023A: Generation and Fine mapping of murine MAbs. Langedijk *et al.* [1991]

No. 579
MAb ID 110.6
HXB2 Location gp160 (311–318)
Author Location gp120 (BRU)
Epitope RGPGRAFV
Neutralizing L (weak)
Immunogen vaccine
Vector/Type: HIV infected-cell lysate *Strain:* B clade BRU *HIV component:* HIV-1
Species (Isotype) mouse (IgG1λ)
Ab Type gp120 V3
References Langedijk *et al.* 1992; Pirofski *et al.* 1993; Thomas *et al.* 1988

- 110.6: Variable region sequenced – heavy chain: V J558-146b.1alpha, D closest to DSP16.2, J H3 – light chain: V lambda1, J lambda1. Pirofski *et al.* [1993]

No. 580
MAb ID polyclonal
HXB2 Location gp160 (311–318)
Author Location gp120 (MN)
Epitope IGPGRAFY
Neutralizing L
Immunogen vaccine
Vector/Type: B. abortus complex *Strain:* B clade MN, B clade SF2 *HIV component:* gp120
Species (Isotype) mouse (IgG2a)
Ab Type gp120 V3
References Golding *et al.* 1995

- Ab is evoked even in mice depleted of CD4+ cells. Golding *et al.* [1995]

No. 581
MAb ID 10/36e
HXB2 Location gp160 (311–321)
Author Location gp120 (311–321 HXB10)
Epitope RGPGRAFVTIG
Neutralizing L (HXB10)
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) rat (IgG2a)
Ab Type gp120 V3
References Peet *et al.* 1998; McKeating *et al.* 1993b; McKeating *et al.* 1992a

- 10/36e: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind, but anti-V3 MAb 10/36e binding was dramatically diminished by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]
- 10/36e: Binding to virion gp120 enhanced by sCD4. McKeating *et al.* [1992a]

No. 582
MAb ID 10/54 (10/54ow/6i/6i)
HXB2 Location gp160 (311–321)
Author Location gp120 (311–321 HXB10)
Epitope RGPGRAFVTIG
Neutralizing L (HXB10)
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) rat (IgG1)
Ab Type gp120 V3
References Peet *et al.* 1998; McKeating *et al.* 1993b; McKeating *et al.* 1993a; McKeating *et al.* 1992a

- 10/54: Called 10/54ow/6i/6i: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind, but anti-V3 MAb 10/54 binding was dramatically diminished by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]
- 10/54: Studied in the context of a neutralization escape mutant. McKeating *et al.* [1993a]
- 10/54: Binding to virion gp120 enhanced by sCD4. McKeating *et al.* [1992a]

No. 583
MAb ID 11/85b (11/85b/14I/14I)
HXB2 Location gp160 (311–321)
Author Location gp120 (311–321 HXB10)
Epitope RGPGRAFVTIG

B Cell

Neutralizing L (HXB2)
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) rat (IgG2b)
Ab Type gp120 V3
References McKeating *et al.* 1993b; McKeating *et al.* 1992a

- 11/85b: Binding to virion gp120 enhanced by sCD4. McKeating *et al.* [1992a]

No. 584
MAb ID polyclonal
HXB2 Location gp160 (311–322)
Author Location gp120 (MN)
Epitope IGPGRAFYTTKN
Neutralizing L (MN ALA-1)
Immunogen vaccine
Vector/Type: human rhinovirus 14 *Strain:* B clade MN *HIV component:* V3
Species (Isotype) guinea pig
Ab Type gp120 V3
References Smith *et al.* 1998

- The tip of the MN V3 loop (IGPGRAFYTTKN) was inserted into cold-causing human rhinovirus 14 (HRV14) – chimeras were immunoselected, and chimeric viruses were neutralized by anti-V3 loop antibodies – chimeric viruses elicited potent NAbs against ALA-1 and MN. Smith *et al.* [1998]

No. 585
MAb ID 0.5β (0.5 beta, 0.5beta)
HXB2 Location gp160 (311–324)
Author Location gp120 (316–330 HXB2)
Epitope RGPGRAFVTIGKIG
Subtype B
Neutralizing L (IIIB)
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* Env
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 V3
Research Contact Shuzo Matsushita or Toshio Hattori of Kumamoto University
References Harada *et al.* 2008; Sirois *et al.* 2007; Garcia *et al.* 2006; Rosen *et al.* 2005; Okada *et al.* 2005; Huang *et al.* 2005a; Harada *et al.* 2004; Kawai *et al.* 2003; Zvi *et al.* 2000; Tugarinov *et al.* 2000; Jagodzinski & Trzeciak 2000; Fortin *et al.* 2000; Tugarinov *et al.* 1999; Faiman & Horovitz 1997; Wyatt *et al.* 1997; Zvi *et al.* 1997; Huang *et al.* 1997; Faiman *et al.* 1996; Jeffs *et al.* 1996; McDougal *et al.* 1996; Warrier *et al.* 1996; Jagodzinski *et al.* 1996; Zvi *et al.* 1995a; Zvi *et al.* 1995b; Broder *et al.* 1994; Boudet *et al.* 1994; Okada *et al.* 1994; Thali *et al.* 1994; Cook *et al.* 1994; Watkins *et al.* 1993; Klasse *et al.* 1993a; Moore *et al.* 1993b; di Marzo Veronese *et al.* 1993; Sperlagh *et al.* 1993; McKeating *et al.* 1992a; Maeda *et al.* 1992; Emini *et al.* 1992; Matsushita *et al.* 1992; D'Souza *et al.* 1991; Nara *et al.* 1990; Reitz *et al.* 1988; Skinner *et al.* 1988a; Skinner *et al.* 1988b; Matsushita *et al.* 1988
Keywords anti-idiotype, antibody binding site definition and exposure, antibody generation, antibody interactions, binding affinity, brain/CSF, coreceptor, complement, enhancing activity, escape, mimics, neutralization, review, structure, variant cross-recognition or cross-neutralization

- 0.5beta: UK Medical Research Council AIDS reagent: ARP3025.
- 0.5beta: NIH AIDS Research and Reference Reagent Program: 1591.
- 0.5β: Post-attachment enhancement (PAE), which augmented the level of HIV-1 cell infection by 1.4-fold, was significantly inhibited by 0.5β mAb. An increased amount of 0.5β mAb showed the same amount of inhibition of PAE, indicating that the PAE inhibition by this Ab could not solely be explained by covering of the V3 loop with Ab molecules. 0.5β mAb was also shown to suppress the fluidity of the viral and plasma envelopes. It is suggested that the binding of 0.5β to the viral surface could affect steric alternations of the viral envelope and restrain the envelope from enhancing its fluidity. Thus, suppression of the fluidity of viral envelope could be one additional mechanism for virus neutralization by 0.5β mAb. Harada *et al.* [2008] (**antibody interactions**, **enhancing activity**, **neutralization**)
- 0.5β Data is summarized on the X-ray crystal structures resolution and NMR studies of 0.5β. Sirois *et al.* [2007] (**review**, **structure**)
- 0.5beta: The affinity of this Ab was measured for three peptides, one representing the sequence of the V3 loop of HIV-1 IIIB strain and the other two having thiazolidine derivatives replacing the proline within the GPGR. None of the replacements had a large effect on binding of the Ab but the replacement with 2,2 dimehylthiazolidine behaved more like the wildtype. This and the structural and conformational studies by NMR and modeling indicate that it can successfully be used to mimic the native peptide. Garcia *et al.* [2006] (**antibody binding site definition and exposure**, **mimics**, **binding affinity**, **structure**)
- 0.5β: The nuclear magnetic resonance structure of V3-reactive antibody-peptide complexes were examined. V3 bound to 0.5β is shown in a 3D figure. Huang *et al.* [2005a] (**antibody binding site definition and exposure**, **structure**)
- 0.5β: Hybridoma cell lines from trans-chromosome knockout mice immunized with HIV-1 infected cells produced two human mAbs, 9F11 and 2G9, that reacted with HIV-1 infected cells. 2G9 induced apoptosis of HIV-1 infected cells and 9F11 was able to induce complement-mediated cytolysis. None of the mAbs are thought to bind directly to HIV-1. Unlike 2G9, 0.5β:did not react with OM10.1 cells maintained in a latently infected state in the presence of AZT, but it did react when the virus replication was activated in the absence of AZT and in the presence of TNF-α. Okada *et al.* [2005] (**antibody interactions**)

B Cell

- 0.5β: The structure of V3 HIV-1 peptides derived from IIIB and MN isolates when bound to 447-52D was determined by NMR. It was observed that the two different V3 peptides assumed same N-terminal strand conformation when bound to this Ab. V3 peptide IIIB bound to Ab 0.5β differed from the same petide bound to 447-52D by 180 degrees N-terminal chain orientation. It is suggested that the conformation of an Ab-bound V3 peptide is dictated not only by the peptide sequence but also by an induced fit to the specific Ab. Dominant interactions of 0.5β with residues at variable positions 313 and 315 and interactions with an insertion may be responsible for the strain specificity of this Ab. Rosen *et al.* [2005] (**antibody binding site definition and exposure**, **co-receptor**, **structure**)
- 0.5beta: Studies on the temperature dependence of infectious virus (increased temperatures up to 37 degress increases infectivity) showed that X4 pseudoviruses that were infectious at room temperature were also more resistant to anti-V3 0.5beta and anti-CXCR4 blocking peptide T140. This implies that virus more heavily populated with functional envelopes are more infectious. Harada *et al.* [2004] (**co-receptor**)
- 0.5beta: 0.5beta was used as a control for gp120 expression relative to Nef expression soon after infection of cultures. The goal of this study was to elicit anti-Nef IgM human Abs in trans-chromosome mice that carry human chromosomes responsible for Ig production. These mice were immunized with recombinant Nef protein. Human heavy chain, mouse light chain anti-Nef IgM were obtained. The hope was that these human IgM anti-Nef chimeric Abs would activate complement mediated cytolysis; C3 deposition was induced but not at high enough levels to induce lysis. Kawai *et al.* [2003] (**complement**)
- 0.5beta: Host encoded intercellular adhesion molecule (ICAM-1) is incorporated by the HIV-1 virion and enhances viral infectivity – ICAM-1 does not modify virus sensitivity to antibodies 0.5beta or 4.8D or sCD4, but neutralizing ability of F105 was diminished in ICAM bearing virions in the presence of lymphocyte function-association antigen-1 (LFA-1) Ab. Fortin *et al.* [2000] (**antibody interactions**)
- 0.5beta: MAbs 0.5beta and G3-42 were used to study synthesis of oligomeric and monomeric forms of Env – inhibition of glycosylation by tunicamycin results in reduction of oligomeric gp120 at the cell surface and of monomer in the cytoplasm – neither MAb recognized non-glycosylated Env precursor. Jagodzinski & Trzeciak [2000]
- 0.5beta: 14/18 residues of peptide P1053, RKSIRIQRGPGRAFVTIG, were shown to be involved in the Ab recognition site using NMR – QRGPGR forms a beta-hairpin turn at the center of the binding pocket. Tugarinov *et al.* [2000] (**antibody binding site definition and exposure**)
- 0.5beta: NMR and mutation cycles were employed to generate a model of the peptide-antibody complex, showing aa residues that interact or do not contribute to the binding of MAb 0.5beta Fv with the peptide – F96(L) of 0.5beta binds to Pro13, H52(H) interacts with Ile7, Ile9, Gln10, and D56(H) interacts with Arg11 of the V3 loop peptide – RGPG retains hairpin conformation binds in the center of a groove. Zvi *et al.* [2000] (**structure**)
- 0.5beta: NMR structure reveals that Ab bound IIIB-V3 peptide adopts an unexpected type VI cis proline beta-turn. Tugarinov *et al.* [1999] (**structure**)
- 0.5beta: The Fv fragment was purified and the temperature dependence and effect of mutations was studied. Faiman & Horovitz [1997]
- 0.5beta: Relative to the native peptide, an O-linked alpha-galactosamine modified V3 peptide enhanced binding to 0.5 beta, while an N-linked beta-glucosamine modified peptide showed reduced binding. Huang *et al.* [1997] (**antibody binding site definition and exposure**)
- 0.5beta: Binds both gp120 and soluble gp120+gp41 complex efficiently, suggesting its gp120 epitope is not blocked by gp41 binding. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
- 0.5beta: The structure of a 17 amino acid V3 peptide bound to the Fab was studied using NMR. Zvi *et al.* [1997] (**structure**)
- 0.5beta: For Fv fragment of 0.5beta, the combined variable regions of the heavy and light chain residues, were purified. Binding of the V3 peptide epitope TRKSIRIQRGPGRAFVTIGK was studied through mutagenesis of arginines and the free energy of binding in various salt concentrations. R4A, R8A, and R11A all reduce the free energy; R8 is embedded in the peptide-Fv fragment, while R11 is more solvent exposed. Faiman *et al.* [1996] (**antibody binding site definition and exposure**)
- 0.5beta: The sulfated polysaccharide curdlan sulfate (CRDS) binds to the Envelope of T-tropic viruses and neutralizes virus – CRDS inhibits 0.5beta binding – 0.5beta epitope described as GPGRAFVTIG. Jagodzinski *et al.* [1996]
- 0.5beta: Deletion of the V1V2 regions did not affect anti-V3 Abs ability to bind when compared to intact rec gp120. Jeffs *et al.* [1996] (**antibody binding site definition and exposure**)
- 0.5beta: Synergistic neutralization of HIV-1 when combined with anti-V2 MAb C108G. Warrier *et al.* [1996] (**antibody interactions**)
- 0.5beta: The interactions of the peptide RKSIRIQRGPGRAFVT 0.5beta were studied by NMR, and hydrophobic interactions between the two Is and the V form the base of a 12 amino acid loop with GPGR at the apex. Zvi *et al.* [1995b] (**antibody binding site definition and exposure**)
- 0.5beta: NMR of 0.5beta bound NNTRKSIRIQRGPGRAFVTIGKIG suggests that the bound amino acids are in the region SIRIQRGPGRAFVT. Zvi *et al.* [1995a] (**antibody binding site definition and exposure**)
- 0.5beta: Type-specific neutralization of IIIB – does not neutralize SF2. Broder *et al.* [1994] (**variant cross-recognition or cross-neutralization**)
- 0.5beta: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – this MAb can inhibit gp120 binding to GalCer *in vitro*. Cook *et al.* [1994] (**brain/CSF**)
- 0.5beta: Binding domain aa 310-319: RGPGRAFVTIGKIG – mutations in the V3 loop from basic residues can destroy virus infectivity and syncytium formation: R306T, R309T and R313G can also reduce binding of V3 MAbs with two different binding sites: 9284 and 0.5beta. Okada *et al.* [1994] (**antibody binding site definition and exposure**)

B Cell

- 0.5beta: gp41 mutation that confers resistance to neutralization by anti-CD4 binding site antibodies does not reduce neutralizing efficiency of this V3 region MAb. Thali *et al.* [1994]
- 0.5beta: The gp41 mutation 582(Ala to Thr) results in conformational changes in gp120 that confer neutralization resistance to some antiserum and conformationally sensitive neutralizing MAbs – neutralization efficiency of 0.5beta is not affected. Klasse *et al.* [1993a]; Reitz *et al.* [1988] (**antibody binding site definition and exposure**)
- 0.5beta: Binding to native gp120 100-300 fold greater than to denatured. Moore *et al.* [1993b] (**antibody binding site definition and exposure**)
- 0.5beta: Monoclonal anti-idiotype antibodies that mimic the 0.5beta epitope were generated. Sperlagh *et al.* [1993] (**anti-idiotype**)
- 0.5beta: A neutralization escape mutant (HXB2 A281V) was selected by growth of HXB2 in the presence of broadly neutralizing sera – of the MAbs tested , 0.5beta neutralization was the most profoundly affected by this mutation. Watkins *et al.* [1993] (**escape**)
- 0.5beta: Neutralization of virus carrying an A to T substitution (contrast with MAb M77) di Marzo Veronese *et al.* [1993]
- 0.5beta: sCD4 causes loss of IIIB type-specificity, allowing binding and neutralization of MN, in contrast to MAb mu5.5. Maeda *et al.* [1992]
- 0.5beta: Chimeric mouse-human MAb Cbeta1 was constructed by combining the human Cgamma1 and Ckappa constant regions with the 0.5beta murine MAb – ADCC and neutralizing activity. Matsushita *et al.* [1992] (**complement**)
- 0.5beta: Potent neutralizing activity. D'Souza *et al.* [1991]
- 0.5beta: Emergence of virus resistant to MAb 0.5beta and autologous sera neutralization in IIIB infected chimps. Nara *et al.* [1990] (**escape**)
- 0.5beta: Type-specific neutralization of IIIB – does not neutralize MN or RF. Matsushita *et al.* [1988]; Skinner *et al.* [1988b] (**antibody generation**)

No. 586
MAb ID Cβ1, 0.5β
HXB2 Location gp160 (311–324)
Author Location gp120 (316–330 HXB2)
Epitope RGPGRAFVTIGKIG
Subtype B
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* Env
Species (Isotype) humanized mouse (IgG1)
Ab Type gp120 V3
References Kramer *et al.* 2007; Eda *et al.* 2006b; Mc Cann *et al.* 2005; Matsushita *et al.* 2005; Ferrantelli & Ruprecht 2002; Kimura *et al.* 2002; Matsushita *et al.* 1992; Emini *et al.* 1992
Keywords co-receptor, immunotherapy, neutralization, review

- Cβ1: This review summarizes the use of Cβ1 Ab in passive immunoprophylaxis against HIV in primates. Kramer *et al.* [2007] (**immunotherapy**, **review**)
- Cβ1: This Ab does not neutralize HIV-1 AD8, SHIV 89.6 and SHIV C2/1. Eda *et al.* [2006b]
- Cβ1: This MAb was used as a negative control in KD-247 ex-vivo neutralization studies. It did not suppress viral replication of virus from two patients. Suppression was achieved with KD-247 early on, and decreased later to virus production similar to that found in cultures with Cβ1. Matsushita *et al.* [2005] (**neutralization**)
- Cβ1: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**co-receptor**, **immunotherapy**, **review**)
- Cβ1: Review of passive immunoprophylaxis with human NAbs that also includes this chimeric mouse-human MAb, noting it protected 2/2 Chimpanzees from HIV-1 IIIB infection in the Emini *et al.*study published in 1992. Ferrantelli & Ruprecht [2002]
- Cβ1: Defines epitope as IQRGPGRA – strong neutralizing activity against NL4-3 (X4 virus) and none against JRFL (R5 virus) – used as a control in a study of NAb activity in patients undergoing HAART. Kimura *et al.* [2002]
- Cβ1: passive transfer to chimpanzees confers protection against challenge with homologous cell-free virus – mouse 0.5beta human IgG1 chimera. Emini *et al.* [1992]
- Cβ1: Chimeric mouse-human MAb Cbeta1 was constructed by combining the human Cgamma1 and Ckappa constant regions with the 0.5beta murine MAb – ADCC and neutralizing activity. Matsushita *et al.* [1992]

No. 587
MAb ID C25
HXB2 Location gp160 (312–315)
Author Location (MOKW)
Epitope GPGR
Subtype B
Neutralizing P
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade, B clade MN, B clade RF, Other *HIV component:* V3 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
Research Contact Shuzo Matsushita, Kumamoto University, Japan shuzo@kaiju.medic.kumamoto-u.ac.jp
References Eda *et al.* 2006b; Matsushita *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, binding affinity, variant cross-recognition or cross-neutralization

B Cell

- C25: A new humanized MAb recognizing the V3 tip sequence was generated by transferring the genes of the complementary determining region of the mouse NAb C25 into genes of a human V region. C25 was raised by serial vaccinations of a C3H/HeN mouse with six distinctive B clade V3 loop peptides. KD-247 was shown to neutralize laboratory and primary isolates of CXCR4 and CCR5 viruses that possess a GPGR sequence in the Env V3 tip region more effectively than any of the reference Abs used in the study. Eda *et al.* [2006b] (**antibody binding site definition and exposure**, **antibody generation**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **antibody sequence variable domain**)
- C25: C25 was obtained by sequential immunization of mice with six V3 peptides. C25 was humanized to obtain KD-247, by transfer of C25 complementary determining regions (CDRs) into the human immunoglobulin framework. The properties of KD-247 were evaluated. Matsushita *et al.* [2005] (**antibody generation**)

No. 588
MAb ID 447-52D (447/52-DII, 447-52-D, 447d, 447-52-D, 447-D, 447, 447D)
HXB2 Location gp160 (312–315)
Author Location gp120 (MN)
Epitope GPXR
Subtype B
Neutralizing L P
Immunogen HIV-1 infection
Species (Isotype) human (IgG3λ)
Ab Type gp120 V3
Research Contact Dr. Susan Zolla-Pazner, NYU Med Center NY, NY; Veteran Affairs Med Center NY, NY; or Cellular Products Inc, Buffalo, NY,
References Eda *et al.* 2006a; Yamamoto & Matano 2008; Wu *et al.* 2008; Visciano *et al.* 2008b; Tasca *et al.* 2008; Srivastava *et al.* 2008; Pugach *et al.* 2008; Patel *et al.* 2008; Pantophlet *et al.* 2008; Martin *et al.* 2008; Keele *et al.* 2008; Forsman *et al.* 2008; Forsell *et al.* 2008; Dey *et al.* 2008; Ching *et al.* 2008; Dhillon *et al.* 2008; Binley *et al.* 2008; Sirois *et al.* 2007; McKnight & Aasa-Chapman 2007; Kramer *et al.* 2007; Yuste *et al.* 2006; Pantophlet & Burton 2006; Krachmarov *et al.* 2006; Yoshimura *et al.* 2006; Stanfield *et al.* 2006; Gorny *et al.* 2006; Shibata *et al.* 2007; Sheppard *et al.* 2007b; Wang *et al.* 2007a; Phogat *et al.* 2007; Haynes *et al.* 2006; Cham *et al.* 2006; Chakraborty *et al.* 2006; Holl *et al.* 2006a; Pantophlet *et al.* 2007; Nelson *et al.* 2007; Lin & Nara 2007; Li *et al.* 2007b; Law *et al.* 2007; Kraft *et al.* 2007; Huber & Trkola 2007; Hu *et al.* 2007; Dhillon *et al.* 2007; Derby *et al.* 2007; Moore *et al.* 2006; Holl *et al.* 2006b; Haynes & Montefiori 2006; Eda *et al.* 2006b; Derby *et al.* 2006; Binley *et al.* 2006; Varadarajan *et al.* 2005; Teeraputon *et al.* 2005; Stanfield & Wilson 2005; Srivastava *et al.* 2005; Selvarajah *et al.* 2005; Rosen *et al.* 2005; Pinter *et al.* 2005; Mc Cann *et al.* 2005; Martín-García *et al.* 2005; Lusso *et al.* 2005; Louder *et al.* 2005; Li *et al.* 2005a; Krachmarov *et al.* 2005; Kang *et al.* 2005; Huang *et al.* 2005a; Haynes *et al.* 2005a; Grundner *et al.* 2005; Gorny *et al.* 2005; Gao *et al.* 2005a; Crooks *et al.* 2005; Burton *et al.* 2005; Beddows *et al.* 2005b; Sharpe *et al.* 2004; Pugach *et al.* 2004; Pinter *et al.* 2004; Pantophlet *et al.* 2004; McCaffrey *et al.* 2004; Ling *et al.* 2004; Gorny *et al.* 2004; Binley *et al.* 2004; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Kessler *et al.* 2003; Binley *et al.* 2003; Poignard *et al.* 2003; Ferrantelli & Ruprecht 2002; He *et al.* 2002; Gorny *et al.* 2002; Sharon *et al.* 2002; Srivastava *et al.* 2002; Verrier *et al.* 2001; York *et al.* 2001; Park *et al.* 2000; Nyambi *et al.* 2000; Ly & Stamatatos 2000; Hioe *et al.* 2000; Grovit-Ferbas *et al.* 2000; Gorny *et al.* 2000; Beddows *et al.* 1999; Hioe *et al.* 1999; Nyambi *et al.* 1998; Gorny *et al.* 1998; Connor *et al.* 1998; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Parren *et al.* 1998a; Smith *et al.* 1998; Mondor *et al.* 1998; Inouye *et al.* 1998; Ugolini *et al.* 1997; Gorny *et al.* 1997; Hill *et al.* 1997; Parren *et al.* 1997b; Boots *et al.* 1997; Hioe *et al.* 1997b; Hioe *et al.* 1997a; Fouts *et al.* 1997; Binley *et al.* 1997a; D'Souza *et al.* 1997; Sattentau 1996; Trkola *et al.* 1996a; Jagodzinski *et al.* 1996; Forthal *et al.* 1995; Moore & Ho 1995; Moore *et al.* 1995a; Zolla-Pazner & Sharpe 1995; Zolla-Pazner *et al.* 1995; Sattentau *et al.* 1995; Saarloos *et al.* 1995; Fontenot *et al.* 1995; Sattentau 1995; Moore *et al.* 1994a; Gorny *et al.* 1994; VanCott *et al.* 1994; Laal *et al.* 1994; Conley *et al.* 1994a; Spear *et al.* 1993; Cavacini *et al.* 1993a; Keller *et al.* 1993; Gorny *et al.* 1993; Karwowska *et al.* 1992b; Buchbinder *et al.* 1992; Gorny *et al.* 1992
Keywords acute/early infection, ADCC, antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, assay development, assay standardization/improvement, binding affinity, co-receptor, complement, dendritic cells, enhancing activity, escape, kinetics, mimotopes, neutralization, review, SIV, structure, subtype comparisons, supervised treatment interruptions (STI), Th2, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization, viral fitness and reversion

- 447-52D: 24 broadly neutralizing plasmas from HIV-1 subtype B an C infected individuals were investigated using a series of mapping methods to identify viral epitopes targeted by

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NAbs. V3 Ab activity was measured by three assays where 447-52D was used as a control. A V3 peptide derived from the N-terminal part of the V3 loop, including the crown, potently inhibited neutralization of several HIV-1 isolates by 447-52D, indicating that V3 Abs are commonly directed to the N-terminal part of the V3 loop. Binley *et al.* [2008] (**neutralization**)

- 447D: The study explores how the V1 loop of Env influences the neutralization susceptibilities of heterologous viruses to antibodies elicited by the SF162gp140 immunogen. When the V1 loop of the heterologous isolates was replaced by the V1 loop present on the DF162go140 immunogen, these isolates became susceptible to neutralization by anti-V3 MAb 447D, indicating that the V1 loop plays an important role in the resistance of heterologous viruses to neutralization. Ching *et al.* [2008] (**neutralization**)
- 447-52D: Five amino acids in the gp41 N-terminal region that promote gp140 trimerization (I535, Q543, S553, K567 and R588) were considered. Their influence on the function and antigenic properties of JR-FL Env expressed on the surfaces of pseudoviruses and Env-transfected cells was studied. Various non-neutralizing antibodies bind less strongly to the Env mutant, but neutralizing antibody binding is unaffected. 447-52D captured modestly (but not significantly) fewer mutant pseudovirions than wild type, neutralization was not tested. Dey *et al.* [2008] (**binding affinity**)
- 447-52D: The study determined a crystal structure of Fab 447-52D in complex with a V3 peptide NNTRKSIHLGPGRAFYATGDIIG at 2.1 A resolution. The structure revealed an extended CDR H3 loop that forms a β-sheet with the peptide, with predominantly main-chain hydrogen bonds contacts. There was high structural homology with reported structures of other Fab 447-52D complexes, indicating that the V3 loop may adopt a small set of conserved structures around the crown of the β-hairpin. Dhillon *et al.* [2008] (**structure**)
- 447-52D: Requirements for elicitation of CD4i Abs were examined by immunizing non-primate monkeys, rabbits, and human-CD4 transgenic (huCD4) rabbits with trimeric gp140. The trimers used for the immunizations were inoculated with PBMCs, and CD4-specific binding to live CD3+/CD4+/CD8- cells was verified by recognition of the trimers by 447-52D. Forsell *et al.* [2008]
- 447-52D: Variable domains of three heavy chain Abs, the VHH, were characterized. The Abs were isolated from llamas, who produce immunoglobulins devoid of light chains, immunized with HIV-1 CRF07_BC, to gp120. It was hypothesized that the small size of the VHH, in combination with their protruding CDR3 loops, and their preference for cleft recognition and binding into active sites, may allow for recognition of conserved motifs on gp120 that are occluded from conventional Abs. 447-52D provided some inhibition of binding of the three neutralizing VHH Abs to gp120, suggesting that 447-52D imposes steric hinderance to binding of the VHH Abs to gp120. Forsman *et al.* [2008] (**binding affinity**)
- 447-52D: A mathematical model was developed and used to derive transmitted or founder Env sequences from individuals with acute HIV-1 subtype B infection. All but three of the transmitted or early founder Envs were resistant to neutralization by 447-52D, indicating that the coreceptor binding surfaces on transmitted/founder Envs are conformationally masked. sCD4 could trigger a conformational change in gp120 of these Envs and render the virus susceptible to neutralization by 447-52D. Keele *et al.* [2008] (**neutralization**, **acute/early infection**)
- 447-52D: A new purification method was developed using a high affinity peptide mimicking CD4 as a ligand in affinity chromatography. This allowed the separation in one step of HIV envelope monomer from cell supernatant and capture of pre-purified trimer. Binding of 447-52D to gp120SF162 purified by the miniCD4 affinity chromatography and a multi-step method was comparable, suggesting that the miniCD4 allows the separation of HIV-1 envelope with intact 447-52D epitope. gp140DF162ΔV2 was purified by the miniCD4 method to asses its ability to capture gp140 trimers. Purified gp140DF162ΔV2 was recognized by 447-52D, and the k-off value for 447-52D was reduced compared to gp120SF162 monomer, consistent with the gp140DF162ΔV2 trimeric conformation. Binding of 447-52D to gp140DF162ΔV2 purified by the miniCD4 affinity chromatography and a multi-step method was comparable, suggesting that the SF162 trimer antigenicity was preserved. Martin *et al.* [2008] (**assay development**, **kinetics**, **binding affinity**)
- 447D: 447D neutralized 6 of the 15 subtype B isolates tested, of which 5 were resistant to neutralization by MAbs 19b, 39F, CO11, F2A3, F530, LA21 and LE311. Angle of interaction between 447D and V3 was shown by superimposing the Fab fragment of the Ab with V3. 447D was shown to interact with V3 from a nearly identical angle as MAb 58.2. Pantophlet *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **structure**)
- 447-52D: To examine sequence and conformational differences between subtypes B and C, several experiments were preformed with 11 MAbs regarding binding and neutralization. Both binding and neutralization studies revealed that the 11 MAbs could be divided in three different groups, and that the most differences between the subtypes were located in the stem and turn regions of V3. 447-52D belonged to the group 2 MAbs, which are able to bind subtype B but not subtype C gp120, and are able to bind both V3 peptides. 447-52D was able to bind subtype B V3 in the subtype C Env backbone chimera, but not the reverse, indicating that 447-52D binds to a structure created by the subtype B V3 sequence that is not impacted by the gp120 backbone. For subtype B, 447-52D required an R18 residue in order to bind, but the binding was not significantly affected by the H13R change. For subtype C, Q18R mutation did not restore binding to gp120, but the R13H-Q18R double mutation did. Peptide binding was affected only by the R13H mutation, indicating that the poor binding of Q18R gp120 mutant has a structural basis. 447-52D was not able to neutralize JR-FL isolate, and somewhat neutralized SF162. A chimeric SF162 variant with a JR-FL-like V3 sequence was hypersensitive to neutralization by this Ab. Patel *et al.* [2008] (**neutralization**, **binding affinity**, **subtype comparisons**)
- 447-52D: In order to assess whether small molecule CCR5 inhibitor resistant viruses were more sensitive to neutralization by NAbs, two escape mutant viruses, CC101.19 and D1/85.16, were tested for their sensitivity to neutralization by 447-52D,

compared to the sensitivity of CC1/85 parental isolate and the CCcon.19 control isolate. The CC101.19 escape mutant has 4 sequence changes in V3 while the D1/85.16 has no sequence changes in V3 and relies on other sequence changes for its resistance. None of the control or resistant viruses were sensitive for neutralization by 447-52D, although 447-52D bound strongly to gp120 from CC1/85 and CC101.19. These results indicate that V3-dependent and -independent changes responsible for CCR5 inhibitor resistance do not necessarily alter the exposure of V3 to some of the V3 Abs. Pugach *et al.* [2008] (**co-receptor**, **neutralization**, **binding affinity**)

- 447D: Trimeric envelope glycoproteins with a partial deletion of the V2 loop derived from subtype B SF162 and subtype C TV1 were compared. 447D recognized both B and C trimers with similar efficiency, indicating that the epitope recognized by this Ab is exposed and preserved in the subtype C trimers. Subtype C trimer had many biophysical, biochemical, and immunological characteristics similar to subtype B trimer, except for a difference in the three binding sites for CD4, which showed cooperativity of CD4 binding in subtype C but not in subtype B. Srivastava *et al.* [2008] (**binding affinity**, **subtype comparisons**)
- 447-52D: The neutralization profile of early R5, intermediate R5X4, and late X4 viruses from a rhesus macaque infected with SHIV-SF162P3N was assessed. The parental R5 virus was resistant to neutralization by 447-52D, while both the R5X4 intermediate and the late X4 viruses were sensitive to neutralization by 447-52D. The enhanced neutralization susceptibility of the dual-tropic and the X4 viruses to 447-52D suggests adoption of an increasingly open conformation of the Env gp120 over time. Tasca *et al.* [2008] (**co-receptor**, **neutralization**)
- 447-52D: A significantly higher level of 447-52D bound to gp120 complexed with anti-CD4bs mAbs than to gp120 alone or in complex with other non-CD4bs Abs, indicating that binding of anti-CD4bs Abs to gp120 increases exposure of specific V3 mAb epitopes. Visciano *et al.* [2008b] (**antibody binding site definition and exposure**)
- 447-52D: To test whether the conformation change of Env induced by CD4 affects the breadth and potency of 447-52D neutralization, 447-52D was tested in the presence or absence of sCD4 in neutralization of a panel of 12 subtype B and 12 subtype C Env-pseudoviruses. Without sCD4, 447-52D neutralized 2 subtype B and 0 subtype C viruses. With sCD4 present, 447-52D neutralized 7 subtype B and 1 subtype C virus, indicating that neutralization resistance of some viruses to 447-52D is due to a lack of exposure of the V3 loop. Neutralization of JRFL, ADA, and YU2 isolates by 447-52D increased with increased dose of sCD4. A virus with GPGG sequence at the tip of the V3 loop did not react with 447-52D, indicating that amino acid sequence variation may account for the neutralization resistance of other viruses. The presence of b12 and F105 did not induce 447-52D mediated neutralization of JRFL virus, indicating that b12 and F105 do not induce a conformation alternation in Env that exposes V3 loop to 447-52D. Wu *et al.* [2008] (**neutralization**, **variant cross-recognition or cross-neutralization**)
- 447-52D: Current insights into CTLs and NAbs, and their possible protective mechanisms against establishment of persistent HIV/SIV infection are discussed. Pre- and post-infection sterile and non-sterile protection of NAbs against viral challenge, and potential role of NAbs in antibody-mediated antigen presentation in modification of cellular immunity, are reviewed. 447-52D anti-viral activity in suppression of viral rebound in HIV-1 infected humans undergoing structured treatment interruptions is described. Yamamoto & Matano [2008] (**supervised treatment interruptions (STI)**, **review**)
- 447-52D: 447-52D bound only to V3 peptides from the three isolates (MN, SHIVsf162p3 and clade B consensus) which contain GPGR motif. 447-52D did not recognize one B consensus peptide that did contain GPGR motif. Glycosylation of the position 154 in V1 was more important for the protection of the virus from this Ab than glycosylation of the position 195 in V2. 447-52D neutralized chimeric viruses 89.6/SF162V1, JRFL/SF162V1, YU2/SF162V1 and HxB2/SF162V1 more efficiently than their wildtype counterparts, indicating that the accessibility of the V3 loop is affected by the nature of the V1 loop. Derby *et al.* [2007] (**neutralization**, **binding affinity**)
- 447-52D: This Ab was used to help define the antigenic profile of envelopes used in serum depletion experiments to attempt to define the neutralizing specificities of the broadly cross-reactive neutralizing serum. Peptides containing epitopes for 447-52D did not inhibit neutralization by broadly neutralizing sera from two clade B and one clade A infected asymptomatic individuals, indicating that the V3 epitope for this MAb did not account for the broad neutralizing activity observed. 447-52D bound to JR-FL and JR-CSF gp120 monomers but not to core JR-CSF gp120 monomer. Dhillon *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**)
- 447-52D: HIV-1 env clones resistant to cyanovirin (CV-N), a carbohydrate binding agent, showed amino acid changes that resulted in deglycosylation of high-mannose type residues in the C2-C4 region of gp120. Compared to their parental virus HIV-1 IIIB, these resistant viruses were over 200 times more sensitive to 447-52D, indicating that deglycosylation in CV-N resistant viruses is likely o make the V3 loop more accessible to Abs. Hu *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **escape**)
- 447-52D: This review summarizes current knowledge on the various functional properties of antibodies in HIV-1 infection, including 447-52D mAb, in vivo and in vitro activity of neutralizing Abs, the importance and downfalls of non-neutralizing Abs and antibodies that mediate antibody-dependent cellular cytotoxicity and the complement system, and summarizes data on areas tht need future investigation on Ab-mediated immune control. Huber & Trkola [2007] (**review**)
- 447-52D: Viruses from early and late infection of a macaque with SHIV SF162P4 were resistant to contemporaneous serum that had broadly reactive NAbs. SF162 was highly susceptible to neutralization by anti-V3 MAbs 447D and P3E1, as well as anti-V1 MAb P3C8, while envelopes cloned from this animal at 304 days and at 643 days (time of death) post infection had developed resistance to all three of these antibodies. Kraft *et al.* [2007] (**neutralization**, **escape**)
- 447/52D: This review summarizes 447-52D Ab epitope, properties and neutralization activity. Kramer *et al.* [2007] (**review**)

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- 447-52D: G1 and G2 recombinant gp120 proteins, consisting of 2F5 and 4E10, and 4E10 epitopes, respectively, engrafted into the V1/V2 region of gp120, were tested as an immunogen to see if they could elicit MPER antibody responses. Deletion of V1/V2 from gp120, or its replacement with G1 and G2 grafts, did not greatly affect binding of 447-52D to gp120. Shortening of the N and C termini of the V3 loop enhanced the binding of 447-52D. Law *et al.* [2007] (**vaccine antigen design**)
- 447: 32 human HIV-1 positive sera neutralized most viruses from clades A, B, and C. Two of the sera stood out as particularly potent and broadly reactive. Two CD4-binding site defective mutant Env proteins were generated to evaluate whether Abs to the CD4-binding site are involved in the neutralizing activity of the two sera. The integrity of the wildtype and mutant proteins was tested to their reactivity to the 447 Ab. Li *et al.* [2007b] (**binding affinity**)
- 447-52D: 447-52D structure, binding, neutralization, and strategies that can be used for vaccine antigen design to elicit anti-V3 Abs, are reviewed in detail. Lin & Nara [2007] (**review**, **structure**)
- 447-52D: This review summarizes data on possible vaccine targets for elicitation of neutralizing Abs and discusses whether it is more practical to design a clade-specific than a clade-generic HIV-1 vaccine. Development of a neutralizing Ab response in HIV-1 infected individuals is reviewed, including data that show no apparent division of different HIV-1 subtypes into clade-related neutralization groups. Also, a summary of the neutralizing activity of mAb 447-52D in different HIV-1 clades is provided. McKnight & Aasa-Chapman [2007] (**variant cross-recognition or cross-neutralization**, **review**)
- 447-52D: Z13e1, a high affinity variant of Fab Z13, was identified through targeted mutagenesis and affinity selection against gp41 and an MPER peptide. Z13e1 showed 100-fold improvement in binding affinity for MPER antigens over Z13. 447-52D was used as a control in this study. 447-52D was shown to clearly bind to monomers of gp120-gp41 while trimer binding was negligible, in accordance with its modest neutralization potency against HIV-1 JR-FL. Nelson *et al.* [2007] (**vaccine antigen design**)
- 447-52D: In this study the neutralization breadth of F425 B4e8 was assessed using a panel of 40 primary HIV-1 isolates, and 447-52D was found to have a similar profile, and was used as a control to gauge the effects of the amino acid substitutions in the V3 region. As expected, replacing Arg 315 with Ala or Gln and Pro 313 with Ala reduced binding affinity of this 447-52D substantially. Ala substitutions of residues in positions 304-309 and 319-320 also unexpectedly resulted in diminished binding affinity of the Ab. Pantophlet *et al.* [2007] (**antibody binding site definition and exposure**, **subtype comparisons**)
- 447-52D: This review provides information on the HIV-1 glycoprotein properties that make it challenging to target with neutralizing Abs. 447-52D neutralization properties and binding to HIV-1 envelope, and current strategies to develop versions of the Env spike with functional trimer properties for elicitation of broadly neutralizing Abs, such as 447-52D, are discussed. In addition, approaches to target cellular molecules, such as CD4, CCR5, CXCR4, and MHC molecules, with therapeutic Abs are reviewed. Phogat *et al.* [2007] (**review**)
- 447-52D: This Ab was used in the analysis of clade C gp140 (97CN54) antigenicity and was shown to bind with relatively high avidity to the molecule and to dissociate substantially within 420 s. It was also used as a positive control in the neutralization assay. Sheppard *et al.* [2007b] (**neutralization**, **variant cross-recognition or cross-neutralization**, **kinetics**, **binding affinity**)
- 447-52D: Escape variants with the V3 P313L mutation, or V2 R166K, D167N and P175L mutations, were resistant or partially resistant, respectively, to 447-52D. Binding of 447-52D to surface-expressed Env proteins with the V2 mutations was lowered compared to the binding to viruses with no mutations. Binding to surface-expressed Env proteins with the V3 mutation was comparable to the negative controle values. Binding affinity of this Ab for different combinations of V2 and V3 mutants was also tested. Shibata *et al.* [2007] (**escape**, **binding affinity**)
- 447-52D: Data is summarized on the X-ray crystal structures resolution and NMR studies of 447-52D. Sirois *et al.* [2007] (**review**, **structure**)
- 447-52D: Compared to the full-length Con-S gp160, chimeric VLPs containing Con-S ΔCFI gp145 with transmembrane (TM) and cytoplasmic tail (CT) sequences derived from the mouse mammary tumor virus (MMTV), showed higher binding capacity to 447-52D. Chimeric VLPs with only CT derived from MMTV also showed higher binding capacity to 447-52D than the full-length Con-S gp160, however, not as high as the chimeric CT-TM VLPs. Wang *et al.* [2007a] (**binding affinity**)
- 447-52D: 447-52D was not found to inhibit binding of gp120 to DC-SIGN. This Ab bound to Fc-gp120 construct but not to the chimeras missing the V3 loop. Binley *et al.* [2006] (**binding affinity**)
- 447-52D: Guinea-pigs were immunized with 447-52D epitope inserted at three different surface V3 loop locations in the small Escherichia coli Trx protein in order to generate a competent immunogen. Only one complex was shown to successfully generate anti-V3 Abs capable of out-competing 447-52D binding to gp120 and recognizing the same epitope as this Ab. However, these 447-52D-like Abs were not able to affect neutralization of JRFL and BAL. Chakraborty *et al.* [2006] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **binding affinity**)
- 447-52D: Cloned Envs (clades A, B, C, D, F1, CRF01_AE, CRF02_AG, CRF06_cpx and CRF11_cpx) derived from donors either with or without broadly cross-reactive neutralizing antibodies were shown to be of comparable susceptibility to neutralization by 447-52D. Cham *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 447D: Macaques were immunized with SF162gp140, ΔV2gp140, ΔV2ΔV3gp140 and ΔV3gp140 constructs and their antibody responses were compared to the broadly reactive NAb responses in a macaque infected with SHIV SF162P4, and with pooled sera from humans infected with heterologous HIV-1 isolates (HIVIG). 447D recognized SF162gp140 and ΔV2gp140 equally and failed to recog-

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nize ΔV2ΔV3gp140 and ΔV3gp140. Derby *et al.* [2006] (**antibody binding site definition and exposure**)

- 447-52D: The neutralization potency of this Ab against 7 HIV-1 primary isolates was compared to the neutralization potency of the anti-V3 MAb KD-247. Same Ab concentrations were needed for neutralization of the MN, N-NIID, and 92TH022 isolates, while higher concentrations of 447-52D were needed for the neutralization of the rest of the HIV-1 isolates suggesting KD-247 is more potent. Eda *et al.* [2006b]
- 447-52D: This MAb was derived from plasma from a patient with env clade B virus with the GPGR V3 motif. When cross-reactivity was tested, this Ab bound to the V3subtypeB-fusion protein containing GPGR motif but not to the V3subtypeA-fusion protein containing GPGQ motif. This Ab was also shown to be able to neutralize both clade B psSF162 (GPGR) and clade C psMW965 (GPGQ) virus, and four of subtype B and two of non-B primary isolates. Gorny *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)
- 447-52D: This review describes the effectiveness of the current HIV-1 immunogens in eliciting neutralizing antibody responses to different clades of HIV-1. It also summarizes different evasion and antibody escape mechanisms, as well as the most potent neutralizing MAbs and their properties. MAbs reviewed in this article are: 2G12, IgG1b12, 2F5, 4E10, A32, 447-52D and, briefly, D50. Novel immunogen design strategies are also discussed. Haynes & Montefiori [2006] (**neutralization**)
- 447-52D: 29 subtype B V3 peptides were designed and used for immunization of guinea pigs. Peptides that induced Abs that neutralized more than 3 HIV isolates were shown to bind to this Ab better than peptides unable to induce neutralization of any of the HIV-1 primary isolates. Haynes *et al.* [2006] (**neutralization**, **binding affinity**)
- 447-52D: Inhibition of R5 HIV replication by monoclonal and polyclonal IgGs and IgAs in iMDDCs was evaluated. The neutralizing activity of 447-52D was observed to be higher in iMDDCs than in PBLs and PHA-stimulated PBMCs. A 90% reduction of HIV infection was observed without induction of MDDC maturation by this mAb. It was also demonstrated that binding of this mAb to HIV-1 was necessary for inhibition of iMDDC infection. Increased expression of FcγRI on iMDDCs increased inhibition of HIV by 447-52D, suggesting the involvment of this receptor in the HIV-inhibitory activity of this mAb. Holl *et al.* [2006b] (**neutralization**, **dendritic cells**)
- 447-52D: The ability of this Ab to inhibit viral growth was increased when macrophages and immature dendritic cells (iDCs) were used as target cells instead of PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication by this Ab for macrophages and iDCs can occur by two distinct mechanisms, neutralization of infectivity involving only the Fab part of the IgG, and, an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**dendritic cells**)
- 447-52D: This Ab was shown to neutralize SF162 and the neutralization sensitivity increased in the SF162 variant with a JR-FL V3 loop, SF162(JR-FL V3). In contrast, a great reduction in sensitivity to neutralization was observed in the SF162(JR-FL V1/V2) variant and was somewhat restored in the SF162(JR-FL V1/V2/V3) variant, indicating that the masking of the V1/V2 loop plays a much greater role in restricting neutralization sensitivity than the variations in V3. This Ab was shown to neutralize viruses with V3 sequences from several different subtypes (B, F, A1, CRF02_AG, H and CRF01_AE) except subtype C. This Ab failed to neutralize SF162(JR-FL V1/V2) with V3 derived from different HIV-1 clades indicating effective V1/V2-mediated masking of several HIV-1 clades. The effect on the neutralization sensitivity of the residue at the crown of the V3 loop (position 18) was shown to be great for this Ab. Krachmarov *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 447-52D: In addition to gp120-gp41 trimers, HIV-1 particles were shown to bear nonfunctional gp120-gp41 monomers and gp120-depleted gp41 stumps on their surface. 447-52D moderately neutralized wildype virus particles. It effectively bound to nonfunctional monomers but not to gp120-gp41 trimers. Monomer binding did not correlate with neutralization, but it did correlate with virus capture. It is hypothesized that the nonfunctional monomers on the HIV-1 surface serve to divert the Ab response, helping the virus to avoid neutralization. Moore *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**)
- 447-52D: The neutralizing capacity and binding of this Ab to the V3 region of gp120, as well as resistance to neutralization in different HIV-1 clades are reviewed. Pantophlet & Burton [2006] (**antibody binding site definition and exposure**, **neutralization**, **review**, **subtype comparisons**, **structure**)
- 47-52D: Binding of this Ab to three V3 peptides was compared to binding of Ab 2219 to the same peptides. 447-52D was shown to bind to V3 MN and V3 UG1033 but not to V3 UR29. Stanfield *et al.* [2006] (**variant cross-recognition or cross-neutralization**, **binding affinity**)
- 447-52D: The G314E escape variant highly resistant to KD-247 was shown to be more sensitive to 447-52D than the wildtype virus. 447-52D was shown to be able to bind well to both mutant and wildtype surface-expressed Envs. Yoshimura *et al.* [2006] (**escape**, **binding affinity**)
- 447-52D: The epitope recognition sequence for this Ab was introduced into the corresponding region of SIVmac239 either alone or together with epitopes for Abs 2F5 and 4E10. The infectivity and replicative capacity of SIV239/447-52D and SIV239/447-52D/2F5/4E10 were, however, not detectable and too low, respectively, to be used for further analyses. Yuste *et al.* [2006] (**SIV**)
- 447-52D: The major infectivity and neutralization differences between a PBMC-derived HIV-1 W61D strain and its T-cell line adapted counterpart were conferred by the interactions of three Env amino acid substitutions, E440G, D457G and H564N. Chimeric Env-pseudotyped virus Ch5, containing all three of the mutations, was more neutralization sensitive to 447-52D than Ch2, which did not contain any of these mutations. Env-pseudotyped viruses containing D457G mutation alone, or in combination with E440G or H564N, were also more sensitive to neutralization by 447-52D than Ch2. Beddows *et al.* [2005b] (**neutralization**)

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- 447-52D: The structure of the 447-52D MAb and its mechanisms of the V3 loop GPGR motif recognition and binding are reviewed. Engineering of Abs based on revealed structures of broadly neutralizing MAbs is discussed. Burton *et al.* [2005] (**antibody binding site definition and exposure**, **review**, **structure**)
- 447-52D: MAbs were investigated in differnt neutralization formats, including the standard format that measures activity over the entire infection period and several formats that emphasize various stages of infection. Visualization of Env-Ab binding was conducted by BN-PAGE band shifts. 447-52D binding to trimer was completely dependent on sCD4, consistent with neutralization. Crooks *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **assay standardization/improvement**)
- 447-52D: Monomeric gp120 and trimeric gp140CF proteins synthesized from an artificial group M consensus Env gene (CON6) bound well to 447-52D, indicating correct exposure of the 447-52D epitope. Gao *et al.* [2005a] (**antibody binding site definition and exposure**)
- 447-52d: 2909 is a human anti-Env NAb that was selected by a neutralization assay and binds to the quaternary structure on the intact virion. ELISA-based competition assays and subsequent mutational analysis determined that the CD4BS and V2 and V3 loops contribute to the 2909 epitope: 2909 binding was inhibited by MAbs 447-52d (anti-V3), 830A (anti-V2), and IgG1b12 (anti-CD4BS) and sCD4. 2909 was not inhibited by MAbs 670, 1418, nor 2G12. Gorny *et al.* [2005]
- 447-D: This Ab was used as a control in a peptide adsorption assay. 447-D neutralized the SF162 primary isolate to 95%. When 447-D was pre-incubated with BaL or YU2 V3 loop peptides, nearly all neutralizing activity was inhibited. Grundner *et al.* [2005] (**neutralization**)
- 447-52D: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 447-52D has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)
- 447-52D: The crystal and nuclear magnetic resonance structures of V3-reactive antibody-peptide complexes were examined. 447-52D completely surrounded V3, suggesting a high degree of accessibility for generating an immune response. Accessibility of V3 to this MAb is shown in a 3D figure. Huang *et al.* [2005a] (**antibody binding site definition and exposure**, **structure**)
- 447-52D: A series of genetically modified Env proteins were generated and expressed in both insect and animal cells to be monitored for their antigenic characteristics. For 447-52D, five of the modified proteins expressed in insect cells, including 3G mutant (mutations in 3 glycosylation sites), dV1V2 mutant (V1V2 deletions), 3G-2G, 3G-dV2, and 3G-dV2-1G (1G being a mutation near the TM domain), showed higher binding than the wildtype. Of these, the 3G-dV2-1G mutant showed highest binding to 447-52D, indicating that glycosylation of the gp41 domain may affect exposure of the V3 loop. Expressed in animal cells, mutants dV2 and 3G-dV1V2 showed increased binding to 447-52D at relatively high Ab concentrations compared to the wildtype Env. Kang *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)
- 447-52D: Sera from subtype A infected individuals from Cameroon have antibodies that react strongly with subtype A and subtype B V3 loops in fusion proteins, and neutralize SF162 pseudotypes, while sera from 47 subtype B infected individuals reacted only with subtype B. Sera from Cameroon did not neutralize primary A or B isolates, due to indirect masking by the V1/V2 domain rather than due to loss of the target epitope. Neutralization by anti-V3 B clade specific MAbs 447-52D and 4117C was fully blocked by a clade V3 loop fusion protein, but not an A clade fusion protein, while Cameroonian sera neutralization was fully blocked by both A and B clade fusion proteins. Krachmarov *et al.* [2005] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 447D: Full-length gp160 clones were derived from acute and early human HIV-1 infections and used as env-pseudotyped viruses in neutralization assays for their characterization as neutralization reference agents. 2 out of 19 pseudoviruses were sensitive to neutralization by 447D, as was the SF162.LS strain. Li *et al.* [2005a] (**neutralization**, **assay standardization/improvement**)
- 447: Pseudoviruses expressing HIV-1 envelope glycoproteins from BL01, BR07 and 89.6 strains were compared in neutralization assays to replication competent clone derived from transfection of 293T cells (IMC-293T) and to the IMC-293T derived from a single passage through PBMC (IMC-PBMC). The neutralization responses of pseudoviruses and corresponding IMC-293T to 447 were similar, while a significant decrease in viral neutralization sensitivity to 447 was observed for the BR07 and 89.6 IMC-PBMC viruses. The decrease was associated with an increase in average virion envelope glycoprotein content on the PBMC-derived virus. Louder *et al.* [2005] (**neutralization**, **assay standardization/improvement**)
- 447-52D: The epitope for the MAb D19 is conserved and embedded in V3. D19 is unique in that for R5 viruses, it was cryptic and did not bind without exposure to sCD4, and for X4 and R5X4 isolates it was constitutively exposed. It had an overlapping binding region with MAbs 447-52D, B4e8, and 268-D, but different reactivity patterns and fine specificity. While B4e8 and 447-52D could bind to the R5 virus BaL in the absence of sCD4, treatment with sCD4 did increase the binding of both B4e8 and 447-52D, but did not impact their ability to neutralize BaL. Lusso *et al.* [2005] (**antibody binding site definition and exposure**)
- 447-52D: The HIV-1 Bori-15 variant was adapted from the Bori isolate for replication in microglial cells. Bori-15 had increased replication in microglial cells and a robust syncytium-forming phenotype, ability to use low levels of CD4 for infection, and increased sensitivity to neutralization by sCD4 and 17b. Four amino acid changes in gp120 V1-V2 were responsible for this change. Protein functionality and integrity of soluble, monomeric gp120-molecules derived from parental HIV-1 Bori and microglial-adapted HIV-1 Bori-15 was as-

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sessed in ELISA binding assays using CD4BS MAbs F105 and IgG1b12, glycan-specific 2G12, and V3-specific 447-52D, and were unchanged. Association rates of sCD4 and 17b were not changed, but dissociation rates were 3-fold slower for sCD4 and 14-fold slower for 17b. Martín-García *et al.* [2005] (**antibody binding site definition and exposure**)

- 447-52D: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **review**, **structure**)
- 447-52D: This study is about the V2 MAb C108g, which is type-specific and neutralizes BaL and HXB2. JR-FL is a neutralization resistant strain; modification of JRFL at V2 positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potently neutralize the modified JR-FL. The modification in V2 also increased neutralization sensitivity to V3 MAbs 4117c, 2219, 2191, and 447-52D (447-52D was the only one of the 4 V3 MAbs that could neutralize the unmodified JRFL); but only had minor effects on neutralization by CD4BS MAb 5145A, and broadly neutralizing MAbs IgG1b12, 2G12, and 2F5. Pinter *et al.* [2005] (**antibody binding site definition and exposure**)
- 447-52D: The structure of V3 HIV-1 peptides derived from IIIB and MN isolates when bound to 447-52D was determined by NMR. It was observed that the two different V3 peptides assumed same N-terminal strand conformation when bound to this Ab. V3 peptide IIIB bound to Ab 0.5β differed from the same petide bound to 447-52D by 180 degrees N-terminal chain orientation. It is suggested that the conformation of an Ab-bound V3 peptide is dictated not only by the peptide sequence but also by an induced fit to the specific Ab. Dominant interactions of 447-52D with three conserved N-terminal residues may be responsible for the broadly neutralizing capability of this Ab. Rosen *et al.* [2005] (**antibody binding site definition and exposure**, **co-receptor**, **variant cross-recognition or cross-neutralization**, **structure**)
- 447-52D: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. V3 MAbs (447-52D, 19b, F245-B4e8 and 39F) bound to the GDMR antigen, but either did not bind or had diminished binding to mCHO. Selvarajah *et al.* [2005] (**vaccine-specific epitope characteristics**, **Th2**)
- 447-52D: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**neutralization**, **variant cross-recognition or cross-neutralization**, **review**, **subtype comparisons**)
- 447-52D: This review summarizes data on 447-52D-V3 and 447-52D-V3 peptide X-ray crystallographic structures and NMRs and its neutralization capabilities. The binding mechanism of this Ab to V3 explains its ability to neutralize a wide array of viral isolates. Conformation of the V3 peptide bound to 447-52D is very similar to its conformation when bound to mouse Abs 50.1, 59.1 and 83.1. Stanfield & Wilson [2005] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**, **review**, **structure**)
- 447-52D: A T-cell line adapted strain (TCLA) of CRF01_AE primary isolate DA5 (PI) was more neutralization sensitive to 447-52D than the primary isolate. Mutant virus derived from the CRF01_AE PI strain, that lacked N-linked glycosylation at position 197 in the C2 region of gp120, was significantly more sensitive to neutralization by 447-52D then the PI strain. Mutants at positions 138 in V1 and 461/464 in V5 showed lower sensitivity to neutralization by 447-52D. Deglycosylated subtype B mutants at positions 197 and 234 were slightly more neutralizable by 447-52D. Teeraputon *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **subtype comparisons**)
- 447-52D: gp120 alone and gp120 bound to CD4D12 (the first two domains of human CD4) or to M9 (a 27-residue CD4 analog) were used to immunize guinea pigs. Only sera from the gp120-CD4D12 immunized animals showed broadly neutralizing activity. Sera from gp120-CD4D12 and gp120 immunized animals competed equally well with 447-52D, indicating that the V3-loop was accessible in both immunogens. Varadarajan *et al.* [2005] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- 447-52D: 93 viruses from different clades were tested for their neutralization cross-reactivity using a panel of HIV antibodies. Neutralization outside of the B clade was very rare, and seemed to depend on the presence of a GPGR V3 tip, which is rare outside of the B clade. Binley *et al.* [2004] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 447-52D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. The set that can cross-neutralize primary isolates (2182, 2191, 2219, 2412, 2442, 2456) bind V3 but are conformationally senstitive, suggesting some structural conservation despite sequence variation. These MAbs have distinct epitopes relative to 447-52D, a MAb directed at the tip of the V3 loop that also can neutralize many primary isolates. Although 447-52D was selected using a peptide, it has conformational characteristics. Inter-clade cross-neutralization by anti-V3 conformation-dependent MAbs is reduced. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure**, **review**)

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- 447-52D: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides, but was an exception in that it is cross-neutralizing. 447-52D neutralized 12/13 clade B viruses. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 447-52D: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of the V3 MAbs 694-98D and 447-52D, that both bind near the tip of the loop, was decreased by both thrombin and trypsin. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 447-52D: Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The loss of the any of three glycans within or adjacent to the V3 loop (GM299 V3), C2 (GM292 C2), C3 (GM329 C3) increased neutralization susceptibility to 447-52D, but C4 (GM438 C4) or V5 (GM454 V5) removal did not make SF162 more sensitive. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- 447-52D: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 447-52D. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- 447-52D: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neturalization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. 5/6 anti-V3 MAbs, including 447-52D, had similar binding affinity to soluble SF162 and JR-FL rgp120s, although the V3 loop differs at three positions (HigpgrafyTtgE for JR-FL and TigpgrafyAtgD for SF162). Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 447-52D: A primary isolate, CC1/85, was passaged 19 times in PBMC and gradually acquired increased sensitivity to FAb b12 and sCD4 that was attributed to changes in the the V1V2 loop region, in particular the loss of a potential glycosylation site. The affinity for sCD4 was unchanged in the monomer, suggesting that the structural impact of the change was manifested at the level of the trimer. The passaged virus, CCcon19, retained an R5 phenotype and its neutralization susceptibility to other Abs was essentially the same as CC1/85. 447-52D did not neutralize the primary or passaged variant. Pugach *et al.* [2004] (**variant cross-recognition or cross-neutralization**, **viral fitness and reversion**)
- 447-52D: Analysis of the conformation of 447-52D in complex with the V3MN18 peptide (gp12 aa 310-329, KRKRIHIGPGRAFYTTKN) was undertaken using solid state NMR. The bound peptide had a well defined constrained structure that was in good agreement with solution NMR and crystallographic studies. Sharpe *et al.* [2004] (**structure**)
- 447-52D: The SOS mutant envelope protein introduces a covalent disulfide bond between gp120 surface and gp41 transmembrane proteins into the R5 isolate JR-FL by adding cysteines at residues 501 and 605. Pseudovirions bearing this protein bind to CD4 and co-receptor bearing cells, but do not fuse until treatment with a reducing agent, and are arrested prior to fusion after CD4 and co-receptor engagement. 447-52D was able to neutralize the SOS protein better than the wildtype, but did not neutralize SOS well when added post-attachment, as the V3 loop is involved in co-receptor engagement. Binley *et al.* [2003] (**vaccine antigen design**)
- 447-52D: The Fv fragment (composed of just the light and heavy variable regions, and the smallest intact binding unit of an Ab) of 447-52 D was expressed and purified. Preliminary NMR with the peptide epitope indicates that an NMR structure determination is feasible. Kessler *et al.* [2003] (**antibody sequence variable domain**, **structure**)
- 447-52D: This paper attempts to engineer a gp120 molecule that would focus the immune response onto the IgG1b12 epitope. Adding a glycosylation sequon (P313N) to the V3 loop knocked out binding to anti-V3 MAbs loop 2, 19b and 447-52-D. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- 447-52D: Virion capture assays are not a good predictor of neutralization, and the presentation of epitopes using this assay seems to be different from that of functional Envelope spikes on primary isolates – F105 and b6 could efficiently block the b12-mediated capture of infectious virions in a virus capture, but did not inhibit b12 neutralization – Ab 447-52D was able to potently neutralize 89.6 and to neutralize JR-CSF at a high concentration but poorly neutralized ADA – b12 was potent at neutralizing the three primary virions JR-CSF, ADA, and 89.6, but anti-V3 Abs 447-52D and 19b, which did not neutralize JR-CSF and ADA, captured amounts of p24 equal to or higher than the amounts captured by the neutralizing Ab b12. Poignard *et al.* [2003] (**antibody binding site definition and exposure**, **assay development**, **variant cross-recognition or cross-neutralization**)
- 447-52D: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates.

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Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the V3 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)

- 447-52D: Review of NAbs. Ferrantelli & Ruprecht [2002]
- 447-52D: Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions of clades A(N=2), B(N=4), and F(N=2), limited binding to C(N=3) and D(N=3), and did not bind to CRF01(subtype E, N=2) – the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control), MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades) – 447-52D bound to primary isolates from all clades except CRF01 (E), was conformationally sensitive and showed the some of the most potent neutralizing activity. Gorny *et al.* [2002] (**variant cross-recognition or cross-neutralization**)
- 447-52D: Transgenic mice carrying human genes allowing production of fully human MAbs were used to rapidly create a panel of anti-HIV gp120 MAb producing hybridomas by immunization with HIV SF162 gp120 – the previously described human MAbs 5145A(CD4BS) , 4117C (plus others, V3) and 697D (and SC258, V2) were used as controls. He *et al.* [2002]
- 447-52D: The feasibility of determining the NMR structure of the V3(MN) peptide bound to the 447-52D Fab fragment was tested and a general strategy for obtaining NMR structures of V3 peptide-Fab fragments developed – preliminary NMR spectra for 447-52D complexed to a 23 amino acid V3 peptide was obtained. Sharon *et al.* [2002] (**structure**)
- 447-52D: Oligomeric gp140 (o-gp140) derived from R5 primary isolate US4 was characterized for use as a vaccine reagent—antigen capture ELISA was used to compare the antigenicity of gp120 and o-gp140 using a panel of well characterized MAbs—447-D recognized the gp120 monomer much more readily than o-gp140, suggesting the V3 loop is less exposed on o-gp140 and on intact virions. Srivastava *et al.* [2002] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- 447-52D: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001] (**antibody interactions**, **variant cross-recognition or cross-neutralization**)
- 447-52D: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAbs alters some step after binding – the dissociation constant, Kd of 447-52D for the cell associated primary and TCLA Envs was equal, 3nM. York *et al.* [2001] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **binding affinity**)
- 447-52D: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – V3 MAbs 447-52D, 838-D, and 1334 bound with a 7-10 fold preference for the oligomer. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)
- 447-52D: To determine the antigenicity of virus killed by thermal and chemical inactivation, retention of conformation-dependent neutralization epitopes was examined, and exposure of CD4BS epitopes was found to be enhanced (MAbs IgG1b12, 205-46-9, and 205-43-1) – binding to 2G12 and 447-52D epitopes was essentially unaltered – the 17b CD4i epitope was also exposed. Grovit-Ferbas *et al.* [2000] (**vaccine antigen design**)
- 447-52D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – CD4BS MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – V3 MAbs 447-52-D and 268-10-D did not effect proliferation. Hioe *et al.* [2000]
- 447-52D: Called 447D – SF162 is a neutralization-resistant HIV-1 isolate – N-linked glycosylation modifications in the V2 loop of the SF162 gp120 revealed that these sites prevent neutralization by CD4BS MAbs (IgG1b12 and IgGCD4), and protect against neutralization by V3 MAbs (447D and 391-95D) – V2-region glycosylation site mutations did not alter neutralization resistance to V2 MAbs (G3.4 and G3.136) or CD4i MAbs (17b and 48d) – V2 glycosylation site modification allows infection of macrophages, probably due to glycosylated forms requiring fewer CCR5 molecules for viral entry. Ly & Stamatatos [2000] (**antibody binding site definition and exposure**)
- 447-52D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 447-52D showed the highest cross-reactivity, bound to 24/26 viruses tested, but achieved 90% neutralization only against MN, 50% against CA5, and no neutralization was observed for 3 other isolates tested. Nyambi *et al.* [2000] (**subtype comparisons**)

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- 447-52D: Six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000] (**antibody binding site definition and exposure**)
- 447-52D: rgp120 derived from a R5X4 subtype B virus, HIV-1 W61D, was used to vaccinate healthy volunteers and the resulting sera were compared with sera from HIV-1 positive subjects and neutralizing MAbs – TCLA strains showed enhanced 447-52D neutralization sensitivity relative to PBMC-adapted lines (32X increase between HIV-1 (M2424/PBMC(p0)) and HIV-1 (M2424/H9(p9)) and a >128X increase between HIV-1 (W61D/PBMC) and HIV-1 (W61D/SupT1) isolates) Beddows *et al.* [1999] (**variant cross-recognition or cross-neutralization**)
- 447-52D: The presence of leukocyte function-associated molecule 1 (LFA-1) promotes virus infectivity and hinders neutralization, and anti-LFA-1 MAbs can enhance the neutralizing effect of anti-HIV V3 MAb 447-52D and anti-HIV CD4BS MAb IgG1b12 – non-neutralizing anti-HIV CD4BS MAb 654-D did not become neutralizing in the presence of anti-LFA-1 MAbs. Hioe *et al.* [1999]
- 447-52D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a] (**review**, **subtype comparisons**)
- 447-52D: MAb peptide-reactivity pattern clustered with the immunological related MAbs: 1334, 419, 504, 447, 453 and 537 – the core amino acids GP tended to be critical for reactivity in this group – 447 reacted with peptides containing GPGR, but also with many lacking this sequence (GPGQ, for example), and it failed to react with 2/14 peptides containing GPGR, illustrating the importance of context. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 447-52D: Ab from gp120 vaccinated individuals prior to infection, who subsequently became HIV infected, could not achieve 90% neutralization of the primary virus by which the individuals were ultimately infected – these viruses were not particularly refractive to neutralization, as determined by their susceptibility to neutralization by MAbs 2G12, IgG1b12, 2F5 and 447-52D. Connor *et al.* [1998]
- 447-52D: Kinetic parameters were measured, and the association rates were similar, but dissociation rate constants were quite variable for V3 MAbs, 1324E was comparable to 447-52D. Gorny *et al.* [1998] (**kinetics**)
- 447-52D: Called 447-D – 447-D resistance took longer to acquire in virus with the M184V substituted RT, and had the form (AAC N to TAC Y) at position 5 of the V3 loop, rather than the GPGR to GPGR resistance found with wildtype RT. Inouye *et al.* [1998]
- 447-52D: Inhibits binding of Hx10 to both CD4 positive and negative HeLa cells. Mondor *et al.* [1998] (**variant cross-recognition or cross-neutralization**)
- 447-52D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – 447-52D was the most potent and cross-reactive of 18 human MAbs tested and was the only MAb which bound to virions from isolates CA20 (subtype F), CA13 (subtype H), and VI526 (subtype G) Nyambi *et al.* [1998] (**subtype comparisons**)
- 447-52D: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**antibody binding site definition and exposure**)
- 447-52D: Called 447-52-D – The tip of the MN V3 loop was inserted into cold causing human rhinovirus 14 (HRV14) – chimeras were immunoselected, and chimeric viruses were neutralized by anti-V3 loop antibodies, and 447-52D was among the Abs used – chimeric viruses elicited potent NAbs in guinea pigs against ALA-1 and MN. Smith *et al.* [1998] (**vaccine antigen design**)
- 447-52D: Abs that recognize discontinuous epitopes can identify mimotopes from a phage peptide display library – 447-52D has an epitope involving the tip of the V3 loop, that was previously studied with this method Keller *et al.* [1993] – in Keller *et al.*, with no competition, LxGPxR was the most common six-mer, 38% of the peptides – after competition with a gp120 IIIB ligand (QRGPGR)i, RGPxR was the most common and one peptide had the sequence QRGPGR, showing type specific mimotopes can be enriched by strain specific ligand competition protocols Boots *et al.* [1997]. Boots *et al.* [1997]; Keller *et al.* [1993] (**antibody binding site definition and exposure**, **mimotopes**)
- 447-52D: In a multilaboratory blinded study, failed to consistently neutralize any of nine B clade primary isolates – many of these isolates had the GPGR motif at the apex of the V3 loop. D'Souza *et al.* [1997] (**variant cross-recognition or cross-neutralization**, **assay standardization/improvement**)
- 447-52D: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – 447-52D bound monomer, oligomer, and neutralized JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
- 447-52D: Used as a control for comparison to five V3 RF selected antibodies – 447-52D was reactive with A, B, and C clade peptides, but not E. Gorny *et al.* [1997] (**subtype comparisons**)
- 447-52D: Called 447 – gp120 can inhibit MIP-1alpha from binding to CCR5, but this inhibitory effect is blocked by preincubation of gp120 with three anti-V3 MAbs: 447, 257, 1027 – MAb 670 which binds in the C5 region had no effect. Hill *et al.* [1997] (**co-receptor**)
- 447-52D: Tested using a resting cell neutralization assay. Hioe *et al.* [1997a] (**assay standardization/improvement**)
- 447-52D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D)and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail

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of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 447-52D: Neutralizes TCLA strains but not primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 447-52D: Viral binding inhibition by 447-D was correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5) Ugolini *et al.* [1997] (**antibody binding site definition and exposure**)
- 447-52D: Called 447-52-D – The sulfated polysaccharide curdlan sulfate (CRDS) binds to the Envelope of T-tropic viruses and neutralizes virus – CRDS inhibits 447-52D binding. Jagodzinski *et al.* [1996] (**antibody binding site definition and exposure**)
- 447-52D: Review: called 447-52-D – only four epitopes have been described which can stimulate a useful neutralizing response to a broad spectrum of primary isolates, represented by the binding sites of MAbs: 447-52-D, 2G12, Fab b12, and 2F5. Sattentau [1996] (**variant cross-recognition or cross-neutralization**, **review**)
- 447-52D: Neutralizes JR-FL – strongly inhibits gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a] (**co-receptor**, **variant cross-recognition or cross-neutralization**)
- 447-52D: Called 447 – The tip of the V3 loop was presented in a mucin backbone – higher valency correlates with stronger affinity constant. Fontenot *et al.* [1995] (**vaccine antigen design**)
- 447-52D: Neutralizing (- complement), no ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995] (**ADCC**, **complement**, **enhancing activity**)
- 447-52D: Binding affected by identity of amino acids flanking GPGR core – poor breadth of primary virus neutralization. Moore *et al.* [1995a] (**variant cross-recognition or cross-neutralization**)
- 447-52D: Review: the V3 loop motif GPGR is not common outside subtype B isolates, MAb 19b is more cross-reactive than 447-52D. Moore & Ho [1995] (**variant cross-recognition or cross-neutralization**)
- 447-52D: Ab-mediated activation of complement on HIV+ cells is higher than Ab independent activation—what has been termed "Ab independent" in fact results in part from IgM in normal human serum that is HIV-cross-reactive. Saarloos *et al.* [1995] (**complement**)
- 447-52D: Called 447d – Formalin inactivation of virus at 0.1% formalin for 10 hours at 4 degrees was optimal for inactivation of virus while maintaining epitope integrity. Sattentau *et al.* [1995] (**vaccine antigen design**)
- 447-52D: Serotyping study using flow-cytometry – bound only to GPGR V3 loop tips. Zolla-Pazner *et al.* [1995] (**antibody binding site definition and exposure**)
- 447-52D: Neutralization of primary and prototype laboratory HIV-1 isolates using a resting cell assay enhances sensitivity. Zolla-Pazner & Sharpe [1995] (**assay development**, **variant cross-recognition or cross-neutralization**)
- 447-52D: Requires GPxR at the tip of the V3 loop, common in B clade – neutralized primary isolates. Conley *et al.* [1994a] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 447-52D: Mild oxidation of carbohydrate moieties does not alter binding. Gorny *et al.* [1994] (**antibody binding site definition and exposure**)
- 447-52D: Neutralization synergy in combination with CD4 binding domain MAbs. Laal *et al.* [1994] (**antibody interactions**)
- 447-52D: Competition studies with human sera from seroconverting individuals showed that anti-CD4 BS antibodies can arise very early in infection, comparable or prior to anti-V3 antibodies. Moore *et al.* [1994a] (**acute/early infection**)
- 447-52D: GPGQ in MAL resulted in enhanced dissociation – GPGQ in CM234 or K14T did not bind – binding affected by identity of amino acids flanking GPGR core. VanCott *et al.* [1994] (**antibody binding site definition and exposure**)
- 447-52D: Additive neutralization of MN and SF2 when combined with CD4 binding site MAb F105 – supra-additive neutralization of RF. Cavacini *et al.* [1993a] (**antibody interactions**)
- 447-52D: Neutralizes MN and IIIB: GPGR, and binds SF2: GPGR. Gorny *et al.* [1993] (**variant cross-recognition or cross-neutralization**)
- 447-52D: Peptide phage library showed that any of the residues ADGLMNQRS in the X position tolerated in peptides that react well with the antibody. Keller *et al.* [1993] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 447-52D: Complement mediated virolysis of IIIB, but not in the presence of sCD4. Spear *et al.* [1993] (**complement**)
- 447-52D: 60-fold increase in neutralization potency when combined 1:1 with human MAb 588-D. Buchbinder *et al.* [1992] (**antibody interactions**)
- 447-52D: Requires GPXR at the tip of the V3 loop – neutralizes a broad array of B clade lab isolates. Gorny *et al.* [1992] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 447-52D: Reacts with MN, NY5, CDC4, SF2, RF, WM52, and HXB2. Karwowska *et al.* [1992b] (**variant cross-recognition or cross-neutralization**)

No. 589
MAb ID NM-01 (hNM01, hNM-01)
HXB2 Location gp160 (312–315)
Author Location gp120 (MN)
Epitope GPGR
Neutralizing L
Immunogen vaccine
Vector/Type: human rhinovirus 14 *Strain:* B clade MN *HIV component:* V3
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
Research Contact M. Terada, Jason Grabely
References Zwick *et al.* 2003; Nakamura *et al.* 2000; Smith *et al.* 1998; Yoshida *et al.* 1997; Ohno *et al.* 1991
Keywords antibody interactions, complement, immunotherapy

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- NM-01: Called hNM01. scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. The humanized version of this MAb was one of the V3 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- NM-01: Called hNM01. The CDR region of the murine MAb NM-01 was put into a human IgG frame. The epitope recognition was preserved, but the neutralizing potency of the humanized form was enhanced. It could activate complement. Nakamura *et al.* [2000] (**complement**, **immunotherapy**)
- NM-01: The tip of the MN V3 loop was inserted into cold-causing human rhinovirus 14 (HRV14) – chimeras were immunoselected, and chimeric viruses were neutralized by anti-V3 loop antibodies, and NM-01 was among the Abs used – chimeric viruses elicited potent NAbs in guinea pigs against ALA-1 and MN. Smith *et al.* [1998]
- NM-01: Resistance mutation selected by propagation of molecular cloned isolate in the presence of NM-01. Yoshida *et al.* [1997]

No. 590
MAb ID 1026
HXB2 Location gp160 (312–317)
Author Location gp120 (MN)
Epitope GPGRAF
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN *HIV component:* gp120
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
References Bou-Habib *et al.* 1994; Nakamura *et al.* 1993

- 1026: Greater affinity for T cell-tropic strain T-CSF, derived from JR-CSF, than to the primary isolate JR-CSF. Bou-Habib *et al.* [1994]
- 1026: Bound diverse strains, neutralizing activity against MN, close to GPGRAF. Nakamura *et al.* [1993]

No. 591
MAb ID 1034
HXB2 Location gp160 (312–317)
Author Location gp120 (MN)
Epitope GPGRAF
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN *HIV component:* gp120
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
References Berman *et al.* 1997; Bou-Habib *et al.* 1994

- 1034: Binds to 5/7 isolates from breakthrough cases from a MN gp120 vaccine trial. Berman *et al.* [1997]
- 1034: Greater affinity for T cell tropic T-CSF, derived from JR-CSF, than to the primary isolate JR-CSF, close to GPGRAF. Bou-Habib *et al.* [1994]

No. 592
MAb ID 59.1 (R/V3-59.1)
HXB2 Location gp160 (312–317)
Author Location gp120 (308–313 MN)
Epitope GPGRAF
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade MN *HIV component:* V3
Species (Isotype) mouse (IgG1)
Ab Type gp120 V3
Research Contact Mary White-Scharf and A. Profy, Repligen Corporation
References Pantophlet *et al.* 2008; Sirois *et al.* 2007; Stanfield & Wilson 2005; Huang *et al.* 2005a; York *et al.* 2001; Stanfield *et al.* 1999; Smith *et al.* 1998; Ghiara *et al.* 1997; Seligman *et al.* 1996; D'Souza *et al.* 1994; Bou-Habib *et al.* 1994; Ghiara *et al.* 1993; Potts *et al.* 1993; White-Scharf *et al.* 1993; D'Souza *et al.* 1991
Keywords antibody binding site definition and exposure, review, structure

- 59.1: Angle of interaction between 59.1 and V3 was shown by superimposing the Fab fragment of the Ab with V3. Pantophlet *et al.* [2008] (**antibody binding site definition and exposure**, **structure**)
- 59.1: Data is summarized on the X-ray crystal structures resolution and NMR studies of 59.1. Sirois *et al.* [2007] (**review**, **structure**)
- 59.1: The crystal structure of V3-reactive antibody-peptide complexes were examined. 59.1 completely surrounded V3, suggesting a high degree of accessibility for generating an immune response. Accessibility of V3 to this MAb is shown in a 3D figure. Huang *et al.* [2005a] (**antibody binding site definition and exposure**, **structure**)
- 59.1: This review summarizes data on crystallographic structures of 59.1 binding to its V3 peptide antigens. Conformation of the V3 peptide bound to 59.1 is very similar to its conformation when bound to 447-52D. Stanfield & Wilson [2005] (**antibody binding site definition and exposure**, **review**, **structure**)
- 59.1: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAbs alters some step after binding. York *et al.* [2001]
- 59.1: The crystal structure of V3 loop peptides bound to Fabs was obtained – conformational changes in the tip of the V3 loop (GPGR) were observed when different MAbs were bound. Stanfield *et al.* [1999]

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- 59.1: The tip of the MN V3 loop was inserted into cold causing human rhinovirus 14 (HRV14) – chimeras were immunoselected, and chimeric viruses were neutralized by anti-V3 loop antibodies, and 59.1 was among the Abs used – chimeric viruses elicited potent NAbs in guinea pigs against ALA-1 and MN. Smith *et al.* [1998]
- 59.1: A conformationally restricted analog of the tip of the V3 loop was constructed and bound with Fab 59.1 – crystal structure shows interactions between 59.1 and an MN peptide and 59.1 and the modified peptide are similar, but NMR studies reveal that the modified peptide is more ordered in solution, retaining the Fab bound form. Ghiara *et al.* [1997]
- 59.1: Competition ELISAs with serial deletions produced longer estimate of epitope length than x-ray crystallography or Alanine substitution, RIHIGPGRAFYTT, suggesting significance of non-contact residues. Seligman *et al.* [1996]
- 59.1: Greater affinity for T-cell tropic strain T-CSF than the primary isolate JR-CSF, from which T-CSF was derived. Bou-Habib *et al.* [1994]
- 59.1: Multi-lab study for antibody characterization and assay comparison – neutralizes MN and IIIB. D'Souza *et al.* [1994]
- 59.1: Crystal structure of a 24 amino acid peptide from the V3 loop bound to 59.1 Fab fragment – contact residues IGPGRAF. Ghiara *et al.* [1993]
- 59.1: Synergistic neutralization of MN when combined with sCD4 or the CD4BS MAb F105. Potts *et al.* [1993]
- 59.1: Epitope defined by peptide reactivity and binding affinity with amino acid substitutions – GPGRAF. White-Scharf *et al.* [1993]
- 59.1: Called R/V3-59.1 – potent neutralizing MAb. D'Souza *et al.* [1991]

No. 593
MAb ID polyclonal
HXB2 Location gp160 (312–317)
Author Location gp120 (316–321)
Epitope `GPGRAF`
Neutralizing
Immunogen vaccine
Vector/Type: protein, polyepitope *HIV component:* gp160 *Adjuvant:* BSA
Species (Isotype) rabbit
Ab Type gp120 V3
References Lu *et al.* 2000b; Lu *et al.* 2000c

- High titer response to ELDKWA and RILAVERYLKD was observed upon vaccination with multiple-epitope vaccine CG-GPGRAFY-G-ELDKWA-G-RILAVERYLKD conjugated to BSA, a weak response to GPGRAFY – immunization with CG-(ELDKWA-GPGRAFY)_2-K was also tried, yielding a strong Ab response to ELDKWA, weak to GPGRAF – gp160 vaccination yielded strong Ab response but not to any of the peptides studied here. Lu *et al.* [2000c,b]

No. 594
MAb ID polyclonal
HXB2 Location gp160 (312–318)
Author Location gp160
Epitope `GPGRAFY`
Subtype A, B, C, D, F, G, multiple, O
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 C2
References Dong *et al.* 2005b
Keywords antibody binding site definition and exposure, subtype comparisons

- The genetic variability of the neutralizing epitope GPGRAFY was studied and its distribution in different subtypes was assessed. The dominant motifs of the epitope were unequally distributed in different HIV-1 subtypes, and it was shown to be one amino acid shorter in the majority of HIV-1 group O-strains compared to the group-M strains. Dong *et al.* [2005b] (**antibody binding site definition and exposure**, **subtype comparisons**)

No. 595
MAb ID 10E3
HXB2 Location gp160 (312–318)
Author Location gp120 (317–323 IIIB)
Epitope `GPGRAFY`
Neutralizing
Immunogen vaccine
Vector/Type: peptide keyhole limpet hemocyanin (KLH) conjugate *Strain:* B clade IIIB *HIV component:* V3
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
References Li *et al.* 2002; Tian *et al.* 2001
Keywords vaccine antigen design

- 10E3: A polyepitope vaccine was designed based on a recombinant GST fusion protein containing three repeats of the 2F5 core epitope ELDKWA combined with the V3 region peptide GPGRAFY. Abs raised in mice could recognize the peptides, sgp41, and CHO-WT cells that expressed HIV-1 Env on their surface. Li *et al.* [2002] (**vaccine antigen design**)
- 10E3: Peptides GPGRAFY and ELDKWAG were conjugated to KLH and used to raise mouse monoclonal Ab – MAb hybridomas were generated with defined specificity – 10E3 binds to the peptide GPGRAFY and to rgp160. Tian *et al.* [2001]

No. 596
MAb ID polyclonal
HXB2 Location gp160 (312–318)
Author Location gp120 (317–323)
Epitope `GPGRAFY`
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* V3 *Adjuvant:* BSA
Species (Isotype) rabbit, mouse
Ab Type gp120 V3
References Yu *et al.* 2000

- High levels of epitope-specific Abs were induced by the peptide-BSA conjugates C-(GPGRAF)_4-BSA or C-(TRPNNNTRKSIRIQRGPGRAFYTIG KI)-BSA but not by rgp160 vaccine. Yu *et al.* [2000]

No. 597
MAb ID N11-20 (110-H)
HXB2 Location gp160 (312–320)

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Author Location gp120 (317–325)
Epitope GPGRAFVTI
Neutralizing L (LAI)
Immunogen
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 V3
Research Contact J. C. Mazie, Hybridolab, Institut Pasteur
References Valenzuela *et al.* 1998

- N11-20: Neutralization of LAI in CEM cells by anti-V3 MAbs 110.4 and N11-20 is through inhibition of virus binding to the cell. Valenzuela *et al.* [1998]

No. 598
MAb ID 5025A (5025)
HXB2 Location gp160 (313–317)
Author Location gp120 (313–317 BH10)
Epitope pgRAF
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade BH10 *HIV component:* V3
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
Research Contact Paul Durda, Du Pont de Nemours and Co
References D'Souza *et al.* 1991; Langedijk *et al.* 1991

- 5025: Called 5025 – strain specific weakly neutralizing. D'Souza *et al.* [1991]
- 5025A: Generation and fine mapping of murine MAbs. Langedijk *et al.* [1991]

No. 599
MAb ID N70-1.9b
HXB2 Location gp160 (313–318)
Author Location gp120 (316–322)
Epitope PGRAFY
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
Ab Type gp120 V3
References Gorny & Zolla-Pazner 2004; Scott *et al.* 1990; Robinson *et al.* 1990a
Keywords ADCC, review, variant cross-recognition or cross-neutralization

- N70-1.9b: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- N70-1.9b: Type specificity. Robinson *et al.* [1990a] (**variant cross-recognition or cross-neutralization**)
- N70-1.9b: Type specific neutralization, ADCC directed against MN infected cells. Scott *et al.* [1990] (**ADCC**, **variant cross-recognition or cross-neutralization**)

No. 600
MAb ID 902
HXB2 Location gp160 (313–324)
Author Location gp120 (IIIB)
Epitope PGRAFVTIGKIG
Neutralizing L
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp160
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 V3
Research Contact Bruce Chesebro, Rocky Mountain National Laboratory, Montana
References Usami *et al.* 2005; Ling *et al.* 2004; Sakaida *et al.* 1997; Earl *et al.* 1994; Broder *et al.* 1994; Laman *et al.* 1993; Chesebro & Wehrly 1988
Keywords antibody binding site definition and exposure, rate of progression

- 902: NIH AIDS Research and Reference Reagent Program: 522.
- 902: 902 did not bind to monomeric nor to oligomeric gp41, it bound to gp120. Binding of this Ab to H9/IIIB-infected cells gave a weak signal which was slightly decreased by sCD4 pretreatment. Binding to H9/MN-infected cells gave no signal regardless of sCD4 pretreatment. Sera from both long-term survivors and AIDS patients enhanced binding of 902 to H9/IIIB-infected cells. Usami *et al.* [2005] (**antibody binding site definition and exposure**, **rate of progression**)
- 902: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of the V3 MAbs 694-98D and 447-52D, that both bind near the tip of the loop, was decreased by both thrombin and trypsin, 932 binding was only decreased by trypsin. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 902: V3-BH10 peptide with loop-structure inhibits IL-2 induced T-cell proliferation, thought to be due to altering intracellular signaling, and MAb 908 can block the peptide inhibition. Sakaida *et al.* [1997]
- 902: Epitope may be partially masked or altered in the oligomeric molecule. Broder *et al.* [1994]
- 902: Used as a control in a study of the influence of oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]
- 902: Strain specific neutralization of HIV. Chesebro & Wehrly [1988]

No. 601
MAb ID 694/98-D (694/98, 694.8, 694/98D)
HXB2 Location gp160 (314–317)
Author Location gp120 (IIIB)
Epitope GRAF
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
Research Contact Dr. Zolla-Pazner, Veterans Affairs Center, NY, NY. zollas01@endeavor.med.nyu.edu
References Visciano *et al.* 2008b; Harada *et al.* 2008; Tuen *et al.* 2005; Ling *et al.* 2004; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Zwick *et al.* 2003; Zhang *et al.* 2002; He

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et al. 2002; Edwards *et al.* 2002; Park *et al.* 2000; Nyambi *et al.* 2000; Altmeyer *et al.* 1999; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Schonning *et al.* 1998; Nyambi *et al.* 1998; Andrus *et al.* 1998; Li *et al.* 1998; Smith *et al.* 1998; Zolla-Pazner *et al.* 1997; Li *et al.* 1997; Forthal *et al.* 1995; Zolla-Pazner *et al.* 1995; VanCott *et al.* 1995; Cook *et al.* 1994; VanCott *et al.* 1994; Laal *et al.* 1994; Gorny *et al.* 1994; Spear *et al.* 1993; Cavacini *et al.* 1993a; Gorny *et al.* 1993; Gorny *et al.* 1992; Gorny *et al.* 1991; Skinner *et al.* 1988b

Keywords antibody binding site definition and exposure, antibody interactions, binding affinity, enhancing activity, neutralization, review, vaccine antigen design, variant cross-recognition or cross-neutralization

- 694/98-D: Post-attachment enhancement (PAE), which augmented the level of HIV-1 cell infection by 1.4-fold, was significantly inhibited by 694/98-D mAb. 694/98-D was also shown to suppress the fluidity of the viral and plasma envelopes. It is suggested that the binding of 694/98-D to the viral surface could affect steric alternations of the viral envelope and restrain the envelope from enhancing its fluidity. Thus, suppression of the fluidity of viral envelope could be one additional mechanism for virus neutralization by 694/98-D. Harada *et al.* [2008] (**antibody interactions**, **enhancing activity**, **neutralization**)
- 694/98D: A significantly higher level of 694/98D bound to gp120 complexed with six different anti-CD4bs Abs than to gp120 alone or in complex with other non-CD4bs Abs, indicating that binding of anti-CD4bs Abs to gp120 increases exposure of specific V3 mAb epitopes. Immunization of mice with gp120 in complex with 694/98D did not elicit higher and faster gp120-specific Ab responses than immunization with gp120 alone or gp120 in complex with other mAbs, in contrast to immunization with gp120/anti-CD4bs mAb complexes. Sera from gp120-694/98D immunized mice showed weak or no neutralizing activity against both homologous and heterologous HIV-1 isolates. Visciano *et al.* [2008b] (**neutralization**, **vaccine antigen design**)
- 694/98D: This MAb bound with high affinity to gp120IIIb. 694/98D did not disassociate from gp120 at acidic pH, but it had no inhibitory effect on gp120 antigen presentation by MHC class II. 694/98D had minimal effect on the rate of gp120 fragmentation by lysosomal enzyme digestion. Tuen *et al.* [2005] (**antibody interactions**, **binding affinity**)
- 694/98D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- 694/98-D: Called 694/98. V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using IIIB gp120. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 694-98D: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of the V3 MAbs 694-98D and 447-52D, that both bind near the tip of the loop, was decreased by both thrombin and trypsin. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 694/98D: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the V3 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- 694/98-D: Called 694/98D – Truncation of the gp41 cytoplasmic domain of X4, R5, and X4R5 viruses forces a conformation that more closely resembles the CD4 bound state of the external Envelope, enhancing binding of CD4i MAbs 17b and 48d and of CD4BS MAbs F105, b12, and in most cases of glycosylation site dependent MAb 2G12 and the anti-gp41 MAb 246D – in contrast, binding of the anti-V2 MAb 697D and the anti-V3 MAb 694/98D were not affected – viruses bearing the truncation were more sensitive to neutralization by MAbs 48d, b12, and 2G12 – the anti-C5 MAb 1331A was used to track levels of cell surface expression of the mutated proteins. Edwards *et al.* [2002]
- 694/98-D: Called 694 – Transgenic mice carrying human genes allowing production of fully human MAbs were used to rapidly create a panel of anti-HIV gp120 MAb producing hybridomas by immunization with HIV SF162 gp120 – the previously described human MAbs 5145A(CD4BS) , 4117C (plus others, V3) and 697D (and SC258, V2) were used as controls. He *et al.* [2002]
- 694/98-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 694/98-D showed intermediate reactivity. Nyambi *et al.* [2000]
- 694/98-D: Called 694/98D – six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000]
- 694/98-D: A Semliki Forest virus (SFV) expression system carrying BX08 env was used to study the conformation of

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gp120 – intracytoplasmic gp120 was recognized by the anti-V3 MAbs K24 and F5.5, while gp120 at the plasma membrane was detected only by conformation dependent MAbs 2G12, 670-D and 694/98D and not linear V3 MAbs – expression in rat brain also showed that surface-expressed Env was recognized only by the conformation-dependent antibodies and not by anti-V3 antibodies. Altmeyer *et al.* [1999]

- 694/98-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a]
- 694/98-D: MAb peptide reactivity pattern clustered with immunological related MAbs: 1108, 386, 268, 311, 257, 694.8 – the amino acids HI tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b]
- 694/98-D: Used to study pre- and post-exposure prophylaxis Hu-PBL-SCID mice infected by an intraperitoneal injection of HIV-1 LAI – MAb half-life in plasma in mice is 9 days – 2 hours post-694/98-D mice were challenged with LAI, and at an Ab concentration of 1.32 mg/Kg, 50% of the mice were infected – one of the infected mice carried the resistant form GRTF rather than GRAF (critical amino acids for binding are GRA) – post-exposure prophylaxis was effective if delivered 15 min post-exposure, but declined to 50% if delivered 60 min post-exposure, and similar time constraints have been observed for HIVIG, 2F5 and 2G12, in contrast to MAb BAT123 that could protect delivered 4 hours post infection. Andrus *et al.* [1998]
- 694/98-D: Neutralization synergy was observed when the MAbs 694/98-D (V3), 2F5 (gp41), and 2G12 (gp120 discontinuous) were used in combination, and even greater neutralizing potential was seen with the addition of a fourth MAb, F105 (CD4 BS) Li *et al.* [1998]
- 694/98-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – 694/98-D bound only to B and D clade virions and had limited cross reactivity. Nyambi *et al.* [1998]
- 694/98-D: In a study of the influence of the glycan at position 306 of the V3 loop on MAb recognition, anti-V3 MAbs were found to neutralize an HIV-BRU mutant virus that lacks the V3 loop glycan more efficiently than HIV-BRU. Schonning *et al.* [1998]
- 694/98-D: The tip of the MN V3 loop was inserted into cold causing human rhinovirus 14 (HRV14) – chimeras were immunoselected, and chimeric viruses were neutralized by anti-V3 loop antibodies, and 694/98-D was among the Abs used – chimeric viruses elicited potent NAbs in guinea pigs against ALA-1 and MN. Smith *et al.* [1998]
- 694/98-D: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env – could only achieve 50% neutralization alone – all Ab combinations tested showed synergistic neutralization – 694/98-D has synergistic response with MAbs F105, 15e, b12, 2F5, 17b, 2G12, and 48d, and with HIVIG. Li *et al.* [1997]
- 694/98-D: ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995]
- 694/98-D: Human HIV-1 infected sera and MAb 694/98 have high reactivity to MN and RF infected H9 cells, but Genentech rec gp120 IIIB vaccine recipients do not. VanCott *et al.* [1995]
- 694/98-D: Serotyping study using flow-cytometry – bound GRAX bearing virus in 10/11 cases – somewhat conformation dependent. Zolla-Pazner *et al.* [1995]
- 694/98-D: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – V3 MAbs can inhibit gp120 binding to GalCer *in vitro* – binding of GalCer to gp120 inhibited but did not completely block MAb binding. Cook *et al.* [1994]
- 694/98-D: 50% neutralization of HIV-IIIB at a concentration of 0.15mug/ml. Gorny *et al.* [1994]
- 694/98-D: Potent neutralization of IIIB – no neutralization synergy in combination with CD4 binding domain MAbs. Laal *et al.* [1994]
- 694/98-D: GRVY did not alter peptide binding – GRVI and GQAW enhanced dissociation – GQVF and GQAL did not bind. VanCott *et al.* [1994]
- 694/98-D: Neutralizes MN and IIIB (GRAF) – binds SF2 (GRAF) – binding reactivity: MN, IIIB, SF2, NY5, RF, CDC4, WM52. Gorny *et al.* [1993]
- 694/98-D: Called 694-D – complement mediated virolysis of IIIB, but not in the presence of sCD4. Spear *et al.* [1993]
- 694/98-D: Type-specific lab isolate neutralization was observed – binds with 1-3 fold greater affinity to gp120 than to peptides. Gorny *et al.* [1992]
- 694/98-D: This MAb was first described here. Skinner *et al.* [1988b]

No. 602
MAb ID MO101/V3,C4
HXB2 Location gp160 (314–323)
Author Location gp120 (314–323)
Epitope `GRAFVTIGKI+LGVAPTKAKR`
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgM)
Ab Type gp120 V3-C4
References Ohlin *et al.* 1992

- MO101: Generated in response to IIIB Env 286-467 upon *in vitro* stimulation of uninfected-donor lymphocytes – reacts with peptides 314-323 + 494-503 from the V3 and C4 regions. Ohlin *et al.* [1992]

No. 603
MAb ID MO101/V3,C4
HXB2 Location gp160 (314–323)
Author Location gp120 (314–323)
Epitope `GRAFVTIGKI+LGVAPTKAKR`
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgM)
Ab Type gp120 V3-C5
References Ohlin *et al.* 1992

- MO101: Generated through *in vitro* stimulation of uninfected-donor lymphocytes with pB1 containing IIIB Env 286-467 – reacts with peptides from the V3 and C4 regions, positions 314-323 + 494-503, peptides GRAFVTIGKI + LGVAPTKAKR. Ohlin *et al.* [1992]

No. 604
MAb ID MO101/V3,C4

HXB2 Location gp160 (314–323)
Author Location gp120 (494–503)
Epitope GRAFVTIGKI+LGVAPTKAKR
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgM)
Ab Type gp120 V3-C5
References Ohlin *et al.* 1992

- MO101: Generated through *in vitro* stimulation of uninfected-donor lymphocytes with pB1 containing IIIB Env 286-467 – reacts with peptides from the V3 and C4 regions, positions 314-323 + 494-503, peptides GRAFVTIGKI + LGVAPTKAKR. Ohlin *et al.* [1992]

No. 605
MAb ID 9205 (NEA-9205 NEA9205)
HXB2 Location gp160 (315–317)
Author Location gp120 (IIIB)
Epitope RAF
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* V3
Species (Isotype) mouse (IgG1)
Ab Type gp120 V3
Research Contact NEN, Boston MA, commercial
References Huskens *et al.* 2007; Gram *et al.* 2002; Schonning *et al.* 1999; Schonning *et al.* 1998; Fontenot *et al.* 1995; VanCott *et al.* 1994; Allaway *et al.* 1993; Trujillo *et al.* 1993; Durda *et al.* 1990
Keywords variant cross-recognition or cross-neutralization

- 9205 database comment: Also see MAb called 5023A.
- 9205: 2G12 cross-neutralization and escape was the emphasis of this study. The Mab 9205 was used as a control. 9205 did not bind to nor inhibit the strains NDK or HE, while it did neutralize NL43 and MN. Huskens *et al.* [2007] (**variant cross-recognition or cross-neutralization**)
- 9205: Called NEA9205 – gp120 capture ELISAs with MAbs D7324 (anti-C-term) or 9205 (anti-V3) were compared in a study of orientation of glycosylation sites – CD4 binding could only inhibit deglycosylation when gp120 was bound to the plate by D7324, not by 9205, while Abs from HIV-1 infected people inhibited deglycosylation most effectively when gp120 was caught by 9205. Gram *et al.* [2002]
- 9205: Called NEA-9205 – the stoichiometry of MAb neutralization was tested and the data indicated that binding for neutralization was was incremental not all or none, i.e., each envelope oligomer binds a single MAb and each Env oligomer bound reduces the chances of infection – 9205 binds only to Env with a glycosylation site mutation in the V3 loop, A308T. Schonning *et al.* [1999]
- 9205: Called NEA-9205 – The N306 glycan of the V3 loop makes the tip of the V3 loop inaccessible to this MAb in oligomeric Env, loss of this glycan enhances neutralization sensitivity. Schonning *et al.* [1998]
- 9205: Neutralizes IIIB but not MN – significantly slower dissociation constant for IIIB than MN. VanCott *et al.* [1994]
- 9205: Synergy with combinations of CD4-based molecules in inhibition of HIV-1 Env mediated cell fusion. Allaway *et al.* [1993]
- 9205: Called NEA-9205, epitope RIQRGPGRAFVTIGK – reacts with three human brain proteins of 35, 55, 110 kd molecular weight – similar to 9284 – RAF is the core reactivity. Trujillo *et al.* [1993]

No. 606
MAb ID 110.I
HXB2 Location gp160 (316–322)
Author Location gp120 (316–322)
Epitope AFVTIGK
Neutralizing L
Immunogen vaccine
Vector/Type: protein *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 V3
Research Contact F. Traincard, Pasteur Institute, France
References Parren *et al.* 1998a; Wyatt *et al.* 1997; Poignard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; Moore *et al.* 1994c; Moore *et al.* 1993b

- 110.I: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- 110.I: Binds both gp120 and soluble gp120+gp41 complex efficiently, suggesting its gp120 epitope is not blocked by gp41 binding. Wyatt *et al.* [1997]
- 110.I: Reciprocal binding inhibition with other anti-V3 and anti-C4 MAbs – and enhances binding of some anti-V2 MAbs – binding enhanced by some anti-CD4 binding site MAbs. Moore & Sodroski [1996]
- 110.I: Epitope suggested to be RAFVTIGK – V3 MAbs 9284, BAT123, 110.5, and 110.I could each significantly increase gp120 dissociation from virus, mimicking sCD4, and expose the gp41 epitope for MAb 50-69, in contrast to anti-V2 MAbs. Poignard *et al.* [1996a]
- 110.I: Binds equally well to monomer and oligomer, rapid association and potent neutralization of lab strains. Sattentau & Moore [1995]
- 110.I: Binds to carboxy-terminal side of the V3 loop – inhibits binding of C4 region MAb G3-299. Moore *et al.* [1993b]

No. 607
MAb ID anti-HIV-2 polyclonal
HXB2 Location gp160 (317–320)
Author Location gp120 (315–318 SBL6669 HIV-2)
Epitope FHSQ+WCR
Subtype HIV-2
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* HIV-2 SBL6669-ISY *HIV component:* V3
Species (Isotype) guinea pig (IgG)
Ab Type gp120 V3
References Morner *et al.* 1999

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Keywords HIV-2

- Neutralizing Abs against HIV-2 V3 are produced when peptides spanning two non-contiguous parts of the V3 loop are used for vaccination including amino acids 315-318 near the tip (FHSQ) and 329-331 (WCR) at the C-term Cys. Morner *et al.* [1999] (**HIV-2**)

No. 608
MAb ID B2C
HXB2 Location gp160 (319–321)
Author Location gp120 (HIV2ROD)
Epitope HYQ
Subtype HIV-2
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* HIV-2 ROD
Species (Isotype) mouse
Ab Type gp120 C3
References Matsushita *et al.* 1995

- B2C: Viral neutralization was type-specific for HIV-2 ROD. HYQ is the core binding region. Matsushita *et al.* [1995]

No. 609
MAb ID IIIB-V3-01
HXB2 Location gp160 (320–328)
Author Location gp120 (IIIB)
Epitope IGKIGNMRQ
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* V3
Species (Isotype) mouse (IgG1)
Ab Type gp120 V3
Research Contact Jon Laman
References Kanduc *et al.* 2008; Laman *et al.* 1993

- IIIB-V3-01: UK Medical Research Council AIDS reagent: ARP3046.
- IIIB-V3-01: NIH AIDS Research and Reference Reagent Program: 1726.
- IIIB-V3-01: Similarity level of the IIIB-V3-01 binding site pentapeptide IGNMR to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- IIIB-V3-01: Specific for carboxy-terminal flank of the IIIB V3 loop – epitope is hidden native gp120, exposed on denaturation. Laman *et al.* [1993]

No. 610
MAb ID D/6D1
HXB2 Location gp160 (346–377)
Author Location gp120 (351–382 LAI)
Epitope ASKLREQFGNNKTIIFKQSSGGDPEIVTHSFN
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 V4
References Bristow *et al.* 1994

- D/6D1: V4 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp120 and rgp160. Bristow *et al.* [1994]

No. 611
MAb ID 2H1B
HXB2 Location gp160 (357–362)
Author Location gp120 (370–376 HIV2ROD)
Epitope RNISFKA
Subtype HIV-2
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *Strain:* HIV-2 ROD
Species (Isotype) mouse
Ab Type gp120 C3
References Kanduc *et al.* 2008; Matsushita *et al.* 1995

- 2H1B: Similarity level of the 2H1B binding site pentapeptide SFKA to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 4 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 2H1B: Binds in WB, but binds poorly to Env on the cell surface. Matsushita *et al.* [1995]

No. 612
MAb ID 4D7/4
HXB2 Location gp160 (360–380)
Author Location gp120 (361–380 LAI)
Epitope IFKQSSGGDPEIVTHSFNCGG
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 V4
Research Contact S. Ranjbar, NIBSC, UK
References Moore *et al.* 1994c

- 4D7/4: UK Medical Research Council AIDS reagent: ARP3051.
- 4D7/4: C3 region – the relative affinity for denatured/native gp120 is >10. Moore *et al.* [1994c]

No. 613
MAb ID 36.1(ARP 329)
HXB2 Location gp160 (361–381)
Author Location gp120 (362–381 LAI)
Epitope FKQSSGGDPEIVTHSFNCGGE
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 V4
References Moore *et al.* 1994c; Thiriart *et al.* 1989

- 36.1: UK Medical Research Council AIDS reagent: ARP329.

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- 36.1: The relative affinity for denatured/native gp120 is >30 – mutations 380 G/F, 381 E/P impair binding. Moore *et al.* [1994c]

No. 614
MAb ID C12
HXB2 Location gp160 (361–381)
Author Location gp120 (362–381 LAI)
Epitope FKQSSGGDPEIVTHSFNCGGE
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG1)
Ab Type gp120 CD4i, gp120 V4
Research Contact George Lewis
References Lin & Nara 2007; Dorfman *et al.* 2006; Choe *et al.* 2003; Moore *et al.* 1994d; Abacioglu *et al.* 1994; Moore *et al.* 1994c; Moore & Ho 1993
Keywords antibody binding site definition and exposure, co-receptor, review

- C12: Tyrosine sulfation of C12 and other Abs, and its effect on Ab binding and neutralization, is reviewed. Lin & Nara [2007] (**review**)
- C12: The CDR3 regions of CD4i Abs (E51, 412d, 17b, C12 and 47e) were cloned onto human IgG1 and tested for their ability to inhibit CCR5 binding. Only E51 successfully immunoprecipitated gp120. Dorfman *et al.* [2006] (**co-receptor**)
- C12: C12 was obtained from an HIV-1 infected individual with a potent and broadly neutralizing activity of his serum. It was shown that scFv C12 was sulfate-modified and it is implied that the sulfates are localized exclusively within the heavy chain CDR3 region of this MAb. Binding efficiency of scFv C12 to ADA gp120 was doubled in the presence of CD4, showing that this MAb is a CD4-induced. Association of scFv C12 with ADA gp120-CD4-Ig complex was partially inhibited by a sulfated peptide with a sequence corresponding to the CCR5 amino terminus, indicating that C12 binds a CD4-enhanced epitope overlapping the binding domain of CCR5 amino terminus. scFv C12 was shown to efficiently bind to gp120 of three R5 isolates but not to the HXBc2 X4 isolate. Choe *et al.* [2003] (**antibody binding site definition and exposure**, **co-receptor**)
- C12: C3 region – epitope boundaries mapped by peptide scanning, core FNCGG. Abacioglu *et al.* [1994]
- C12: The relative affinity for denatured/native gp120 is >30 – mutations 380 G/F, 381 E/P, and 384 Y/E impair binding – also binds GEFFYCNSTQLFNS, gp120(380-393 LAI) Moore *et al.* [1994c]
- C12: Bound preferentially to denatured IIIB gp120. Moore & Ho [1993]

No. 615
MAb ID 2F19C
HXB2 Location gp160 (363–365)
Author Location gp120 (HIV2ROD)
Epitope APGK
Subtype HIV-2
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *Strain:* HIV-2 ROD
Species (Isotype) mouse
Ab Type gp120 C3
References Matsushita *et al.* 1995

- 2F19C: Binds in WB, but binds poorly to Env on the cell surface, APGK is the core binding region. Matsushita *et al.* [1995]

No. 616
MAb ID 110.D
HXB2 Location gp160 (380–393)
Author Location gp120 (380–393 LAI)
Epitope GEFFYCNSTQLFNS
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C3
Research Contact F. Traincard, Pasteur Institute, France
References Kanduc *et al.* 2008; Valenzuela *et al.* 1998; Moore *et al.* 1994c

- 110.D: Similarity level of the 110.D binding site pentapeptide FFYCN to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 110.D: The relative affinity for denatured/native gp120 is >50. Moore *et al.* [1994c]

No. 617
MAb ID B32
HXB2 Location gp160 (380–393)
Author Location gp120 (380–393 LAI)
Epitope GEFFYCNSTQLFNS
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG1)
Ab Type gp120 C3
References Abacioglu *et al.* 1994; Moore *et al.* 1994c

- B32: C3 region – epitope boundaries mapped by peptide scanning – FFY(core) Abacioglu *et al.* [1994]
- B32: The relative affinity for denatured/native gp120 is >100 – mutations 380 G/F, 381 G/P, 382 F/L, 384 Y/E, and 386 N/R impair binding. Moore *et al.* [1994c]

No. 618
MAb ID polyclonal (VEI4)
HXB2 Location gp160 (391–413)
Author Location Env
Epitope FNSTWFNSTWSTEGSNNTEGSDT
Neutralizing
Immunogen HIV-1 infection

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Species (Isotype) human
Ab Type gp120 V4
References Carlos *et al.* 1999

- Antibody response to the epitopes in a vaccine construct (VEI) containing peptides from 5 hypervariable regions of gp120 was detected in the sera of HIV-1 positive subjects, including sera from 6 non-subtype B infections – serum samples from San Francisco, Canada and Puerto Rico cohort showed presence of antibodies against all five VEI hypervariable regions, but most consistently against the V3 region peptide NNNTRKSIRIGPGRAFYTTGDIGNIRQ. Carlos *et al.* [1999]

No. 619
MAb ID B15
HXB2 Location gp160 (395–400)
Author Location gp120 (395–400 BH10)
Epitope WFNSTW
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG2b)
Ab Type gp120 V4
Research Contact George Lewis
References Abacioglu *et al.* 1994; Moore *et al.* 1993b; Moore & Ho 1993

- B15: V4 region – epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]
- B15: Bound preferentially to denatured IIIB gp120. Moore & Ho [1993]
- B15: Binds native BH10 gp120 with 5 fold less affinity than denatured – does not bind native or denatured MN gp120. Moore *et al.* [1993b]

No. 620
MAb ID B34
HXB2 Location gp160 (395–400)
Author Location gp120 (395–400 BH10)
Epitope WFNSTW
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG2b)
Ab Type gp120 V4
References Kanduc *et al.* 2008; Abacioglu *et al.* 1994

- B34: Similarity level of the B34 binding site pentapeptide WFNST to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 1 time, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- B34: V4 region – epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

No. 621
MAb ID 7F11
HXB2 Location gp160 (397–439)
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* gp120
Species (Isotype) mouse
References Nilsen *et al.* 1996; Lasky *et al.* 1987

- 7F11: There is another MAb with this name that binds to integrase. Nilsen *et al.* [1996]

No. 622
MAb ID E51
HXB2 Location gp160 (420–423)
Author Location gp120 (420–423 HXB2)
Epitope IKQI
Subtype B
Neutralizing P
Immunogen
Species (Isotype) human
Ab Type gp120 CD4i, gp120 CCR5BS
Research Contact Joseph Sodroski, joseph_sodroski@dfci.harvard.edu
References Binley *et al.* 2008; Lin & Nara 2007; Yuan *et al.* 2006; Kothe *et al.* 2007; Dorfman *et al.* 2006; Tuen *et al.* 2005; Srivastava *et al.* 2005; Mc Cann *et al.* 2005; Haynes *et al.* 2005a; Choe *et al.* 2003; Xiang *et al.* 2003
Keywords antibody binding site definition and exposure, antibody generation, antibody interactions, binding affinity, co-receptor, neutralization, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- E51: 24 broadly neutralizing plasmas from HIV-1 subtype B an C infected individuals were investigated using a series of mapping methods to identify viral epitopes targeted by NAbs. Activity directed to the CD4i epitope of gp120 was assessed by the abilities of the plasmas to inhibit virus capture by the MAb E51 in the presence of sCD4. CD4i titers for the inhibition were high for all the plasmas, and did not differ between the subtypes, suggesting that the contribution of the CD4i-Abs for the plasma neutralization activity was minimal. Binley *et al.* [2008] (**neutralization**, **subtype comparisons**)
- E51: Four consensus B Env constructs: full length gp160, uncleaved gp160, truncated gp145, and N-linked glycosylation-site deleted (gp160-201N/S) were compared. All were packaged into virions, and all but the fusion defective uncleaved version mediated infection using the CCR5 co-receptor. CD4 inducible MAbs 17b and E51 were tested for the ability to neutralize the various forms of Con B; as anticipated gp160 and gp145 were not neutralized by these two MAbs, but the gp160-201N/S mutant was neutralized with IC50 values of 10 ug/ml, suggesting increased formation and/or exposure of the co-receptor binding site. The poorly infectious clone WITO4160.27 was also somewhat susceptible to neutralization by these clones. Kothe *et al.* [2007] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**)
- E51: E51e structure, sulfation, binding, and neutralization activity are reviewed in detail. Lin & Nara [2007] (**review**)

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- E51: The CDR3 regions of CD4i Abs (E51, 412d, 17b, C12 and 47e) were cloned onto human IgG1 and tested for their ability to inhibit CCR5 binding. Only E51 successfully immunoprecipitated gp120. The sulfated peptide from E51 (pE51) efficiently bound gp120, was enhanced by CD4, and could neutralize HIV-1 more effectively than peptides based on CCR5. pE51 was able to block infection by a range of subtype B isolates. Dorfman *et al.* [2006] (**co-receptor**)
- E51: Interactions of this MAb with gp120 monomer and two cleavage-defective gp140 trimers were studied. It was shown that E51 interactions with the soluble monomers and trimers were dramatically decreased by GA cross-linking of the proteins, indicating that the E51 epitope was affected by cross-linking. Yuan *et al.* [2006] (**antibody binding site definition and exposure**, **antibody interactions**, **binding affinity**)
- E51: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. E51 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)
- E51: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **co-receptor**, **neutralization**, **review**)
- E51: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **vaccine antigen design**, **review**)
- E51: This Ab bound with an intermediate affinity to gp120IIIb, it did not prevent uptake of gp120 by APCs, and had no inhibitory effect on gp120 antigen presentation by MHC class II. E51 disassociated from gp120 at acidic pH. Lysosomal enzyme digestion of gp120 in complex with E51 yielded fragmentation similar to that of gp120 alone, and digestion rate was intermediate, between the rapid digestion of gp120 alone and the slow digestion of gp120 in complex with high-affinity Ab5145A. It is thus concluded that CD4i Ab E51 does not have an inhibitory effect on gp120 processing and presentation. Tuen *et al.* [2005] (**antibody interactions**, **binding affinity**)
- E51: E51 was obtained from an HIV-1 infected individual with a potent ELISA response to the gp120. It was shown that this MAb could be sulfate-modified. The results indicated that the sulfates present on E51 are localized on tyrosines within its heavy chain CDR3 region and that they contribute to E51s ability to associate with gp120 of the ADA isoalte. Binding efficiency of E51 to ADA gp120 was increased by 25% in the presence of CD4, showing that E51 is a CD4i Ab. Association of E51 with ADA gp120-CD4-Ig complex was inhibited by a sulfated peptide with a sequence corresponding to the CCR5 amino terminus, indicating that E51 binds a CD4-enhanced epitope overlapping the binding domain of CCR5 amino terminus. Neutralization assays showed that E51 neutralizes primary R5 and R5X4 isolates more efficiently, and X4 isolates less efficiently, than CD4i Abs 17b and 48d. scFv E51 was shown to efficiently bind to gp120 of three R5 isolates and to the HXBc2 X4 isolate. Choe *et al.* [2003] (**antibody binding site definition and exposure**, **co-receptor**, **neutralization**)
- E51: E51 recognizes a highly conserved epitope localized in the basic β19-strand (gp120 aa420-423), a region involved in CCR5 binding. The MAb was isolated from a EBV transformed B-cell line established from an HIV+ individual undergoing early STI. Fab fragments were also produced. E51, like CD4i MAb 17b, blocks CCR5 binding to sCD4-bound gp120. The presence of sCD4 induces a conformational change in gp120, which enhances ligand recognition. The substitutions E381R, F383S, R419D I420R, K421D, Q422L, I423S, and Y435S (HXB2 numbering) all severely reduce 17b and E51 binding. All but I423S also diminish CCR5 binding by more than 50%. The mutation F383S also inhibits sCD4 binding and CD4BS MAb F105 binding, and K421D inhibits F105 binding, but not sCD4. E51 has more cross-neutralizing potency than other prototype CD4i MAbs (17b) for B and C clade isolates. E51 and 17b both neutralized HIV-1 clade B strains HXBc2 and ADA, while JR-FL and 89.6 were only neutralized by E51, not 17b. Clade C strains MCGP1.3 and SA32 were both inhibited by 17b and E51, but E51 was more potent against SA32. Xiang *et al.* [2003] (**antibody binding site definition and exposure**, **antibody generation**, **co-receptor**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No.	623
MAb ID	JL413
HXB2 Location	gp160 (421–436)
Author Location	gp160 (421–436)
Epitope	KQIINMWQEVGKAMYA
Subtype	B
Neutralizing	P
Immunogen	autoimmune disease
Species (Isotype)	human
Ab Type	gp120 CD4BS
References	Karle *et al.* 2004
Keywords	antibody generation, antibody sequence variable domain, co-receptor, subtype comparisons

- JL413: Phage display was used to create a library of gp120-binding single-chain fragments containing V domain (scFv) constructs derived from PBMC of lupus patients. Lupus patients rarely get HIV/AIDS and can make antibodies that bind to a conserved gp120 determinant. The scFV clone JL413 was able to induce dose-dependent, cross-clade neutralization of primary HIV-1 isolates ZA009 (R5, clade C); BR004 (R5,

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clade C); Ug046 (X4, clade D); SF162 (R5, clade B), and 231135 (clade B). The scFV clone JL413 recognizes a linear region that overlaps the CD4 T-cell binding site, in contrast to HIV-induced MAbs that bind to this region and are conformation dependent. Karle *et al.* [2004] (**antibody generation**, **co-receptor**, **subtype comparisons**, **antibody sequence variable domain**)

No. 624
MAb ID 5C2E5
HXB2 Location gp160 (422–431)
Author Location gp120 (406–415 IIIB)
Epitope `QFINMWQEVK`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 C4
Research Contact T. Gregory and R. Ward, Genentech, San Francisco
References Kanduc *et al.* 2008; Cordell *et al.* 1991; Lasky *et al.* 1987

- 5C2E5: Similarity level of the 5C2E5 binding site pentapeptide MWQEV to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 5C2E5: Cross-competition with MAbs 5C2E5, ICR38.8f and ICR38.1a. Cordell *et al.* [1991]
- 5C2E5: Blocks the gp120-CD4 interaction. Lasky *et al.* [1987]

No. 625
MAb ID G3-211
HXB2 Location gp160 (423–437)
Author Location gp120 (423–437 IIIB)
Epitope `IINMWQKVGKAMYAP`
Neutralizing L
Immunogen vaccine
Vector/Type: virus derived protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 C4
References Sun *et al.* 1989

- G3-211: G3-211, 42, 299, 508, 519, 536, 537: Cross-react with diverse strains by immunofluorescence – blocks HIV binding to CD4+ cells – different neutralization efficiencies. Sun *et al.* [1989]

No. 626
MAb ID G3-537
HXB2 Location gp160 (423–437)
Author Location gp120 (423–437 IIIB)
Epitope `IINMWQKVGKAMYAP`
Neutralizing L
Immunogen vaccine
Vector/Type: virus derived protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 C4
References Zwick *et al.* 2003; McKeating *et al.* 1992b; Ho *et al.* 1991b; Sun *et al.* 1989
Keywords antibody interactions

- G3-537: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the C4 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- G3-537: Weakly neutralizing – binds to a linear binding domain of gp120, NMWQEVGKAMYAPPISG. McKeating *et al.* [1992b]
- G3-537, 211, 299, 508, 519, 536, 42: Cross-react with diverse strains by immunofluorescence – blocks HIV binding to CD4+ cells – different neutralization efficiencies. Sun *et al.* [1989]

No. 627
MAb ID polyclonal
HXB2 Location gp160 (425–436)
Author Location gp120
Epitope `NMWQEVGKAMYA`
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *Adjuvant:* Cholera toxin (CT)
Species (Isotype) mouse (IgA)
Ab Type gp120 CD4BS
References Bukawa *et al.* 1995

- Polyclonal secretory IgA antibody raised by mucosal immunization is able to neutralize IIIB, SF2, and MN – HIV-1 neutralization may be due to the V3, CD4 or HPG30 component of the multicomponent peptide immunogen. Bukawa *et al.* [1995]

No. 628
MAb ID 1795
HXB2 Location gp160 (425–441)
Author Location gp120 (425–441 IIIB)
Epitope `NMWQEVGKAMYAPPISG`
Neutralizing L
Immunogen vaccine
Vector/Type: poliovirus *HIV component:* Env
Species (Isotype)
Ab Type gp120 CD4BS
References McKeating *et al.* 1992b

- 1795: CD4 binding site – weakly neutralizing – binding inhibited by WQEVGKAMYA, GKAM may be involved. McKeating *et al.* [1992b]

No. 629
MAb ID ICR38.1a (38.1a, 388/389, ARP388/389)

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HXB2 Location gp160 (429–438)
Author Location gp120 (427–436 BRU)
Epitope EVGKAMYAPP
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) rat (IgG2b)
Ab Type gp120 C3, gp120 C4
References Holl *et al.* 2006a; Vella *et al.* 2002; Kropelin *et al.* 1998; Peet *et al.* 1998; Jeffs *et al.* 1996; Moore *et al.* 1993b; McKeating *et al.* 1993a; McKeating *et al.* 1993b; McKeating *et al.* 1992c; McKeating *et al.* 1992a; McKeating *et al.* 1992b; Cordell *et al.* 1991
Keywords antibody binding site definition and exposure, dendritic cells

- ICR38.1a: UK Medical Research Council AIDS reagent: ARP388/ARP389.
- ICR38: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**dendritic cells**)
- ICR38.1a: Called ARP388/ARP389: Herpesvirus saimiri-immortalized CD4+ T lymphocytes (HVS T cells) were used to isolate virus and perform HIV-1 neutralization assays, and compared with a standard PBMC protocol – neutralization sensitivities to a panel of MAbs and to homologous or heterologous plasma/sera were similar for HVS T cells (CN-2 cells) and PBMCs – lists epitope as WQEVGKAMYA. Vella *et al.* [2002] (**antibody binding site definition and exposure**)
- ICR38.1a: Called 388/389 – anti-C1 region MAb 87-135/9 blocks gp120 interaction with CD4+ cells – blocking activity is additive when combined with antibodies which bind in the C4 region of gp120 (F105, 388/389, and b12) Kropelin *et al.* [1998]
- ICR38.1a: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind – ICR38.1a was not affected by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]
- ICR38.1a: Called 38.1a – 10 to 20 fold increased binding when V1/V2 or V1/V2 and V3 were deleted from gp120. Jeffs *et al.* [1996]
- ICR38.1a: Studied in the context of a neutralization escape mutant. McKeating *et al.* [1993a]
- ICR38.1a: Unreactive with solid-phase decapeptide, competed in solution phase assay – ICR 38.1a and ICR 38.8f were initially reported to be independent MAbs, but are actually subclones of the same MAb. Moore *et al.* [1993b]
- ICR38.1a: Weakly neutralizing – binds linear determinant in the CD4 binding domain – cross-competition with MAbs G3-536, 5C2E5, and ICR38.8f. Cordell *et al.* [1991]; McKeating *et al.* [1992b]
- ICR38.1a: Unable to exert a synergistic effect in combination with V3 directed MAbs, in contrast to MAb 39.13g, that binds to a conformational epitope involved in CD4 binding. McKeating *et al.* [1992a]

No. 630
MAb ID G3-299
HXB2 Location gp160 (429–438)
Author Location gp120 (429–438 BRU)
Epitope EVGKAMYAPP
Neutralizing L
Immunogen vaccine
Vector/Type: virus derived protein *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 C4
Research Contact M. Fung and Tanox Biosystems Inc and David Ho, ADARC, NY
References Zwick *et al.* 2003; Kwong *et al.* 2002; Parren *et al.* 1998a; Wyatt *et al.* 1997; Ditzel *et al.* 1997; Binley *et al.* 1997a; Poignard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; Moore *et al.* 1993b; Sun *et al.* 1989
Keywords antibody binding site definition and exposure, antibody interactions

- G3-299: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the C4-V3 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- G3-299: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-299) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Authors describe the G3-299 epitope as V3 loop/outer domain. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)

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- G3-299: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- G3-299: Binds both gp120 and soluble gp120+gp41 complex efficiently, suggesting its gp120 epitope is not blocked by gp41 binding. Wyatt *et al.* [1997]
- G3-299: Discontinuous V3-C4 epitope, binding enhanced by a few anti-C1, anti-CD4 binding site, and V2 MAbs – binding reciprocally inhibited by anti-V3 MAbs – G3-229 enhances the binding of some anti-V2 MAbs. Moore & Sodroski [1996]
- G3-299: Epitope described as KQIINMWQKVGKAMYAPPIS – binding resulted in slight gp120 dissociation from virus and exposure of the gp41 epitope for MAb 50-69. Poignard *et al.* [1996a]
- G3-299: Binds with higher affinity to monomer than to oligomer, slow association rate, although faster than other C4 MAbs tested, with more potent neutralization of lab strain. Sattentau & Moore [1995]
- G3-299: C4 region – binds HXB2 20mer KQIINMWQKVGKAMYAPPIS, and SF-2 and MN gp120s – G3-42, G3-299 lower affinity than G3-508, G3-519, and G3-536 – bound native gp120, not denatured – poor peptide binding, epitope spans V3-C4 regions – 433A/L, 435Y/H and 430V/S substitutions impaired binding, V3 loop cleavage or insertion abolished binding. Moore *et al.* [1993b]
- G3-299: Best neutralization of IIIB in panel of 7 MAbs that bind overlapping epitope. Sun *et al.* [1989]

No.	631
MAb ID	G3-42 (G3 42)
HXB2 Location	gp160 (429–438)
Author Location	gp120 (429–438 BRU)
Epitope	EVGKAMYAPP
Neutralizing	L
Immunogen	vaccine *Vector/Type:* virus derived protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype)	mouse (IgG1)
Ab Type	gp120 C4
Research Contact	Tanox Biosystems Inc and David Ho, ADARC, NY, NY
References	Koefoed *et al.* 2005; Zwick *et al.* 2003; Jagodzinski & Trzeciak 2000; Binley *et al.* 1999; Binley *et al.* 1997a; Trkola *et al.* 1996a; Poignard *et al.* 1996a; Moore & Sodroski 1996; Jagodzinski *et al.* 1996; Sattentau & Moore 1995; Thali *et al.* 1993; Moore *et al.* 1993b; Sun *et al.* 1989
Keywords	antibody binding site definition and exposure, antibody interactions

- G3-42: IgG antibody phage display libraries were created from HIV-1 + individuals after pre-selection of PBMC with gp120, as an alternative to using bone marrow for generating libraries. G3-42 was among a set of Abs used for competition studies to define the binding sites of the newly isolated MAbs, representing a MAb with a linear C4/V3 epitope. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**)
- G3-42: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the C4-V3 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- 0.5beta: MAbs 0.5beta and G3-42 were used to study synthesis of oligomeric and monomeric forms of Env – inhibition of glycosylation by tunicamycin results in reduction of oligomeric gp120 at the cell surface and of monomer in the cytoplasm – neither MAb recognized non-glycosylated Env precursor. Jagodzinski & Trzeciak [2000]
- G3-42: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999]
- G3-42: The sulfated polysaccharide curdlan sulfate (CRDS) binds to the Envelope of T-tropic viruses and neutralizes virus – CRDS potently inhibits G3-42 binding – G3-42 epitope described as KVGKAMYAPP. Jagodzinski *et al.* [1996]
- G3-42: Inhibits binding of many anti-V3, -CD4 binding site, and -C4 region MAbs – enhances binding of some anti-V2 region MAbs. Moore & Sodroski [1996]
- G3-42: Epitope described as KQIINMWQKVGKAMYAPPIS – binding resulted in slight gp120 dissociation from virus and exposure of the gp41 epitope for MAb 50-69. Poignard *et al.* [1996a]
- G3-42: Called G3 42 – Does not inhibit gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study – described as V3-C4 discontinuous epitope. Trkola *et al.* [1996a]
- G3-42: Binds with higher affinity to monomer than to oligomer, slow association rate. Sattentau & Moore [1995]
- G3-42: C4 region – binds HXB2 20mer KQIINMWQKVGKAMYAPPIS, and SF-2 and MN gp120s – G3-42, G3-299 have lower affinity than G3-508, G3-519, and G3-536 – bound native gp120, not denatured – poor peptide binding, epitope spans V3-C4 regions – 433A/L, 435Y/H and 430V/S substitutions impaired binding, V3 loop insertion abolished binding. Moore *et al.* [1993b]

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- G3-42: Inhibits binding of CD4 inducible MAb 48d. Thali *et al.* [1993]
- G3-42: Neutralization of IIIB but not RF. Sun *et al.* [1989]

No. 632
MAb ID G3-508 (G3 508)
HXB2 Location gp160 (429–438)
Author Location gp120 (429–438 BRU)
Epitope EVGKAMYAPP
Neutralizing L
Immunogen vaccine
Vector/Type: virus derived protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 C4
Research Contact M. Fung and Tanox Biosystems Inc and David Ho, ADARC, NY
References Binley *et al.* 1998; Parren *et al.* 1998a; Binley *et al.* 1997a; Trkola *et al.* 1996a; Poignard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; Moore *et al.* 1993b; Thali *et al.* 1993; Sun *et al.* 1989

- G3-508: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
- G3-508: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- G3-508: Inhibits binding of some V3, C4 and CD4 binding site MAbs, enhances binding of V2 region MAbs. Moore & Sodroski [1996]
- G3-508: Binding resulted in slight gp120 dissociation from virus and exposure of the gp41 epitope for MAb 50-69. Poignard *et al.* [1996a]
- G3-508: Called G3 508 – inhibits gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]
- G3-508: Binds with higher affinity to monomer than to oligomer, slow association rate. Sattentau & Moore [1995]
- G3-508: C4 region – binds HXB2 20mer KQIINMWQKVGKAMYAPPIS, and SF-2 and MN gp120s – bound denatured with 10 fold greater affinity than native – 433A/L, 435Y/H and 430V/S substitutions impaired binding. Moore *et al.* [1993b]
- G3-508: Inhibits binding of CD4 inducible MAb 48d. Thali *et al.* [1993]
- G3-508: Neutralization of IIIB and RF. Sun *et al.* [1989]

No. 633
MAb ID G3-519
HXB2 Location gp160 (429–438)
Author Location gp120 (429–438 BRU)
Epitope EVGKAMYAPP
Neutralizing L
Immunogen vaccine
Vector/Type: virus derived protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 C4
Research Contact Tanox Biosystems Inc and David Ho, ADARC, NY
References Zwick *et al.* 2003; Binley *et al.* 1999; Parren *et al.* 1998a; Wyatt *et al.* 1997; Binley *et al.* 1997a; Poignard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; D'Souza *et al.* 1994; Moore *et al.* 1993b; Moore & Ho 1993; Sun *et al.* 1989
Keywords antibody interactions

- G3-519: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the C4 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- G3-519: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999]
- G3-519: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- G3-519: Binds both gp120 and soluble gp120+gp41 complex efficiently, suggesting its gp120 epitope is not blocked by gp41 binding. Wyatt *et al.* [1997]
- G3-519: Non-reciprocal enhanced binding in the presence of the C5 MAb 1C1 and the C1 MAb 135/9 – reciprocal enhanced binding with some V2 MAbs. Inhibited binding the presence of some C4, V3 and CD4 binding site MAbs. Moore & Sodroski [1996]
- G3-519: Epitope described as KVGKAMYAPP – binding resulted in slight gp120 dissociation from virus but no signifi-

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cant exposure of the gp41 epitope for MAb 50-69. Poignard *et al.* [1996a]

- G3-519: Binds with higher affinity to monomer than to oligomer, slow association rate. Sattentau & Moore [1995]
- G3-519: Included in a multi-lab study for antibody characterization, and binding and neutralization assay comparison, also binds IIIB: IINMWQKVGKAMYAPP. D'Souza *et al.* [1994]
- G3-519: Neutralizes IIIB, is reactive with SF-2 gp120, mild inhibition of HIV-1 + sera binding to IIIB gp120. Moore & Ho [1993]
- G3-519: C4 region – binds HXB2 20mer KQIINMWQKVGKAMYAPPIS, and SF-2 and MN gp120s – bound denatured with 5 fold greater affinity than native – 433A/L, 435Y/H, 438P/R and 430V/S substitutions impaired binding. Moore *et al.* [1993b]
- G3-519: Best neutralization of RF in panel of 7 MAbs that bind overlapping epitope. Sun *et al.* [1989]

No. 634
MAb ID G3-536
HXB2 Location gp160 (429–438)
Author Location gp120 (429–438 BRU)
Epitope `EVGKAMYAPP`
Neutralizing L
Immunogen vaccine
Vector/Type: virus derived protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 C4
Research Contact Tanox Biosystems Inc and David Ho, ADARC, NY
References Parren *et al.* 1998a; Poignard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; Gorny *et al.* 1994; Moore *et al.* 1993b; Moore & Ho 1993; McKeating *et al.* 1992b; Cordell *et al.* 1991; Ho *et al.* 1991b; Sun *et al.* 1989

- G3-536: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- G3-536: Inhibits binding of some V3, C4 and CD4 binding site MAbs, enhances binding of V2 region MAbs. Moore & Sodroski [1996]
- G3-536: Epitope described as KVGKAMYAPP. Poignard *et al.* [1996a]
- G3-536: Binds with higher affinity to monomer than to oligomer, slow association rate. Sattentau & Moore [1995]
- G3-536: Enhances binding of anti-V2 MAb 697-D. Gorny *et al.* [1994]
- G3-536: Neutralizes IIIB, is reactive with SF-2 gp120, mild inhibition of HIV-1 + sera binding to IIIB gp120. Moore & Ho [1993]
- G3-536: C4 region – binds HXB2 20mer KQIINMWQKVGKAMYAPPIS, and SF-2 and MN gp120s – bound denatured with 15 fold greater affinity than native – 433A/L, 435Y/H, 438P/R, and 430V/S substitutions impaired binding. Moore *et al.* [1993b]
- G3-536: Weakly neutralizing – binds to a linear determinant in the CD4 binding domain of gp120. McKeating *et al.* [1992b]
- G3-536: Cross-competition with MAbs 5C2E5, ICR38.8f and ICR38.1a. Cordell *et al.* [1991]
- G3-536: Weak neutralization of IIIB and RF – cross-react with diverse strains by immunofluorescence – blocks HIV binding to CD4+ cells – epitope:IINMWQKVGKAMYAP. Sun *et al.* [1989]

No. 635
MAb ID ICR38.8f
HXB2 Location gp160 (429–438)
Author Location gp120 (429–438 BRU)
Epitope `EVGKAMYAPP`
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) rat (IgG2b)
Ab Type gp120 C4
References Moore *et al.* 1993b; Cordell *et al.* 1991

- ICR38.8f:ICR 38.1a and ICR 38.8f were initially reported to be independent MAbs, but are actually subclones of the same MAb. Moore *et al.* [1993b]
- ICR38.8f: Weakly neutralizing – binds linear determinant in the CD4 binding domain – cross-competition with ICR38.1a, 5C2E5, and G3-536. Cordell *et al.* [1991]

No. 636
MAb ID MO86/C3
HXB2 Location gp160 (429–443)
Author Location gp120 (429–443)
Epitope `EVGKAMYAPPISGQI`
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgM)
Ab Type gp120 C4
References Kanduc *et al.* 2008; Ohlin *et al.* 1992

- MO86/C3: Similarity level of the MO86/C3 binding site pentapeptide KAMYA to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- MO86: Generated in response to IIIB Env 286-467 upon *in vitro* stimulation of uninfected-donor lymphocytes. Ohlin *et al.* [1992]

No. 637
MAb ID 13H8
HXB2 Location gp160 (431–440)
Author Location gp120 (412–453)
Epitope `GKAMYAPPIS`
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN
Species (Isotype) mouse (IgG)
Ab Type gp120 C4
References Jeffs *et al.* 1996; Nakamura *et al.* 1993; Nakamura *et al.* 1992

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- 13H8: Binds V3 and C4 peptides (J. P. Moore, per. comm.)
- 13H8: 3 and 4.5 fold increased binding when V1/V2 or V1/V2 and V3 were deleted from gp120, respectively. Jeffs *et al.* [1996]
- 13H8: Bound diverse strains, neutralizing activity against MN. Nakamura *et al.* [1993]
- 13H8: Cross blocks 5C2 in IIIB-rsgp160 ELISA – reactive with diverse strains in rgp120 ELISA. Nakamura *et al.* [1992]

No. 638
MAb ID G45-60
HXB2 Location gp160 (431–440)
Author Location gp120 (429–438 BRU)
Epitope GKAMYAPPIS
Neutralizing L
Immunogen vaccine
Vector/Type: virus derived protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 C4
References Jagodzinski *et al.* 1996; Moore & Sodroski 1996; Gorny *et al.* 1994; Moore *et al.* 1993b; Sun *et al.* 1989

- G45-60: The sulfated polysaccharide curdlan sulfate (CRDS) binds to the Envelope of T-tropic viruses and neutralizes virus CRDS inhibits G45-60 binding. Jagodzinski *et al.* [1996]
- G45-60: Non-reciprocal enhancement of G45-60 binding by some C1 and C5 antibodies – reciprocal enhancement of some V2 region MAbs – reciprocal inhibition with many MAbs that bind to the V3, C4 and CD4 binding site regions. Moore & Sodroski [1996]
- G45-60: Enhances binding of anti-V2 MAb 697-D. Gorny *et al.* [1994]
- G45-60: C4 region – binds HXB2 20mer KQIIN-MWQKVGKAMYAPPI, decapeptide flanking peptides also bound – bound equivalently to native and denatured gp120 – 433A/L and 435Y/H (not 430V/S) substitutions impaired binding. Moore *et al.* [1993b]

No. 639
MAb ID polyclonal
HXB2 Location gp160 (432–451)
Author Location gp120 (42–61 LAI)
Epitope KAMYAPPISGQIRCSSNITG
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: vaccinia *HIV component:* Env
Species (Isotype) mouse
Ab Type gp120 C4
References Collado *et al.* 2000

- Vaccinia p14 can elicit NAbs and p39 tends to be immunodominant, so these two proteins were fused to regions of HIV-1 Env – reduced glycosylation was noted when p14 or p39 was placed in the N-term region of the fusion protein – chimeric proteins shifted the Env Ab response from V3 to either a C1 or C4 domain, depending on the construct – all chimeric Env proteins: 14kEnv, 39kEnv, and Env39k elicited a strong Ab response to the C1 region of gp120 (LFCAS-DAKAYDTEVHNVWAT), and Env39k mounted a strong response to the C4 region (KAMYAPPISGQIRCSSNITG) Collado *et al.* [2000]

No. 640
MAb ID 1662
HXB2 Location gp160 (433–439)
Author Location gp120 (IIIB)
Epitope AMYAPPI
Neutralizing no
Immunogen vaccine
Vector/Type: poliovirus *HIV component:* Env
Species (Isotype)
Ab Type gp120 C4
References McKeating *et al.* 1992b

- 1662: Did not bind to native gp120, epitope not exposed. McKeating *et al.* [1992b]

No. 641
MAb ID 1663
HXB2 Location gp160 (433–439)
Author Location gp120 (IIIB)
Epitope AMYAPPI
Neutralizing no
Immunogen vaccine
Vector/Type: poliovirus *HIV component:* Env
Species (Isotype)
Ab Type gp120 C4
References McKeating *et al.* 1992b

- 1663: Did not bind to native gp120, epitope not exposed. McKeating *et al.* [1992b]

No. 642
MAb ID 1664
HXB2 Location gp160 (433–439)
Author Location gp120 (IIIB)
Epitope AMYAPPI
Neutralizing no
Immunogen vaccine
Vector/Type: poliovirus *HIV component:* Env
Species (Isotype)
Ab Type gp120 C4
References McKeating *et al.* 1992b

- 1664: Did not bind to native gp120, epitope not exposed. McKeating *et al.* [1992b]

No. 643
MAb ID 1697
HXB2 Location gp160 (433–439)
Author Location gp120 (IIIB)
Epitope AMYAPPI
Neutralizing no
Immunogen vaccine
Vector/Type: poliovirus *HIV component:* Env
Species (Isotype)

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Ab Type gp120 C4
References McKeating *et al.* 1992b
- 1697: Did not bind to native gp120, epitope not exposed. McKeating *et al.* [1992b]

No. 644
MAb ID 1794
HXB2 Location gp160 (433–442)
Author Location gp120 (IIIB)
Epitope AMYAPPISGQ
Neutralizing no
Immunogen vaccine
Vector/Type: poliovirus *HIV component:* Env
Species (Isotype)
Ab Type gp120 C4
References McKeating *et al.* 1992b
- 1794: Did not bind to native gp120, epitope not exposed. McKeating *et al.* [1992b]

No. 645
MAb ID 1804
HXB2 Location gp160 (433–442)
Author Location gp120 (IIIB)
Epitope AMYAPPISGQ
Neutralizing no
Immunogen vaccine
Vector/Type: poliovirus *HIV component:* Env
Species (Isotype)
Ab Type gp120 C4
References McKeating *et al.* 1992b
- 1804: Did not bind to native gp120, epitope not exposed. McKeating *et al.* [1992b]

No. 646
MAb ID 1807
HXB2 Location gp160 (433–442)
Author Location gp120 (IIIB)
Epitope AMYAPPISGQ
Neutralizing no
Immunogen vaccine
Vector/Type: poliovirus *HIV component:* Env
Species (Isotype)
Ab Type gp120 C4
References McKeating *et al.* 1992b
- 1807: Did not bind to native gp120, epitope not exposed. McKeating *et al.* [1992b]

No. 647
MAb ID 1808
HXB2 Location gp160 (433–442)
Author Location gp120 (IIIB)
Epitope AMYAPPISGQ
Neutralizing no
Immunogen vaccine
Vector/Type: poliovirus *HIV component:* Env
Species (Isotype)
Ab Type gp120 C4
References McKeating *et al.* 1992b
- 1808: Did not bind to native gp120, epitope not exposed. McKeating *et al.* [1992b]

No. 648
MAb ID polyclonal (VEI5)
HXB2 Location gp160 (454–474)
Author Location Env
Epitope LTRDGGNNNNESEIFRPGGGD
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V1, gp120 V2, gp120 V3, gp120 V4, gp120 V5
References Carlos *et al.* 1999
- Antibody response to the epitopes in a vaccine construct (VEI) containing peptides from 5 hypervariable regions of gp120 was detected in the sera of HIV-1 positive subjects, including sera from 6 non-subtype B infections – serum samples from San Francisco, Canada and Puerto Rico cohort showed presence of antibodies against all five VEI hypervariable regions, but most consistently against the V3 region peptide NNNTRKSIRIGPGRAFYTTGDIGNIRQ. Carlos *et al.* [1999]

No. 649
MAb ID polyclonal
HXB2 Location gp160 (460–467)
Author Location gp120 (LAI)
Epitope NNNNGSEI
Subtype B
Neutralizing
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) human
Ab Type gp120 V5
References Loomis-Price *et al.* 1997
- HIV-1 + positive individuals were given a gp160 vaccine as immunotherapy, and this region was the most reactive new epitope as measured by a modified Pepscan technique which improved sensitivity – 4/14 showed vaccine-induced reactivity. Loomis-Price *et al.* [1997]

No. 650
MAb ID CRA1 (CRA-1, CRA1(ARP 323))
HXB2 Location gp160 (461–470)
Author Location gp120 (451–470 LAI)
Epitope SNNESEIFRL
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 V5-C5
Research Contact M. Page, NIBSC, UK

References Koefoed *et al.* 2005; Yang *et al.* 2000; Trkola *et al.* 1996a; Moore & Sodroski 1996; Moore *et al.* 1994c; Moore *et al.* 1994d; Moore & Ho 1993

Keywords antibody binding site definition and exposure

- CRA1: UK Medical Research Council AIDS reagent: ARP323.
- CRA1: IgG antibody phage display libraries were created from HIV-1 + individuals after pre-selection of PBMC with gp120, as an HIV-1 + alternative to using bone marrow for generating libraries. CRA1 was among a set of Abs used for competition studies to define the binding sites of the newly isolated MAbs, representing a MAb with a linear C5 epitope. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**)
- CRA1: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000]
- CRA1: C5 region linear epitope, binds weakly to nondenatured monomeric gp120 – reciprocal binding inhibition with anti-C5 antibodies 1C1 and M91 – non-reciprocal binding enhancement some C1 and V2 antibodies – non-reciprocal binding inhibition of some CD4 binding site antibodies. Moore & Sodroski [1996]
- CRA1: Does not neutralize JR-FL nor block gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]
- CRA1: Some C5 mutations abrogate binding 470 P/L or G, 475 M/S, some C2 mutations enhance binding. Moore *et al.* [1994d]
- CRA1: The relative affinity for denatured/native gp120 is 24 – C5 mutations 470 P/L or G, 475 M/S impairs binding to the native gp120 – only mutation 470 P/L impairs binding to denatured. Moore *et al.* [1994c]
- CRA1: Bound preferentially to denatured IIIB and SF2 gp120. Moore & Ho [1993]

No. 651
MAb ID M91
HXB2 Location gp160 (461–470)
Author Location gp120 (451–470 LAI)
Epitope SNNESEIFRL
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Env
Species (Isotype) rat (IgG2a)
Ab Type gp120 V5-C5
Research Contact Fulvia di Marzo Veronese

References Zwick *et al.* 2003; Yang *et al.* 2000; Binley *et al.* 1998; Ditzel *et al.* 1997; Moore & Sodroski 1996; Moore *et al.* 1994d; Moore *et al.* 1994c; di Marzo Veronese *et al.* 1992

Keywords antibody interactions

- M91: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a C5-binding MAb that had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
- M91: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000]
- M91: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
- M91: C5 region linear epitope, binds weakly to nondenatured monomeric gp120 – M91 binding was enhanced by 1C1, but 1C1 binding was inhibited by M91 – non-reciprocal binding enhancement of C1 and V2 antibodies – non-reciprocal binding inhibition of CD4 binding site antibodies. Moore & Sodroski [1996]
- M91: The relative affinity for denatured/native gp120 is 24 – mutation in position 470 P/L impairs binding. Moore *et al.* [1994c]
- M91: 470 P/L impairs binding, but not 475 D/V, in contrast to CRA1 – some C2 mutations can enhance binding. Moore *et al.* [1994d]
- M91: Immunoblot reactive, RIP negative, but precipitates deglycosylated gp120 – reacts with strains IIIB, 451, MN, RF, and RUTZ. di Marzo Veronese *et al.* [1992]

No. 652
MAb ID 9201
HXB2 Location gp160 (471–482)
Author Location gp120 (475–486 LAI)
Epitope GGGDMRDNWRSE
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: peptide
Species (Isotype) mouse (IgG1)
Ab Type gp120 C5

Research Contact Du Pont de Nemours, Boston, MA
References Dairou *et al.* 2004; McDougal *et al.* 1996
Keywords antibody binding site definition and exposure

- 9201: This paper describes a slightly different epitope, stating 9201 was raised against the peptide MRDNWRSELIKY, located within the alpha 5 helix in the C5 terminal region of gp120. Two MAbs were used to determine the photodamage location in HIV-1 Env induced by sulfonated anionic porphyrins. The negatively charged porphyrins interact with positive charge in the V3 loop. When light activated, they damage amino acid side chains in the C5 region of Env, as evidenced by inhibition of binding of C5 MAb 9201, but not V3 MAb 13105100. Anionic porphyrins could be used in targeted photodynamic decontamination of biological fluids, such as blood, killing HIV without disabling the function of desirable transfusion products. Dairou *et al.* [2004] (**antibody binding site definition and exposure**)
- 9201: Does not neutralize LAI. This paper notes the peptide binding region is GGGDMRDNWRSE. McDougal *et al.* [1996] (**antibody binding site definition and exposure**)

No. 653
MAb ID 1C1
HXB2 Location gp160 (471–490)
Author Location gp120 (471–490 LAI)
Epitope `GGGDMRDNWRSELYKYKVVK`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C5
Research Contact Repligen Inc, Cambridge, MA, commercial
References Zwick *et al.* 2003; Moore & Sodroski 1996; VanCott *et al.* 1995; Moore *et al.* 1994d; Moore *et al.* 1994c
Keywords antibody interactions

- 1C1: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a C5-binding MAb that had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
- 1C1: C5 region linear epitope, binds weakly to nondenatured monomeric gp120 – M91 binding was enhanced by 1C1, but 1C1 binding was inhibited by M91 – non-reciprocal binding enhancement of some C1 and V2 antibodies – non-reciprocal binding inhibition of some CD4 binding site antibodies. Moore & Sodroski [1996]
- 1C1: Linear epitope not exposed on conformationally intact gp120. VanCott *et al.* [1995]
- 1C1: The relative affinity for denatured/native gp120 is 15. Moore *et al.* [1994c]
- 1C1: C2 and V3 regions substitutions can influence binding. Moore *et al.* [1994d]

No. 654
MAb ID 3F5
HXB2 Location gp160 (471–490)
Author Location gp120 (471–490 LAI)
Epitope `GGGDMRDNWRSELYKYKVVK`
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C5
Research Contact S. Nigida, NCI, USA
References Moore *et al.* 1994c

- 3F5: The relative affinity for denatured/native gp120 is 100. Moore *et al.* [1994c]

No. 655
MAb ID 5F4/1
HXB2 Location gp160 (471–490)
Author Location gp120 (471–490 LAI)
Epitope `GGGDMRDNWRSELYKYKVVK`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* HIV-2 ROD
Species (Isotype) mouse
Ab Type gp120 C5
Research Contact S. Ranjbar, NIBSC, UK
References Moore *et al.* 1994c

- 5F4/1: V5-C5 region – preferentially binds SDS-DTT denatured gp120 (>10 fold) – mutation 485 K/V impairs binding. Moore *et al.* [1994c]

No. 656
MAb ID 660-178
HXB2 Location gp160 (471–490)
Author Location gp120 (471–490 LAI)
Epitope `GGGDMRDNWRSELYKYKVVK`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C5
Research Contact G. Robey, Abbott Labs
References Moore *et al.* 1994d; Moore *et al.* 1994c

- 660-178: The relative affinity for denatured/native gp120 is >100. Moore *et al.* [1994c]
- 660-178: DeltaV1/V2 and DeltaV1/V2/V3 reduce binding – C2 and C5 mutations enhance binding. Moore *et al.* [1994d]

No. 657
MAb ID 9301
HXB2 Location gp160 (471–490)
Author Location gp120 (471–490 LAI)
Epitope `GGGDMRDNWRSELYKYKVVK`
Subtype B
Neutralizing
Immunogen vaccine

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Vector/Type: protein *Strain:* B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C5
Research Contact Dupont, commercial
References Wagner *et al.* 1996; Moore *et al.* 1994d; Moore *et al.* 1994c; Moore & Ho 1993; Skinner *et al.* 1988b

- 9301: Wagner *et al.* claim that Nea 9301 is anti-V3 – might they have meant MAb 9305? Wagner *et al.* [1996]
- 9301: The relative affinity for denatured/native gp120 is 19. Moore *et al.* [1994d]
- 9301: Bound preferentially to denatured IIIB gp120. Moore & Ho [1993]

No. 658
MAb ID B221 (221)
HXB2 Location gp160 (471–490)
Author Location gp120 (471–490 LAI)
Epitope `GGGDMRDNWRSELYKYKVVK`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43 *HIV component:* gp160
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 C5
Research Contact Rod Daniels
References Billington *et al.* 2007; Holl *et al.* 2006a; Moore *et al.* 1994d; Moore *et al.* 1994c; Bristow *et al.* 1994; Moore & Ho 1993
Keywords dendritic cells, neutralization

- B221: UK Medical Research Council AIDS reagent: ARP301.
- B221: Called 221. The MAb CA13 binds to the conserved C1 epitope EDIISLW and was used in conjunction with MAb 221, a MAb that binds to the gp120 C-terminal end, to explore the composition and stability of a highly stable trimeric rgp140 derived from a HIV-1 subtype D isolate containing inter-monomer V3-derived disulfide bonds and lacking gp120/gp41 proteolytic processing. The stability of the trimer indicates it may be a good candidate for structural studies. Billington *et al.* [2007]
- 221: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication occurs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- B221: MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp160 IIIB:NL43, MicroGenSys. Bristow *et al.* [1994]
- B221: The relative affinity for denatured/native gp120 is 12 – mutation 477 D/V impairs binding. Moore *et al.* [1994c]
- B221: Called 221 – C2 and V3 substitutions influence binding. Moore *et al.* [1994d]
- B221: Called 221 – bound preferentially to denatured IIIB gp120. Moore & Ho [1993]

No. 659
MAb ID 8C6/1
HXB2 Location gp160 (471–490)
Author Location gp120 (471–490 LAI)
Epitope `GGGDMRDNWRSELYKYKVVK`
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI
Species (Isotype) mouse (IgG)
Ab Type gp120 V5-C5
Research Contact S. Ranjbar, NIBSC, UK
References Moore *et al.* 1994c

- 8C6/1: UK Medical Research Council AIDS reagent: ARP3052.
- 8C6/1: V5-C5 region – preferentially binds SDS-DTT denatured gp120 (>30 fold) – mutation 485 K/V impairs binding. Moore *et al.* [1994c]

No. 660
MAb ID H11
HXB2 Location gp160 (472–477)
Author Location gp120 (472–477 HXB2)
Epitope `GGDMRD`
Subtype B
Neutralizing
Immunogen
Species (Isotype) mouse
Ab Type gp120 C5
References Pincus *et al.* 1996; Pincus & McClure 1993

- H11: Binds to gp120 but not to infected cells – when linked to ricin A, the immunotoxin did not mediate cell killing – sCD4 has no effect. Pincus & McClure [1993]; Pincus *et al.* [1996]

No. 661
MAb ID W2
HXB2 Location gp160 (472–491)
Author Location gp120 (472–491 LAI)
Epitope `GGDMRDNWRSELYKYKVVKI`
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade LAI *HIV component:* Env
Species (Isotype) mouse (IgG)
Ab Type gp120 C5
Research Contact D. Weiner, U. Penn., USA
References Moore *et al.* 1994c

- W2: The relative affinity for denatured/native gp120 is 30 – mutation 485 K/V impairs binding. Moore *et al.* [1994c]

No. 662
MAb ID M38
HXB2 Location gp160 (485–504)
Author Location gp120 (490–508)
Epitope `KYKVVKEIPLGVAPTKAKRR`
Neutralizing no
Immunogen vaccine
Vector/Type: virus *Strain:* B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse
Ab Type gp120 C5

References Maksiutov *et al.* 2002; Beretta & Dalgleish 1994; DeSantis *et al.* 1994; Lopalco *et al.* 1993; Grassi *et al.* 1991; Beretta *et al.* 1987

- M38: This epitope is similar to a fragment of the human protein mast/stem cell growth factor receptor precursor, VVPTKADKRRSV, as well as to a fragment of IFN-related IFRD2 (PC4-B) protein, ARTKARSRVRDKRA. Maksiutov *et al.* [2002]
- M38: Infected individuals have HLA class I-gp120 cross-reactive antibodies. DeSantis *et al.* [1994]
- M38: Binds to the carboxy terminus of gp120, in a gp41 binding region, and also to denatured human HLAs (antigenic homology) Lopalco *et al.* [1993]
- M38: Binds to gp120 and to a 80 kd human protein expressed on a small fraction of mononuclear cells in the lymph nodes. Beretta *et al.* [1987]

No. 663
MAb ID polyclonal
HXB2 Location gp160 (490–511)
Author Location gp120 (495–516 BRU)
Epitope KIEPLGVAPTKAKRRVVQREKR
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human
References Maksiutov *et al.* 2002; Hernandez *et al.* 2000

- This epitope is similar to a fragment of the human protein mast/stem cell growth factor receptor precursor, VVPTKADKRRSV, as well as to a fragment of IFN-related IFRD2 (PC4-B) protein, ARTKARSRVRDKRA. Maksiutov *et al.* [2002]
- Chimeric peptide combining two peptides gp160(495-516 and 584-612) served as a specific and broadly reactive antigen for diagnostic detection of HIV-1. Hernandez *et al.* [2000]

No. 664
MAb ID 110.1
HXB2 Location gp160 (491–500)
Author Location gp120 (491–500 LAI)
Epitope IEPLGVAPTK
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: HIV infected-cell lysate *Strain:* B clade BRU *HIV component:* HIV-1
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 C5
Research Contact Genetic Systems Corp, Seattle WA, E. Kinney-Thomas
References Kanduc *et al.* 2008; Maksiutov *et al.* 2002; Valenzuela *et al.* 1998; Binley *et al.* 1997a; McDougal *et al.* 1996; Cook *et al.* 1994; Moore *et al.* 1994c; Callahan *et al.* 1991; Pincus *et al.* 1991; Thomas *et al.* 1988; Linsley *et al.* 1988; Gosting *et al.* 1987
Keywords antibody binding site definition and exposure, immunotoxin

- 110.1 database comment: There is another antibody with this ID that binds to gp120, but at aa 200-217.
- 110.1: Similarity level of the 110.1 binding site pentapeptide IPIHY to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 110.1: This epitope is similar to a fragment of the human protein mast/stem cell growth factor receptor precursor, VVPTKADKRRSV. Maksiutov *et al.* [2002]
- 110.1: Does not effect LAI viral binding or entry into CEM cells. Valenzuela *et al.* [1998]
- 110.1: Does not neutralize HIV-1 LAI. McDougal *et al.* [1996]
- 110.1: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – MAbs against the carboxy-terminus of gp120 inhibit gp120 binding to GalCer but not as potently as anti-V3 MAbs – binding of GalCer to gp120 does not inhibit MAb binding. Cook *et al.* [1994]
- 110.1: The relative affinity for denatured/native gp120 is 0.7. Moore *et al.* [1994c] (**antibody binding site definition and exposure**)
- 110.1: Polyanionic polysaccharides were proposed to inhibit viral functions such as binding and syncytia formation through interations mediated through the local high positive charge density in the V3 loop. The binding of this antibody is not inhibited by dextransulfate, in contrast to anti-V3 antibodies. Callahan *et al.* [1991]
- 110.1: Difference was noted in the epitope: mapped to aa 421-429 (KQIINMWQE), the T1 sequence – poor efficacy as an immunotoxin when linked to RAC. Pincus *et al.* [1991] (**antibody binding site definition and exposure**, **immunotoxin**)
- 110.1: Referred to as 110-1 – does not inhibit CD4-gp120 binding or neutralize HIV-1 strains. Linsley *et al.* [1988]

No. 665
MAb ID 42F
HXB2 Location gp160 (491–500)
Author Location gp120 (491–500 HXB2)
Epitope IEPLGVAPTK
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 C5
References Maksiutov *et al.* 2002; Alsmadi & Tilley 1998; Alsmadi *et al.* 1997

- 42F: This epitope is similar to a fragment of the human protein mast/stem cell growth factor receptor precursor, VVPTKADKRRSV. Maksiutov *et al.* [2002]
- 42F: A study of 6 anti-Env MAbs and their ability to bind or direct ADCC against target cells infected with IIIB, MN, SF-2, and RF – bound and directed lysis against strains IIIB, MN, SF-2, and RF, but not a clone of MN. Alsmadi & Tilley [1998]
- 42F: 42F and 43F were isolated from a long term non-progressor by EBV transformation of PBMC – samples were taken 14 months apart – both MAbs stained diverse strains of infected cells and directed ADCC – were more potent for

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ADCC if the cell was infected with HIV-1, rather than just presenting absorbed gp120. Alsmadi *et al.* [1997]

No. 666
MAb ID 43F
HXB2 Location gp160 (491–500)
Author Location gp120 (491–500 HXB2)
Epitope `IEPLGVAPTK`
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 C5
References Maksiutov *et al.* 2002; Alsmadi *et al.* 1997

- 43F: This epitope is similar to a fragment of the human protein mast/stem cell growth factor receptor precursor, VVPTKADKRRSV. Maksiutov *et al.* [2002]
- 43F: 42F and 43F were isolated from a long term non-progressor by EBV transformation of PBMC – samples were taken 14 months apart – both MAbs stained diverse strains of infected cells and directed ADCC – were more potent for ADCC if the cell was infected with HIV-1, rather than just presenting absorbed gp120. Alsmadi *et al.* [1997]

No. 667
MAb ID RV110026
HXB2 Location gp160 (491–500)
Author Location gp120 (491–500 LAI)
Epitope `IEPLGVAPTK`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade LAI
Species (Isotype) human
Ab Type gp120 C5
Research Contact Commercial, Olympus Inc
References Maksiutov *et al.* 2002; Moore *et al.* 1994d; Moore *et al.* 1994c

- RV110026: This epitope is similar to a fragment of the human protein mast/stem cell growth factor receptor precursor, VVPTKADKRRSV. Maksiutov *et al.* [2002]
- RV110026: Preferentially binds SDS-DTT denatured gp120 (15 fold using R1/87 as capture reagent) Moore *et al.* [1994c]

No. 668
MAb ID Chim 1 (C-1)
HXB2 Location gp160 (492–498)
Author Location gp120 (492–498 HXB2)
Epitope `EPLGVAP`
Subtype B
Neutralizing
Immunogen
Species (Isotype) humanized chimpanzee
References Pincus *et al.* 1996; Pincus & McClure 1993

- Chim 1: Binds to gp120 but not to infected cells – when linked to ricin A, the immunotoxin did not mediate cell killing – sCD4 has no effect. Pincus & McClure [1993]; Pincus *et al.* [1996]

No. 669
MAb ID 105-306
HXB2 Location gp160 (492–500)
Author Location gp120 (HAM112, O group)
Epitope `KPFSVAPTP`
Subtype O
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* O group HAM112 *HIV component:* gp160
Species (Isotype) mouse (IgG1κ)
Ab Type C-term
References Scheffel *et al.* 1999

- 105-306: Overlapping peptides based on group O HAM112 Env were tested for MAb reactivity – 105-306 bound to two overlapping peptides. Scheffel *et al.* [1999]

No. 670
MAb ID GV1G2
HXB2 Location gp160 (494–499)
Author Location gp120 (494–499 IIIB)
Epitope `LGVAPT`
Neutralizing
Immunogen vaccine
Vector/Type: protein-Ab complex *HIV component:* gp120-Mab complex
Species (Isotype) mouse
Ab Type gp120 C5
References Denisova *et al.* 1996

- GV1G2: When anti-V3 MAb M77 was bound to gp120 and used as an immunogen, it stimulated many MAbs to linear epitopes – MAbs GV12F6 and GV3H1 are homologous to GV1G2 and were generated in the same experiment. Denisova *et al.* [1996]

No. 671
MAb ID 750-D
HXB2 Location gp160 (498–504)
Author Location gp120 (503–509)
Epitope `PTKAKRR`
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG3λ)
Ab Type C-term
References Hioe *et al.* 2000; Forthal *et al.* 1995

- 750-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – CD4BS MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – C5 MAbs 450-D and 750-D did not effect proliferation. Hioe *et al.* [2000]
- 750-D: Not neutralizing, positive ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995]

No. 672
MAb ID 450-D (450-D-3, 450D, 450)
HXB2 Location gp160 (498–504)
Author Location gp120 (475–486 BH10)
Epitope `PTKAKRR(orRRVVQRE,orMRDNWRSELYKY-dependingonreference)`
Neutralizing no

Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 C5
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU Med Center, NY, NY
References Visciano *et al.* 2008a; Holl *et al.* 2006a; Verrier *et al.* 2001; Hioe *et al.* 2001; Hioe *et al.* 2000; Hioe *et al.* 1997b; Li *et al.* 1997; Manca *et al.* 1995a; Forthal *et al.* 1995; Cook *et al.* 1994; Gorny *et al.* 1994; Laal *et al.* 1994; Spear *et al.* 1993; Karwowska *et al.* 1992b; Karwowska *et al.* 1992a; Durda *et al.* 1988
Keywords dendritic cells, neutralization

- 450: A mouse CD4 T cell clone proliferated well in response to gp120 alone, and while this response was inhibited when gp120 was complexed with anti-CD4bs Abs, the addition of 450 mAb did not cause any inhibition. These results indicate that anti-CD4bs Abs, but not anti-C5 Abs, inhibit CD4 T cell responses in the murine system. Visciano *et al.* [2008a]
- 450-D: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 450-D: CD4BS MAbs when complexed with gp120, inhibit proliferation of gp120-specific CD4 T-cells and IFN gamma production – 450-D does not have this effect and was used as a control in this study. Hioe *et al.* [2001]
- 450-D: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001]
- 450-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – CD4BS MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – C5 MAbs 450-D and 750-D did not effect proliferation. Hioe *et al.* [2000]
- 450-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D)and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b]
- 450-D: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env – 50% neutralization could not be achieved at a maximal concentration of 6 mug/ml. Li *et al.* [1997]
- 450-D: No neutralizing activity, no ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995]
- 450-D: Virions complexed to gp120 Ab facilitate presentation of p66 RT epitopes to Th cells. Manca *et al.* [1995a]
- 450-D: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – MAbs against the carboxy-terminus of gp120 do not inhibit gp120 binding to GalCer – binding of GalCer to gp120 does not inhibit MAb binding. Cook *et al.* [1994]
- 450-D: Epitope is defined as PTKAKRR. Gorny *et al.* [1994]
- 450-D: Not neutralizing alone, could synergize anti-CD4 binding site antibody neutralization. Laal *et al.* [1994]
- 450-D: Did not mediate deposition of complement component C3 on HIV infected cells. Spear *et al.* [1993]
- 450-D: Bound to MN, SF-2 and IIIB, but was not neutralizing. Karwowska *et al.* [1992a]

No. 673
MAb ID 670-D (670, 670D, 670-30D)
HXB2 Location gp160 (498–504)
Author Location gp120 (503–509)
Epitope PTKAKRR
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 C5
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU, NY
References Visciano *et al.* 2008a; Harada *et al.* 2008; Holl *et al.* 2006a; Kim *et al.* 2005; Kang *et al.* 2005; Gorny *et al.* 2005; Zwick *et al.* 2003; Verrier *et al.* 2001; Nyambi *et al.* 2000; Gorny & Zolla-Pazner 2000; Altmeyer *et al.* 1999; Nyambi *et al.* 1998; Gorny *et al.* 1998; Hioe *et al.* 1997b; Gorny *et al.* 1997; Hill *et al.* 1997; Forthal *et al.* 1995; Zolla-Pazner *et al.* 1995
Keywords antibody binding site definition and exposure, antibody interactions, binding affinity, dendritic cells, enhancing activity, neutralization

- 670-30D: Post-attachment enhancement (PAE), which augmented the level of HIV-1 cell infection by 1.4-fold, was not inhibited by 670-30D non-neutralizing mAB, but was inhibited by anti-V3 neutralizing mAbs 0.5β and 694/98-D. Unlike the neutralizing Abs, 670-30D did not suppress the fluidity of the viral and plasma envelopes. It is suggested that the binding of the neutralizing Abs to the viral surface could affect steric alternations of the viral envelope and restrain the envelope from enhancing its fluidity. Thus, suppression of the fluidity of viral envelope could be one additional mechanism for virus neutralization by anti-V3 neutralizing mAbs. Harada *et al.* [2008] (**antibody interactions**, **enhancing activity**, **neutralization**)

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- 670: Mice immunized with gp120-654 complex showed lower levels of lymphoproliferation than mice immunized with gp120-670 complex, indicating that anti-CD4bs Abs supress the induction of CD4 T cell responses in vivo, while anti-C5 Abs do not. However, mice immunized with gp120/654 Ab displayed faster kinetics and higher levels of gp120-specific serum IgG and IgA, but not IgM, indicating that immunization with gp120 in the presence of anti-CD4 Ab alters the immunogenicity of gp120 such that the immune response is dominated by anti-gp120 IgG. Visciano *et al.* [2008a]
- 670D: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 670: 2909 is a human anti-Env NAb that was selected by neutralization assay and binds to the quaternary structure on the intact virion. ELISA-based competition assays and subsequent mutational analysis determined that the CD4BS and V2 and V3 loops contribute to the 2909 epitope: 2909 binding was inhibited by MAbs 447-52d (anti-V3), 830A (anti-V2), and IgG1b12 (anti-CD4BS) and sCD4. 2909 was not inhibited by MAbs 670, 1418, nor 2G12. Gorny *et al.* [2005]
- 670-30D: A series of genetically modified Env proteins were generated and expressed in both insect and animal cells to be monitored for their antigenic characteristics. 670-30D did not show differences in binding affinities to any of the modified Env proteins or the wildtype. Kang *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)
- 670-30D: A trimeric recombinant gp140 construct was developed for immunization studies. Its structural integrity was assessed by a panel of MAbs. 670-30D recognized both the trimeric gp140 and the monomeric gp120, however, it showed preference for gp120. Kim *et al.* [2005] (**antibody binding site definition and exposure**)
- 670-D: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a C5-binding MAb that had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
- 670-D: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001]
- 670-D: A gp120 C5 MAb used as a negative control in a study of anti-gp41 MAbs. Gorny & Zolla-Pazner [2000]
- 670-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 4 C5 MAbs, 2 bound well, 2 bound weakly – MAb 670-D bound 21/26, and was the most cross-reactive C5 MAb. Nyambi *et al.* [2000]
- 670-D: A Semliki Forest virus (SFV) expression system carrying BX08 env was used to study the conformation of gp120 – intracytoplasmic gp120 was recognized by the anti-V3 MAbs K24 and F5.5, while gp120 at the plasma membrane was detected only by conformation dependent MAbs 2G12, 670-D and 694/98D and not V3 MAbs – expression in rat brain also showed that surface-expressed Env was recognized only by the conformation-dependent antibodies and not by anti-V3 antibodies. Altmeyer *et al.* [1999]
- 670-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – anti-C5 Abs 670-D and 1331A bound to 3/4 B clade viruses (they didn't bind to IIIB), and to subtype D MAL – 670-D also reacted with subtype A. Nyambi *et al.* [1998]
- 670-D: gp120 can inhibit MIP-1alpha from binding to CCR5, but this inhibitory effect is blocked by pre-incubation of gp120 with three anti-V3 MAbs: 447, 257, 1027 – MAb 670 which binds in the C5 region had no effect. Hill *et al.* [1997]
- 670-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D)and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b]
- 670-D: Not neutralizing, positive ADCC activity, and no viral enhancing activity, numbering provided suggests epitope is RRVVQRE. Forthal *et al.* [1995]
- 670-D: Group specific cross-clade binding in serotyping study using flow-cytometry. Zolla-Pazner *et al.* [1995]

No.	674
MAb ID	158F3
HXB2 Location	gp160 (499–511)
Author Location	gp120 (BaL)
Epitope	TKAKRRVVQREKR
Subtype	B
Neutralizing	no
Immunogen	vaccine *Vector/Type:* gp120-CD4 complex *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype)	humanized mouse (IgG2κ)
Ab Type	C-term
Research Contact	Abraham Pinter, Lab. of Retrovirology, Public Research Institute, pinter@phri.org
References	He *et al.* 2003
Keywords	antibody binding site definition and exposure, vaccine antigen design

- 158F3: Vaccination of a gp120-CD4 fusion complex in six transgenic XMG2 XenoMouse mice that produce human IgG2 with K light chain did not produce any neutralizing antibodies. 36/39 MAbs derived from one of these mice were in one

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of two competition groups that were conformational and specific for the complex, suggesting this chimeric vaccine may be of little value, as immunodominant responses are to epitopes unique to the complex, not present in native Env. This MAb is one of the 3/36 non-neutralizing MAbs that bound to linear epitopes on gp120. He *et al.* [2003] (**antibody binding site definition and exposure**, **vaccine antigen design**)

No. 675
MAb ID 161D7
HXB2 Location gp160 (499–511)
Author Location gp120 (BaL)
Epitope TKAKRRVVQREKR
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: gp120-CD4 complex *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) humanized mouse (IgG2κ)
Ab Type C-term
Research Contact Abraham Pinter, Lab. of Retrovirology, Public Research Institute, pinter@phri.org
References He *et al.* 2003
Keywords antibody binding site definition and exposure, vaccine antigen design

- 161D7: Vaccination of a gp120-CD4 fusion complex in six transgenic XMG2 XenoMouse mice that produce human IgG2 with K light chain did not produce any neutralizing antibodies. 36/39 MAbs derived from one of these mice were in one of two competition groups that were conformational and specific for the complex, suggesting this chimeric vaccine may be of little value, as immunodominant responses are to epitopes unique to the complex, not present in native Env. This MAb is one of the 3/36 non-neutralizing MAbs that bound to linear epitopes on gp120. He *et al.* [2003] (**antibody binding site definition and exposure**, **vaccine antigen design**)

No. 676
MAb ID polyclonal
HXB2 Location gp160 (503–509)
Author Location gp120 (471–477)
Epitope RRVVQRE
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp120
Species (Isotype) mouse (IgG)
References Jeyarajah *et al.* 1998

- Mice were immunized with peptide APTKAKRRVVQREKR – epitope excision and extraction combined with mass spectrometry was used to map the fine structure of epitopes recognized by polyclonal Ab to HIV-1 Env – a major epitope was identified between positions 472 and 478. Jeyarajah *et al.* [1998]

No. 677
MAb ID 722-D
HXB2 Location gp160 (503–509)
Author Location gp120 (503–509)
Epitope RRVVQRE
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type C-term
References Holl *et al.* 2006a; Forthal *et al.* 1995; Laal *et al.* 1994
Keywords dendritic cells, neutralization

- 722-D: This Ab did not inhibit HIV-1 BaL replication in macrophages. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 722-D: No neutralizing activity, no ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995]
- 722-D: Not neutralizing alone, could synergize anti-CD4 binding site antibody neutralization. Laal *et al.* [1994]

No. 678
MAb ID polyclonal
HXB2 Location gp160 (503–511)
Author Location gp120 (508–516)
Epitope RRVVQREKR
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type C-term
References Loomis-Price *et al.* 1997; Palker *et al.* 1987

- Most HIV-1 + individuals have an antibody response to this epitope – in this study, reactivity to RRVVQREKR was used as a positive control for HIV-1 + gp160 vaccine recipients. Loomis-Price *et al.* [1997]

No. 679
MAb ID 1331A
HXB2 Location gp160 (503–511)
Author Location gp120 (510–516)
Epitope dwVVQREKR
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG3λ)
Ab Type gp120 C5
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Visciano *et al.* 2008b; Holl *et al.* 2006a; Zwick *et al.* 2003; Edwards *et al.* 2002; Gorny *et al.* 2002; Nyambi *et al.* 2000; Hochleitner *et al.* 2000b; Gorny *et al.* 2000; Nyambi *et al.* 1998
Keywords antibody binding site definition and exposure, neutralization

- 1331A: A significantly higher level of anti-V3 Abs (694/98D and 447-52D) and anti-C1 mAb (EH21) bound to gp120 complexed with anti-CD4bs mAbs than to gp120 alone or in complex with other non-CD4bs Abs, while no enhancement was seen with the binding of 1331A, indicating that binding of anti-CD4bs Abs to gp120 increases exposure of specific V3 and C1, but not C5, mAb epitopes. Visciano *et al.* [2008b] (**antibody binding site definition and exposure**)

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- 1331A: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**)
- 1331A: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a C5-binding MAb that had no impact on 4KG5 binding. Zwick *et al.* [2003]
- 1331A: Truncation of the gp41 cytoplasmic domain of X4, R5, and X4R5 viruses forces a conformation that more closely resembles the CD4 bound state of the external Envelope, enhancing binding of CD4i MAbs 17b and 48d and of CD4BS MAbs F105, b12, and in most cases of glycosylation site dependent MAb 2G12 and the anti-gp41 MAb 246D – in contrast, binding of the anti-V2 MAb 697D and the anti-V3 MAb 694/98D were not affected – viruses bearing the truncation were more sensitive to neutralization by MAbs 48d, b12, and 2G12 – the anti-C5 MAb 1331A was used to track levels of cell surface expression of the mutated proteins. Edwards *et al.* [2002]
- 1331A: Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions and the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control as binding was not diminished by treating gp120 with DTT or sodium metaperiodate to reduce disulfide bonds), and MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades). Gorny *et al.* [2002]
- 1331A: Core epitope dwVVQREKR maps to gp120(510-516) – binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – C5 MAbs 858-D, 989-D and 1331A bound with a 5-10 fold preference for the monomer. Gorny *et al.* [2000]
- 1331A: The Ab binding site was studied with epitope excision (protein is bound in native conformation to immobilized MAb, then digested with proteolytic enzymes) and extraction (protein is digested then allowed to react with Ab), followed by mass spectroscopy – two non-contiguous aa in C5 were protected, E-507 and I-487, which are thought to be located on opposite sides of hydrophobic pocket involved in gp120/gp41 interaction. Hochleitner *et al.* [2000b]
- 1331A: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 4 C5 MAbs, 2 bound well, 2 bound weakly – MAb 858-D bound only 4/26, the worst of all anti-C5 MAbs tested, while MAb 1331A, which shares the same core epitope (positions 495-516), bound to 18/26. Nyambi *et al.* [2000]
- 1331A: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – anti-C5 Abs 670-D and 1331A bound to 3/4 B clade viruses (they don't bind to IIIB), and to subtype D MAL. Nyambi *et al.* [1998]

No. 680
MAb ID 1131-A
HXB2 Location gp160 (505–511)
Author Location gp120 (510–516 LAI)
Epitope VVQREKR
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG3λ)
Ab Type C-term
References Bandres *et al.* 1998

- 1131-A: A very high affinity antibody used in studies that demonstrate that CXCR4 can bind to gp120 in the absence of CD4-gp120 interactions, and that this binding can be enhanced by Env deglycosylation. Bandres *et al.* [1998]

No. 681
MAb ID 858-D
HXB2 Location gp160 (505–511)
Author Location gp120 (510–516 LAI)
Epitope VVQREKR
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type C-term
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Holl *et al.* 2006a; Nyambi *et al.* 2000; Gorny *et al.* 2000; Forthal *et al.* 1995; Zolla-Pazner *et al.* 1995
Keywords dendritic cells, neutralization

- 858-D: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 858-D: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – C5 MAbs 858-D, 989-D and 1331A bound with a 5-10 fold preference for the monomer. Gorny *et al.* [2000]
- 858-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 4 C5 MAbs, 2 bound well, 2 bound weakly – MAb 858-D bound only 4/26, the worst of all anti-C5 MAbs tested, while MAb 1331A, which shares the same core epitope (positions 495-516), bound to 18/26 isolates. Nyambi *et al.* [2000]
- 858-D: No neutralizing activity, no ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995]

B Cell

- 858-D: Group specific cross-clade binding in serotyping study using flow-cytometry. Zolla-Pazner *et al.* [1995]

No. 682
MAb ID 989-D
HXB2 Location gp160 (505–511)
Author Location gp120 (LAI)
Epitope VVQREKR
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type C-term
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Nyambi *et al.* 2000; Gorny *et al.* 2000; Zolla-Pazner *et al.* 1995

- 989-D: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – C5 MAbs 858-D, 989-D and 1331A bound with a 5-10 fold preference for the monomer. Gorny *et al.* [2000]
- 989-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 4 C5 MAbs, 2 bound well, 2 bound weakly – MAb 989-D bound to 6/26 isolates. Nyambi *et al.* [2000]
- 989-D: In serotyping study using flow-cytometry, showed B clade specificity, but only reacted with 7/11 B clade virus. Zolla-Pazner *et al.* [1995]

No. 683
MAb ID 1A1
HXB2 Location gp160 (525–543)
Author Location gp41 (526–543 BH10)
Epitope AAGSTMGAASMTLTVQARQ
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Research Contact H. Katinger, Inst. Appl. Microbiol., Vienna, Austria
References Maksiutov *et al.* 2002; Buchacher *et al.* 1994

- 1A1: This epitope is similar to a fragment of the HLA class II histocompatibility antigen, GGSCMAALTVTLTV. Maksiutov *et al.* [2002]
- 1A1: Human MAb generated using EBV transformation of PBL from HIV-1 + volunteers. Buchacher *et al.* [1994]

No. 684
MAb ID 24G3
HXB2 Location gp160 (525–543)
Author Location gp41 (526–543 BH10)
Epitope AAGSTMGAASMTLTVQARQ
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Research Contact H. Katinger, Inst. Appl. Microbiol., Vienna, Austria
References Maksiutov *et al.* 2002; Buchacher *et al.* 1994; Buchacher *et al.* 1992

- 24G3: This epitope is similar to a fragment of the HLA class II histocompatibility antigen, GGSCMAALTVTLTV. Maksiutov *et al.* [2002]
- 24G3: Human MAb generated by electrofusion of PBL from HIV-1 + volunteers with CB-F7 cells. Buchacher *et al.* [1994]

No. 685
MAb ID 25C2 (IAM 41-25C2)
HXB2 Location gp160 (525–543)
Author Location gp41 (526–543 BH10)
Epitope AAGSTMGAASMTLTVQARQ
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Research Contact H. Katinger, Inst. Appl. Microbiol., Vienna, Austria and Viral Testing Systems, Houston, TX
References Maksiutov *et al.* 2002; Sattentau *et al.* 1995; Buchacher *et al.* 1994; Buchacher *et al.* 1992

- 25C2: This epitope is similar to a fragment of the HLA class II histocompatibility antigen, GGSCMAALTVTLTV. Maksiutov *et al.* [2002]
- 25C2: Called IAM 41-25C2 – Binding domain overlaps sites that are critical for gp120-gp41 association – binding is enhanced by sCD4 – binding region defined as: gp41(21-38 BH10). Sattentau *et al.* [1995]
- 25C2: Human MAb generated by electrofusion of PBL from HIV-1 + volunteers with CB-F7 cells – binds oligomeric and monomeric gp41, and gp160. Buchacher *et al.* [1994]

No. 686
MAb ID 5F3
HXB2 Location gp160 (525–543)
Author Location gp41 (526–543 BH10)
Epitope AAGSTMGAASMTLTVQARQ
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Research Contact H. Katinger, Inst. Appl. Microbiol., Vienna, Austria
References Vincent *et al.* 2008; Ye *et al.* 2006; Sheppard *et al.* 2007b; Holl *et al.* 2006a; Kalia *et al.* 2005; Maksiutov *et al.* 2002; Buchacher *et al.* 1994
Keywords antibody binding site definition and exposure, antibody interactions, binding affinity, dendritic cells, kinetics, neutralization

- 5F3: 5F3 reacted with maltose-binding proteins MBP30 and MBP32, containing both HR1 and HR2 domains of gp41, but did not react with MBP37 and MBP44, containing only the HR2 domain, nor with MBP-HR1, containing only the HR1 domain. In addition, 5F3 bound to MBP44/N36 and MBP-HR1/C34 complexes reaching a plateau at a concentration of $\sim$ 1 µg/ml. In ELISA, 5F3 reacted with the complex formed between MBP-HR1 and H44 (His-targeted protein) and C34, but failed to recognize the mixture of MBP-HR1 and T20,

B Cell

MBP3 and C34, and MBP3 and H44. In addition, 5F3 recognized the peptide complex N36/C34 but not the peptides individually. Vincent *et al.* [2008] (**antibody binding site definition and exposure**)
- 5F3: This Ab was used in the analysis of clade C gp140 (97CN54) antigenicity and was shown to bind with relaively high avidity to the molecule and did not dissociate within 420 s. 5F3 was also used in a competition assay and shown to inhibit binding of N3C5 Ab by 80-90% and of N03B11 by 98-100%, indicating proximity of their epitopes. Sheppard *et al.* [2007b] (**antibody binding site definition and exposure**, **antibody interactions**, **kinetics**, **binding affinity**)
- 5F3: This Ab did not inhibit HIV-1 BaL replication in macrophages. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 5F3: Significant levels of 5F3 were shown to bind to HA/gp41 expressed on cell surfaces and this Ab did stain cells expressing HA/gp41 in a fluorescence assay. However, this Ab did not bind to the surfaces of HIV Env expressing cells and a much smaller percentage of the HIV 89.6 Env expressing cells were stained with this Ab than with 2G12, indicating that this Ab recognition site on gp41 is masked by the gp120 subunit in the HIV Env protein and that it is more easily accessible on the HA/gp41 chimeric protein. Ye *et al.* [2006] (**antibody binding site definition and exposure**, **binding affinity**)
- 5F3: Point mutations in the highly conserved structural motif LLP-2 within the intracytoplasmic tail of gp41 resulted in conformational alternations of both gp41 and gp120. The alternations did not affect virus CD4 binding, coreceptor binding site exposure, or infectivity of the virus, but did result in decreased binding of certain MAbs and increased neutralization resistance to MAbs as well as to human polyclonal HIV-Ig and pooled human sera. 5F3 MAb did not neutralize the LLP-2 mutant nor the wildtype virus. 5F3 exhibited similar levels of binding to both LLP-2 mutant and the wildtype virus. Kalia *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- 5F3: This epitope is similar to a fragment of the HLA class II histocompatibility antigen, GGSCMAALTVTLTV. Maksiutov *et al.* [2002]
- 5F3: Human MAb generated by electrofusion of PBL from HIV-1 + volunteers with CB-F7 cells. Buchacher *et al.* [1994]

No. 687
MAb ID α(566-586)
HXB2 Location gp160 (561–581)
Author Location gp41 (566–586 BRU)
Epitope `AQQHLLQLTVWGIKQLQARIL`
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Poumbourios *et al.* 1992

No. 688
MAb ID PC5009
HXB2 Location gp160 (572–591)
Author Location gp41 (577–596 BRU)
Epitope `GIKQLQARILAVERYLKDQQ`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* gp160
Species (Isotype) mouse
References Poumbourios *et al.* 1992
- PC5009: Recognized only monomeric gp41. Poumbourios *et al.* [1992]

No. 689
MAb ID polyclonal α577-596
HXB2 Location gp160 (572–591)
Author Location gp41 (577–596 BRU)
Epitope `GIKQLQARILAVERYLKDQQ`
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Poumbourios *et al.* 1992
- alpha(577-596): Affinity purified from HIV-1 + plasma – preferentially bind oligomer. Poumbourios *et al.* [1992]

No. 690
MAb ID polyclonal
HXB2 Location gp160 (576–592)
Author Location gp41 (583–599)
Epitope `LQARILAVERYLKDQQL`
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Klasse *et al.* 1993b
- 42 HIV-1 positive human sera were tested against wildtype peptide, and peptide with substitution 589 A to T: 11/42 reacted strongly with wildtype, weakly with A589T – 31 reacted weakly with parental, even more weakly with substituted. Klasse *et al.* [1993b]

No. 691
MAb ID
HXB2 Location gp160 (577–583)
Author Location gp41 (582–589)
Epitope `QARILAV`
Subtype B
Neutralizing yes
Immunogen HIV-1 exposed seronegative
Species (Isotype) human (IgA)
Ab Type Leucine zipper motif
References Clerici *et al.* 2002a
- Six sera from HIV-exposed uninfected individuals(EU), HIV-infected individuals and healthy controls were analyzed for IgA Abs – neutralizing activity was observed with total IgA from both EU and HIV+ – the EU IgA exclusively bound to a distinctive epitope within gp41, QARILAV, in the coiled coil pocket important for gp120-gp41 interactions – sera of QAFILAV-immunized BALB/c mice was neutralizing with the dose-dependent behavior similar to 2F5. Clerici *et al.* [2002a]

No. 692
MAb ID
HXB2 Location gp160 (577–583)
Author Location gp41 (582–589)
Epitope `QARILAV`

B Cell

Subtype B
Neutralizing yes
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41 *Adjuvant:* Keyhole Limpit Haemocyanin (KLH)
Species (Isotype) mouse (IgA)
Ab Type Leucine zipper motif
References Clerici *et al.* 2002a

- Six sera from HIV-exposed uninfected individuals(EU), HIV-infected individuals and healthy controls were analyzed for IgA Abs – neutralizing activity was observed with total IgA from both EU and HIV+ – the EU IgA exclusively bound to a distinctive epitope within gp41, QARILAV – sera of QAFILAV-immunized BALB/c mice was neutralizing with the dose-dependent behavior similar to 2F5. Clerici *et al.* [2002a]

No. 693
MAb ID 1F11
HXB2 Location gp160 (578–612)
Author Location gp41 (579–613 BH10)
Epitope ARILAVERYLKDQQLLGIWGCSGKLICTTAVP-WNA
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Research Contact H. Katinger, Inst. Appl. Microbiol., Vienna, Austria
References Gorny & Zolla-Pazner 2004; Buchacher *et al.* 1994; Buchacher *et al.* 1992
Keywords antibody generation, review

- 1F11: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 1F11: Generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994] (**antibody generation**)

No. 694
MAb ID 1H5
HXB2 Location gp160 (578–612)
Author Location gp41 (579–613 BH10)
Epitope ARILAVERYLKDQQLLGIWGCSGKLICTTAVP-WNA
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
References Gorny & Zolla-Pazner 2004; Buchacher *et al.* 1994; Buchacher *et al.* 1992
Keywords antibody generation, review

- 1H5: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 1H5: Generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994] (**antibody generation**)

No. 695
MAb ID 3D9
HXB2 Location gp160 (578–612)
Author Location gp41 (579–613 BH10)
Epitope ARILAVERYLKDQQLLGIWGCSGKLICTTAVP-WNA
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Research Contact H. Katinger, Inst. Appl. Microbiol., Vienna, Austria
References Gorny & Zolla-Pazner 2004; Buchacher *et al.* 1994; Buchacher *et al.* 1992
Keywords antibody generation, review

- 3D9: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 3D9: Generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994] (**antibody generation**)

No. 696
MAb ID 4B3
HXB2 Location gp160 (578–612)
Author Location gp41 (579–613 BH10)
Epitope ARILAVERYLKDQQLLGIWGCSGKLICTTAVP-WNA
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Research Contact H. Katinger, Inst. Appl. Microbiol., Vienna, Austria
References Gorny & Zolla-Pazner 2004; Chen *et al.* 1994b; Buchacher *et al.* 1994; Buchacher *et al.* 1992
Keywords antibody generation, review

- 4B3: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 4B3: Generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994] (**antibody generation**)

No. 697
MAb ID 4D4
HXB2 Location gp160 (578–612)
Author Location gp41 (579–613 BH10)
Epitope ARILAVERYLKDQQLLGIWGCSGKLICTTAVP-WNA
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Research Contact H. Katinger, Inst. Appl. Microbiol., Vienna, Austria and Viral Testing Systems, Houston, TX

References Gorny & Zolla-Pazner 2004; Binley *et al.* 1999; Sattentau *et al.* 1995; Chen *et al.* 1994b; Buchacher *et al.* 1994; Buchacher *et al.* 1992
Keywords antibody binding site definition and exposure, antibody generation, review, vaccine antigen design

- 4D4: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 4D4: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- 4D4: Generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994] (**antibody generation**)

No. 698
MAb ID 4G2
HXB2 Location gp160 (578–612)
Author Location gp41 (579–613 BH10)
Epitope ARILAVERYLKDQQLLGIWGCSGKLICTTAVP-WNA
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Research Contact H. Katinger, Inst. Appl. Microbiol., Vienna, Austria
References Gorny & Zolla-Pazner 2004; Buchacher *et al.* 1994; Buchacher *et al.* 1992
Keywords antibody generation, review

- 4G2: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 4G2: Generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994] (**antibody generation**)

No. 699
MAb ID polyclonal
HXB2 Location gp160 (579–589)
Author Location gp41 (586–596 IIIB)
Epitope RILAVERYLKD
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41 *Adjuvant:* BSA
Species (Isotype) rabbit, mouse
Ab Type C-domain
References Xiao *et al.* 2000b

- Strong epitope-specific neutralizing antibody responses were induced using the peptide C(RILAVERYLKD)_2-BSA, but not full gp160. Xiao *et al.* [2000b]

No. 700
MAb ID polyclonal
HXB2 Location gp160 (579–589)
Author Location gp41 (586–596)
Epitope RILAVERYLKD
Neutralizing
Immunogen vaccine
Vector/Type: protein, polyepitope *HIV component:* gp160 *Adjuvant:* BSA
Species (Isotype) rabbit
Ab Type N-term
References Lu *et al.* 2000b; Lu *et al.* 2000c

- High titer response to ELDKWA and RILAVERYLKD was observed upon vaccination with multiple-epitope vaccine CG-GPGRAFY-G-ELDKWA-G-RILAVERYLKD conjugated to BSA, a weak response to GPGRAFY – immunization with CG-(ELDKWA-GPGRAFY)_2-K was also tried, yielding a strong Ab response to both ELDKWA and GPGRAFY – gp160 vaccination yielded strong Ab response but not to any of the peptides studied here. Lu *et al.* [2000c,b]

No. 701
MAb ID
HXB2 Location gp160 (579–599)
Author Location gp41 (586–606)
Epitope RILAVERYLKDQQLLGIWGCS
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Wang *et al.* 1986
Keywords assay standardization/improvement

- Immunoabsorbant peptide antigen RIAVERYLKDQQLLGI-WGCS was used in a solid-phase enzyme immunoassay (EIA)to detect gp41-specific Abs in sera of virtually all HIV-1 infected individuals tested, with no false positives. This one 21 amino acid long peptide is recognized by sera from almost all AIDS patients, can be easily synthesized and employed for serological testing for HIV infection. Wang *et al.* [1986] (**assay standardization/improvement**)

No. 702
MAb ID polyclonal
HXB2 Location gp160 (579–599)
Author Location gp41 (583–604)
Epitope RILAVERYLKDQQLLGIWGCS
Neutralizing no
Immunogen vaccine

B Cell

Vector/Type: protein *HIV component:* desialylated gp160
Species (Isotype) rabbit
References Benjouad *et al.* 1993

- MAbs raised against desialylated HIV-1 gp160 cross-react with HIV-2 gp140 due to immunodominant conserved epitope in gp41. Benjouad *et al.* [1993]

No. 703
MAb ID 2A2/26
HXB2 Location gp160 (579–601)
Author Location gp41 (584–606 BRU)
Epitope `RILAVERYLKDQQLLGIWGCSGK`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* gp41
Species (Isotype) mouse (IgG)
References Poumbourios *et al.* 1995; Poumbourios *et al.* 1992

- 2A2/26: Delta 550-561 (Delta LLRAIEAQQHLL), a region important for oligomer formation diminishes binding, Delta (550-561 +571-581) abrogates binding. Poumbourios *et al.* [1995]
- 2A2/26: Immunodominant region, binds both oligomer and monomer. Poumbourios *et al.* [1992]

No. 704
MAb ID 50-69 (SZ-50.69, 50-69D, 50.69)
HXB2 Location gp160 (579–603)
Author Location gp41 (579–603 BH10)
Epitope `RILAVERYLKDQQLLGIWGCSGKLI`
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG2κ)
Ab Type gp41 cluster I
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU, NY
References Vincent *et al.* 2008; Sheppard *et al.* 2007b; Kim *et al.* 2007; Holl *et al.* 2006a; Huang *et al.* 2007b; Usami *et al.* 2005; Kalia *et al.* 2005; McCaffrey *et al.* 2004; Ling *et al.* 2004; Gorny & Zolla-Pazner 2004; Finnegan *et al.* 2002; Follis *et al.* 2002; Verrier *et al.* 2001; Zwick *et al.* 2001b; Nyambi *et al.* 2000; Gorny *et al.* 2000; Gorny & Zolla-Pazner 2000; Mitchell *et al.* 1998; Hioe *et al.* 1997b; Boots *et al.* 1997; Stamatatos *et al.* 1997; Klasse & Sattentau 1996; Binley *et al.* 1996; Poignard *et al.* 1996a; McDougal *et al.* 1996; Manca *et al.* 1995a; Sattentau *et al.* 1995; Chen *et al.* 1995; Laal *et al.* 1994; Spear *et al.* 1993; Eddleston *et al.* 1993; Sattentau & Moore 1991; Robinson *et al.* 1991; Xu *et al.* 1991; Gorny *et al.* 1989; Pinter *et al.* 1989; Till *et al.* 1989
Keywords antibody binding site definition and exposure, antibody interactions, binding affinity, complement, dendritic cells, enhancing activity, immunotoxin, kinetics, mimotopes, neutralization, rate of progression, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- 50-69: NIH AIDS Research and Reference Reagent Program: 531.
- 50-69: 50-69 reacted with maltose-binding protein MBP32, containing both HR1 and HR2 domains of gp41, but did not react with MBP37 and MBP44, containing only the HR2 domain, nor with MBP-HR1, containing only the HR1 domain. In addition, 50-69 bound to MBP44/N36 and MBP-HR1/C34 complexes reaching a plateau at a concentration of ~ 1 µg/ml. In ELISA, 50-69 reacted with the complex formed between MBP-HR1 and H44 (His-targeted protein) and C34, but failed to recognize the mixture of MBP-HR1 and T20, MBP3 and C34, and MBP3 and H44. In addition, 50-69 failed to recognize the peptide complex N36/C34. Vincent *et al.* [2008] (**antibody binding site definition and exposure**)
- 50-69: Increased binding of 50-69 Ab to gp41 in the presence of CD4 was abrogated by the small molecule HIV-1 entry inhibitor IC9564, suggesting that IC9564 arrests gp120 into a fusion-incompetent conformation unable to expose 50-69 epitope. Huang *et al.* [2007b] (**antibody binding site definition and exposure**)
- 50-69: To test the immunogenicity of three molecularly engeneered gp41 variants on the cell surface their reactivity with 50-69 Ab was assessed. The reactivity of 4cSSL24 variant was comparable to gp160 while the other two variants were not recognized by this Ab since the epitope for this Ab was not present in these variants. Kim *et al.* [2007] (**binding affinity**)
- 50-69: This Ab was used in the analysis of clade C gp140 (97CN54) antigenicity and was shown to bind to this molecule. 50-69 was also used in a competition assay where it was shown to mildly inhibit binding of N3C5 Ab and relatively inhibit binding of N03B11 Ab (43-61%), indicating proximity of their epitopes. Sheppard *et al.* [2007b] (**antibody binding site definition and exposure**, **antibody interactions**, **variant cross-recognition or cross-neutralization**, **binding affinity**)
- 50-69: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication occurrs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 50-69: Point mutations in the highly conserved structural motif LLP-2 within the intracytoplasmic tail of gp41 resulted in conformational alternations of both gp41 and gp120. The alternations did not affect virus CD4 binding, coreceptor binding site exposure, or infectivity of the virus, but did result in decreased binding and neutralization by certain MAbs and human sera. 50-69 exhibited similar levels of binding to both the LLP-2 mutant and wildtype viruses, indicating that its epitope was not altered by the mutation. Kalia *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)

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- 50.69: 50.69 was found to bind to both monomeric and oligomeric gp41. Binding of this Ab to H9/IIIB-infected cells gave a strong signal which was increased by sCD4 pretreatment. Binding to H9/MN-infected cells gave a low signal which increased dramatically with sCD4 pretreatment. Sera from both long-term survivors and AIDS patients inhibited binding of 50.69 to H9/IIIB-infected cells. Usami *et al.* [2005] (**antibody binding site definition and exposure**, **rate of progression**)
- 50-69: This is one of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 50-69: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of 17b and F105 was decreased by trypsin, but increased by thrombin. gp41 MAbs 246D, 98.6, 50-69, were decreased by trypsin, unaltered by thrombin, while NAb 2F5 binding was increased by thrombin. Thrombin may increase HIV-induced cell fusion in blood by causing a conformational activating shift in gp120. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 50-69: Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. SF162 and each of the five glycosyation mutants studied were all neutralization resistant to 50-69. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- 50-69: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I MAbs 50-69, F240, 240-D,3D6, and 246-D recognize a nonhelical hydrophobic region, positions 598-604, that forms a disulfide loop in the six-helix bundle. Cluster II MAbs 98-6 and 126-6 recognized residues 644-663 of gp41, a portion of the second heptad repeat. These MAbs were found to behave similarly, so 50-69 and 98-6 were used as representatives. Exposure of cluster I and cluster II epitopes required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor. Binding to CD4 exposed hidden cluster I and II epitopes. The MAbs were found to bind to gp120/gp41 complexes, not to gp41 after shedding of gp120, and were localized to at fusing-cell interfaces. Kinetic and binding results indicate that these MAbs are exposed in transitional structures during the fusion process, possibly the prehairpin intermediate prior to co-receptor binding, although other intermediate structures may be involved. They do not bind once syncytia begin to show extensive cyotplasmic mixing. These MAbs failed to inhibit fusion. The NAb 2F5 has a very different behavior in this study. Finnegan *et al.* [2002] (**antibody binding site definition and exposure**, **kinetics**)
- 50-69: Called 50-69D. Alanine mutations were introduced into the N- and C-terminal alpha-helices of gp41 to destabilize interhelical packing interactions in order to study their inhibitory effect on viral infectivity. These mutations were shown to inhibit viral replication though affecting the conformational transition to the fusion-active form of gp41, and allow increased inhibition by gp41 peptides. 2F5 senstivity is increased in the mutated viruses, presumably because 2F5s neutralization activity is focused on the transition to the fusion active state. No other gp41 MAb against tested, including NC-1, 50-69D, 1281, 98-6D, 246-D and F240, neutralized the parental or the fusion-deficient mutated viruses. Follis *et al.* [2002] (**antibody binding site definition and exposure**)
- 50-69: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001] (**antibody interactions**)
- 50-69: This paper primarily concerns 4E10 and Z13, MAbs that both bind proximally to the 2F5 binding site to a conserved epitope, and that neutralize some primary isolates from clades B, C, and E – MAb 50-69 binding to infected cells is enhanced by sCD4, while 4E10 and Z13 binding is essentially unaltered. Zwick *et al.* [2001b] (**antibody binding site definition and exposure**)
- 50-69: A cluster I epitope that binds to rgp41 567-647, recognizes a peptide N51-C43 complex trimer of heterodimers that approximates the core of the fusogenic form of gp41 – this MAb doesn't react with either of the peptides N51 or C43 individually – MAbs 50-69 and 1367 had similar properties – MAb 50-69 bound the fusogenic form of the protein in liquid phase. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
- 50-69: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, but gp41 MAb 50-69 bound with a 5 fold preference for the oligomer, while other gp41 MAbs (1367, 98-6, 167-D, 1281, 1342, and 1379) did not show a preference. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)
- 50-69: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 cluster I anti-gp41 MAbs which showed good cross clade reactivity – 50-69 bound the majority of isolates although binding was moderate to weak – specifies discontinuous binding site range as aa 579-613. Nyambi *et al.* [2000] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 50-69: Mutations in BH10 gp160, W596Y and T605A, as well as deletions of 605-609 (TTAVP) and 597-609 (GCSGKLICTTAVP), abrogate binding of enhancing MAbs 86, 240D, 50-69, and 246-D – 5/6 enhancing MAbs identified to date bind to the immunodominant region 579-613 – identifies non-contiguous W596-G597-C598 and C604-T605 as mini-

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mal epitope. Mitchell *et al.* [1998] (**antibody binding site definition and exposure**)

- 50-69: Abs that recognize discontinuous epitopes can identify mimotopes from a phage peptide display library – 50-69 maps to an immunodominant domain in gp41 – three groups of peptides were selected, one which seems most closely related to gp41 sequence peptide consensus is WGCxx(RK)(x n)LxC – the analogous gp41 sequence WGCSGKLIC is present in most M group clades, except D with a common L to H substitution. Boots *et al.* [1997] (**mimotopes**)
- 50-69: Binding of anti-gp120 MAbs IgG1b12 or 654-30D does not mediate significant exposure of the gp41 epitopes for MAbs 2F5 and 50-69. Stamatatos *et al.* [1997] (**antibody interactions**)
- 50-69: Binds to a linear epitope located in the cluster I region – binding of 50-69 and 240-D inhibited by Fabs A1, A4, M8B, M26B, M12B and T2. Binley *et al.* [1996] (**antibody binding site definition and exposure**)
- 50-69: Used to test exposure of gp41 upon sCD4 binding. Klasse & Sattentau [1996]
- 50-69: Does not neutralize HIV-1 LAI. McDougal *et al.* [1996] (**variant cross-recognition or cross-neutralization**)
- 50-69: Prebinding of anti-V3, and CD4i MAbs 48d and 17b, but not anti-V2 neutralizing MAbs, expose the 50-69 epitope. Poignard *et al.* [1996a] (**antibody interactions**)
- 50-69: One of several anti-gp41 MAbs that bind to a gp41-maltose binding fusion protein designed to study the leucine zipper domain of gp41, showing that the construct has retained aspects of normal gp41 conformation. Chen *et al.* [1995] (**antibody binding site definition and exposure**)
- 50-69: Virions complexed to gp41 Ab facilitate presentation of p66 RT epitopes to Th cells. Manca *et al.* [1995a]
- 50-69: Preferentially binds oligomer – binding increased after pretreatment of infected cells with sCD4 – binding domain overlaps site that is critical for gp120-gp41 association. Sattentau *et al.* [1995] (**antibody binding site definition and exposure**)
- 50-69: Epitope described as cluster I, 601-604, conformational – does not neutralize IIIB or synergize neutralization by anti-V3 MAb 447-52D or by CD4 BS MAbs. Laal *et al.* [1994] (**antibody binding site definition and exposure**, **antibody interactions**)
- 50-69: Called SZ-50.69 – binds to an epitope within aa 579-613. Eddleston *et al.* [1993] (**antibody binding site definition and exposure**)
- 50-69: Did not mediate deposition of complement component C3 on HIV infected cells unless cells were pre-incubated with sCD4 – complement mediated virolysis of MN and IIIB in the presence of sCD4. Spear *et al.* [1993] (**complement**)
- 50-69: Enhances HIV-1 infection *in vitro* – synergizes with huMAb 120-16 *in vitro* to enhance HIV-1 infection to level approaching that found in polyclonal anti-HIV serum. Robinson *et al.* [1991] (**antibody interactions**, **enhancing activity**)
- 50-69: Two fold increase in binding to gp120 in the presence of bound sCD4. Sattentau & Moore [1991] (**antibody binding site definition and exposure**)
- 50-69: The epitope is affected by the conformation conferred by the two cysteines at amino acids 598 and 604. Xu *et al.* [1991] (**antibody binding site definition and exposure**)
- 50-69: Kills HIV-infected cells when coupled to deglycosylated ricin A chain. Gorny *et al.* [1989] (**immunotoxin**)
- 50-69: Reacts preferentially with gp160 oligomer, compared to gp41 monomer. Pinter *et al.* [1989] (**antibody binding site definition and exposure**)
- 50-69: Combined with deglycosylated A chain of ricin is toxic to lines of HIV-infected T cells (H9) and monocytes (U937). Till *et al.* [1989] (**immunotoxin**)

No. 705
MAb ID 9-11
HXB2 Location gp160 (579–604)
Author Location gp41 (584–609)
Epitope `RILAVERYLKDQQLLGIWGCSGKLIC`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* gp160
Species (Isotype) mouse (IgG1)
References Mani *et al.* 1994

- 9-11: required the C-C disulfide bridge and loop formation, can bind simultaneously with 41-1. Mani *et al.* [1994]

No. 706
MAb ID 98-43
HXB2 Location gp160 (579–604)
Author Location gp41 (579–604 HXB2)
Epitope `RILAVERYLKDQQLLGIWGCSGKLIC`
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG2κ)
References Xu *et al.* 1991; Tyler *et al.* 1990; Gorny *et al.* 1989; Pinter *et al.* 1989

- 98-43: NIH AIDS Research and Reference Reagent Program: 1241.
- 98-43: 579-604 binds in the immunodominant region. Xu *et al.* [1991]
- 98-43: Poor ADCC (in contrast to MAb 120-16, gp41(644-663)). Tyler *et al.* [1990]
- 98-43: Reacts equally well with oligomer and monomer. Pinter *et al.* [1989]

No. 707
MAb ID 41-1 (41.1)
HXB2 Location gp160 (579–608)
Author Location gp41 (584–609)
Epitope `RILAVERYLKDQQLLGIWGCSGKLICTTAV`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* gp160
Species (Isotype) mouse (IgG1κ)
References Pincus *et al.* 1998; Pincus *et al.* 1996; Mani *et al.* 1994; Pincus & McClure 1993; Pincus *et al.* 1991; Dalgleish *et al.* 1988; Gosting *et al.* 1987

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- 41-1 database comment: Also called 41.1, although possibly not, the literature is confusing because two gp41 MAbs that bind to this region with similar names (dash versus period) are listed as murine and human.
- 41-1: Called 41.1, and described as a human MAb, binding 579-604 – a panel of immunotoxins was generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but killing was not directly proportional to binding. Pincus *et al.* [1996]
- 41-1: This antibody to gp41(584-609) Mani *et al.* [1994] seems to have been named the same as a different MAb to gp41(735-752 IIIB) Dalgleish *et al.* [1988]. Dalgleish *et al.* [1988]; Mani *et al.* [1994]
- 41-1: Did not require the C-C disulfide bridge and loop formation, can bind simultaneously with 9-11. Mani *et al.* [1994]
- 41-1: Called 41.1, and described as a human MAb – cross-competes with 41.4 – sCD4 enhances the efficacy of immunotoxins *in vitro* 30-fold – MAb was coupled to ricin A chain (RAC). Pincus & McClure [1993]
- 41-1: Efficacious as an immunotoxin when coupled to RAC – gave linear epitope as gp160 579-603. Pincus *et al.* [1991]
- 41-1: This antibody seems to have been named the same as a different MAb to gp41(735-752). Dalgleish *et al.* [1988]
- 41-1: Broadly reactive. Gosting *et al.* [1987]

No. 708
MAb ID 41.4
HXB2 Location gp160 (579–608)
Author Location gp41 (584–609)
Epitope `RILAVERYLKDQQLLGIWGCSGKLICTTAV`
Neutralizing
Immunogen
Species (Isotype)
Research Contact Jan McClure, Bristol-Myers Squibb Pharmaceutical Res Inst, Seattle, WA
References Pincus & McClure 1993

- 41.4: Binds to peptide weakly, but to gp160 with higher affinity than 41.1, and cross-competes with 41.1 – probably conformational – MAb was coupled to ricin A chain (RAC) – sCD4 enhances the efficacy of immunotoxins *in vitro* 30-fold. Pincus & McClure [1993]

No. 709
MAb ID Fab A1 (A1)
HXB2 Location gp160 (579–608)
Author Location gp41 (584–609 LAI)
Epitope `RILAVERYLKDQQLLGIWGCSGKLICTTAV`
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
References Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords anti-idiotype, antibody generation, antibody sequence variable domain, review

- Fab A1: Called A1. One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- Fab A1: Binds to cluster I region – competes with MAbs 240-D and 50-69 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**anti-idiotype**, **antibody generation**, **antibody sequence variable domain**)

No. 710
MAb ID Fab A4 (A4)
HXB2 Location gp160 (579–608)
Author Location gp41 (584–609 LAI)
Epitope `RILAVERYLKDQQLLGIWGCSGKLICTTAV`
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
References Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab A4: Called A4. One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- Fab A4: Binds to cluster I region – competes with MAbs 240-D and 50-69 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody generation**, **antibody sequence variable domain**)

No. 711
MAb ID Fab M12B (M12B)
HXB2 Location gp160 (579–608)
Author Location gp41 (584–609 LAI)
Epitope `RILAVERYLKDQQLLGIWGCSGKLICTTAV`
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
References Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab M12B: Called M12B. One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- Fab M12B: Binds to cluster I region – competes with MAbs 240-D and 50-69 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody generation**, **antibody sequence variable domain**)

No. 712
MAb ID Fab M26B (M26B)
HXB2 Location gp160 (579–608)
Author Location gp41 (584–609 LAI)
Epitope `RILAVERYLKDQQLLGIWGCSGKLICTTAV`
Subtype B
Neutralizing no

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Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
References Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab M26B: Called M26B. One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- Fab M26B: Binds to cluster I region – competes with MAbs 240-D and 50-69 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody generation**, **antibody sequence variable domain**)

No. 713
MAb ID Fab M8B (M8B)
HXB2 Location gp160 (579–608)
Author Location gp41 (584–609 LAI)
Epitope `RILAVERYLKDQQLLGIWGCSGKLICTTAV`
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
References Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab M8B: Called M8B. One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- Fab M8B: Binds to cluster I region – competes with MAbs 240-D and 50-69 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody generation**, **antibody sequence variable domain**)

No. 714
MAb ID Fab T2 (T2)
HXB2 Location gp160 (579–608)
Author Location gp41 (584–609 LAI)
Epitope `RILAVERYLKDQQLLGIWGCSGKLICTTAV`
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster I
References Nelson *et al.* 2008; Crooks *et al.* 2008; Moore *et al.* 2006; Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, binding affinity, neutralization, review

- T2: The study compared Ab neutralization against the JR-FL primary isolate and trimer binding affinities judged by native PAGE. There was direct quantitative relationship between monovalent Fab-trimer binding and neutralization, implying that neutralization begins as each trimer is occupied by one Ab. In BN-PAGE, neutralizing Fabs and sCD4 were able to shift JR-FL trimers, In contrast, most non-neutralizing Fabs, T2 in particular, bound to monomer, but their epitopes were conformationally occluded on trimers, confirming the exclusive relationship of trimer binding and neutralization. Crooks *et al.* [2008] (**neutralization**, **binding affinity**)
- T2: T2 bound to recombinant r-gp41 (HXB2), but not to N35ccg-N13 peptide, which is a soluble homotrimer corresponding to the HIV-1 gp41 NHR region, and not to other gp41, due to absence of the immunodominant loop. T2 did not neutralize HXB2. As other human-derived Abs in this study, T2 has a long CDR H3 (18 residues), and it was shown to bind to Envs used in typical epitope binding assays, unlike the neutralizing Abs in this study. Nelson *et al.* [2008]
- T2: In addition to gp120-gp41 trimers, HIV-1 particles were shown to bear nonfunctional gp120-gp41 monomers and gp120-depleted gp41 stumps on their surface. T2 did not bind to trimers nor monomers. Although T2 recognizes an epitope on gp41 obscured by proper gp12-gp41 association, it did not bind to gp41 stumps. T2 was, however, able to capture wild-type virus particles with moderate efficiency. Moore *et al.* [2006] (**antibody binding site definition and exposure**)
- Fab T2: Called T2. One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- Fab T2: Binds to cluster I region – competes with MAbs 240-D and 50-69 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody generation**, **antibody sequence variable domain**)

No. 715
MAb ID polyclonal
HXB2 Location gp160 (579–608)
Author Location gp41
Epitope `RVAVERYLKDQQLLGIWGCSGKICTTAV`
Subtype D, multiple
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Barin *et al.* 2005
Keywords acute/early infection, assay development

- A combination of 4 antigenic regions was used to differentiate between early (<180 days) and chronic infection. These regions were: p24; the gp41 peptide spanning the immunodominant epitope (IDE) of gp41, RVAVERYLKDQQLLGIWGCSGKICTTAV, and a subtype D version of this peptide; 5 V3 consensus peptides including A, B, C, D, and CRF01-AE; and Integrase. V3 and the IDE provide the best discrimination, with >20 fold higher levels in chronic infection when assayed by EIA using dried serum spots. Antibodies to Integrase and p24 were not as distinctive, and people tend to lose, not increase, responses to p24 over time. This assay can be

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used to identify samples from early infection with high sensitivity and specificity. Barin *et al.* [2005] (**assay development**, **acute/early infection**)

No. 716
MAb ID 86 (No. 86)
HXB2 Location gp160 (579–613)
Author Location gp41 (586–620 IIIB)
Epitope RILAVERYLKDQQLLGIWGCSGKLICTTAVPW-NAS
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Research Contact Evan Hersh and Yoh-Ichi Matsumoto
References Gorny & Zolla-Pazner 2004; Mitchell *et al.* 1998; Wisnewski *et al.* 1996; Moran *et al.* 1993; Pincus *et al.* 1991; Robinson *et al.* 1990c; Robinson *et al.* 1990b; Sugano *et al.* 1988
Keywords antibody binding site definition and exposure, antibody sequence variable domain, complement, enhancing activity, immunotoxin, review, variant cross-recognition or cross-neutralization

- 86: NIH AIDS Research and Reference Reagent Program: 380.
- 86: This is one of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 86: Mutations in BH10 gp160, W596Y and T605A, as well as deletions of 605-609 (TTAVP) and 597-609 (GCSGKLICTTAVP), abrogate binding of enhancing MAbs 86, 240D, 50-69, and 246-D – 5/6 enhancing MAbs identified to date bind to the immunodominant region 579-613. Mitchell *et al.* [1998] (**enhancing activity**, **variant cross-recognition or cross-neutralization**)
- 86: 86 is V H1 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996] (**antibody sequence variable domain**)
- 86: Heavy (V HI) and light (V kappaI) chain sequenced – enhancing activity – similar germline sequence to MAb S1-1, but very different activity. Moran *et al.* [1993] (**enhancing activity**, **antibody sequence variable domain**)
- 86: Poor immunotoxin activity when coupled to RAC – peptide binding stated to be aa 579-603. Pincus *et al.* [1991] (**antibody binding site definition and exposure**, **immunotoxin**)
- 86: Antibody dependent enhancement (ADE) of HIV-1 IIIB infectivity in the presence of complement. Robinson *et al.* [1990b] (**complement**, **enhancing activity**)
- 86: Peptide 586-620 blocks complement mediated ADE. Robinson *et al.* [1990c] (**enhancing activity**)
- 86: Reacts with gp41 and also reacted weakly with gp120. Sugano *et al.* [1988] (**antibody binding site definition and exposure**)

No. 717
MAb ID polyclonal
HXB2 Location gp160 (580–597)
Author Location gp41 (584–602)
Epitope ILAVERYLKDQQLLGIWG
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human
References Petrov *et al.* 1990

- Immunodominant and broadly reactive peptide. Petrov *et al.* [1990]

No. 718
MAb ID V10-9
HXB2 Location gp160 (580–613)
Author Location gp41 (586–620 IIIB)
Epitope ILAVERYLKDQQLLGIWGCSGKLICTTAVPWN-AS
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
References Gorny & Zolla-Pazner 2004; Robinson *et al.* 1990c; Robinson *et al.* 1990b
Keywords antibody interactions, enhancing activity, review

- V10-9: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- V10-9: Antibody dependent enhancement (ADE) of HIV-1 IIIB infectivity, synergistically enhanced by MAb 120-16. Robinson *et al.* [1990b] (**antibody interactions**, **enhancing activity**)
- V10-9: Peptide 586-620 blocks complement mediated ADE. Robinson *et al.* [1990c] (**enhancing activity**)

No. 719
MAb ID polyclonal
HXB2 Location gp160 (582–589)
Author Location gp41 (589–596)
Epitope AVERYLKD
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Klasse *et al.* 1991

- Substitutions and deletions in peptide 583-599 were systematically studied – alterations in AVERYLKD abrogated the antigenicity of peptides with most of 14 human sera. Klasse *et al.* [1991]

No. 720
MAb ID anti-P1
HXB2 Location gp160 (582–592)
Author Location gp41 (579–613)
Epitope AVERYLKDQQL
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype)
References Ferraz *et al.* 2004
Keywords assay development

B Cell

- The B-cell epitope of P1 was incorporated into the solvent-exposed loop of the E. coli betagalactosidase enzyme for use as an analytical biosensor to permit enzyme substrate analysis to better understand the conversion of conformational stimulous into enzymatic signal. Ferraz *et al.* [2004] (**assay development**)

No. 721
MAb ID polyclonal
HXB2 Location gp160 (584–604)
Author Location gp41 (74–94)
Epitope ERYLKDQLLGIWGCSGKLIC
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Shafferman *et al.* 1989

- Immunogenic domain useful for diagnostics. Shafferman *et al.* [1989]

No. 722
MAb ID polyclonal
HXB2 Location gp160 (584–612)
Author Location gp41 (587–617 BRU)
Epitope ERYLKDQQLLGIWGCSGKLICTTAVPWNA
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human
References Hernandez *et al.* 2000

- Chimeric peptide combining two peptides gp160(495-516 and 584-612) served as a specific and broadly reactive antigen for diagnostic detection of HIV-1. Hernandez *et al.* [2000]

No. 723
MAb ID 2F11
HXB2 Location gp160 (589–600)
Author Location gp41 (589–600 HXB2)
Epitope DQQLLGIWGCSG
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
References Gorny & Zolla-Pazner 2004; Enshell-Seijffers *et al.* 2001; Eaton *et al.* 1994
Keywords ADCC, enhancing activity, review

- 2F11: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 2F11: Monoclonal antibodies to this epitope have distinct phenotypes—41-7 and 1B8.env were found to be not neutralizing, 2F11 possibly enhancing, and clone 3 beneficial. Enshell-Seijffers *et al.* [2001] (**enhancing activity**)
- 2F11: Enhances infectivity even in the absence of complement – does not mediate ADCC or neutralize virus. Eaton *et al.* [1994] (**ADCC**, **enhancing activity**)

No. 724
MAb ID 246-D (SZ-246.D, 246, 246D)
HXB2 Location gp160 (590–597)
Author Location gp41 (579–604 HXB2)
Epitope qqLLGIWg
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster I
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU Med Center, NY, NY
References Vincent *et al.* 2008; Harada *et al.* 2008; Frey *et al.* 2008; Holl *et al.* 2006a; Usami *et al.* 2005; Kalia *et al.* 2005; Ling *et al.* 2004; Gorny & Zolla-Pazner 2004; Finnegan *et al.* 2002; Follis *et al.* 2002; Edwards *et al.* 2002; Gorny *et al.* 2002; Verrier *et al.* 2001; Nyambi *et al.* 2000; Gorny & Zolla-Pazner 2000; Mitchell *et al.* 1998; Hioe *et al.* 1997b; Earl *et al.* 1997; Saarloos *et al.* 1995; Manca *et al.* 1995a; Forthal *et al.* 1995; Eddleston *et al.* 1993; Spear *et al.* 1993; Robinson *et al.* 1991; Xu *et al.* 1991
Keywords antibody binding site definition and exposure, antibody interactions, binding affinity, complement, dendritic cells, enhancing activity, kinetics, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 246-D: NIH AIDS Research and Reference Reagent Program: 1245.
- 246-D: Molecular mechanism of neutralization by MPER antibodies, 2F5 and 4E10, was studied using preparations of trimeric HIV-1 Env protein in the prefusion, the prehairpin intermediate and postfusion conformations. MAb 246-D was used to analyze antigenic properties of construct 92UG-gp140-Fd, derived from isolate 92UG037.8 and stabilized by a C-terminal foldon tag. 92UG-gp140-Fd trimer binds 246-D. There is also strong binding of 246-D with plasmin cleaved 92UG-gp140-Fd. Frey *et al.* [2008] (**antibody binding site definition and exposure**, **binding affinity**)
- 246-D: Post-attachment enhancement (PAE), which augmented the level of HIV-1 cell infection by 1.4-fold, was not inhibited by 246-D non-neutralizing mAB, but was inhibited by anti-V3 neutralizing mAbs 0.5β and 694/98-D. Unlike the neutralizing Abs, 246-D did not suppress the fluidity of the viral and plasma envelopes. It is suggested that the binding of the neutralizing Abs to the viral surface could affect steric alternations of the viral envelope and restrain the envelope from enhancing its fluidity. Thus, suppression of the fluidity of viral envelope could be one additional mechanism for virus neutralization by anti-V3 neutralizing mAbs. Harada *et al.* [2008] (**antibody interactions**, **enhancing activity**, **neutralization**)
- 246-D: 246-D reacted with maltose-binding proteins MBP30 and MBP32, containing both HR1 and HR2 domains of gp41, and with MBP37, containing only the HR2 domain, but not with MBP-HR1, containing only the HR1 domain. In addition, 246-D did not react with MBP44/N36, MBP-HR1/T20, MBP-HR1/H44, and MBP-HR1/C23 complexes. Vincent *et al.* [2008] (**antibody binding site definition and exposure**)

B Cell

- 246-D: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication by this Ab for macrophages and iDCs occurrs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. It is also suggested that this Ab is directed against epitopes distinct from those recognized by NAbs and that it will not imapair virus entry into PBMCs but that it could participate in the protection of mucosal HIV transmission by preventing the infection of macrophages and iDCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 246D: Point mutations in the highly conserved structural motif LLP-2 within the intracytoplasmic tail of gp41 resulted in conformational alternations of both gp41 and gp120. The alternations did not affect virus CD4 binding, coreceptor binding site exposure, or infectivity of the virus, but did result in decreased binding and neutralization by certain MAbs and human sera. 246D exhibited similar levels of binding to both the LLP-2 mutant and wildtype viruses, indicating that its epitope was not altered by the mutation. Kalia *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)
- 246D: 246D was found to bind to both monomeric and oligomeric gp41. Binding of this Ab to H9/IIIB-infected cells gave a strong signal which was increased by sCD4 pretreatment. Binding to H9/MN-infected cells gave a low signal which increased dramatically with sCD4 pretreatment. Usami *et al.* [2005] (**antibody binding site definition and exposure**)
- 246-D: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 246-D: Called 246D. The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of 17b and F105 was decreased by trypsin, but increased by thrombin. gp41 MAbs 246D, 98.6, 50-69, were decreased by trypsin, unaltered by thrombin, while NAb 2F5 binding was increased by thrombin. Thrombin may increase HIV-induced cell fusion in blood by causing a conformational activating shift in gp120. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 246-D: Called 246D – Truncation of the gp41 cytoplasmic domain of X4, R5, and X4R5 viruses forces a conformation that more closely resembles the CD4 bound state of the external Envelope, enhancing binding of CD4i MAbs 17b and 48d and of CD4BS MAbs F105, b12, and in most cases of glycosylation site dependent MAb 2G12 and the anti-gp41 MAb 246D – in contrast, binding of the anti-V2 MAb 697D and the anti-V3 MAb 694/98D were not affected – viruses bearing the truncation were more sensitive to neutralization by MAbs 48d, b12, and 2G12 – the anti-C5 MAb 1331A was used to track levels of cell surface expression of the mutated proteins. Edwards *et al.* [2002] (**antibody binding site definition and exposure**)
- 246-D: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I MAbs 50-69, F240, 240-D,3D6, and 246-D recognize a nonhelical hydrophobic region, positions 598-604, that forms a disulfide loop in the six-helix bundle. Cluster II MAbs 98-6 and 126-6 recognized residues 644-663 of gp41, a portion of the second heptad repeat. These MAbs were found to behave similarly, so 50-69 and 98-6 were used as representatives. Exposure of cluster I and cluster II epitopes required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor. Binding to CD4 exposed hidden cluster I and II epitopes. The MAbs were found to bind to gp120/gp41 complexes, not to gp41 after shedding of gp120, and were localized to at fusing-cell interfaces. Kinetic and binding results indicate that these MAbs are exposed in transitional structures during the fusion process, possibly the prehairpin intermediate prior to co-receptor binding, although other intermediate structures may be involved. They do not bind once syncytia begin to show extensive cyotplasmic mixing. These MAbs failed to inhibit fusion. The NAb 2F5 has a very different behavior in this study. Finnegan *et al.* [2002] (**antibody binding site definition and exposure**, **kinetics**)
- 246-D: Alanine mutations were introduced into the N- and C-terminal alpha-helices of gp41 to destabilize interhelical packing interactions in order to study their inhibitory effect on viral infectivity. These mutations were shown to inhibit viral replication though affecting the conformational transition to the fusion-active form of gp41, and allow increased inhibition by gp41 peptides. 2F5 senstivity is increased in the mutated viruses, presumably because 2F5s neutralization activity is focused on the transition to the fusion active state. No other gp41 MAb against tested, including NC-1, 50-69D, 1281, 98-6D, 246-D and F240, neutralized the parental or the fusion-deficient mutated viruses. Follis *et al.* [2002] (**antibody binding site definition and exposure**)
- 246-D: Called 246 – Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions and the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control), and MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades tested, A, B, C, D, F and CRF01 (clade E). Gorny *et al.* [2002] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 246-D: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001] (**antibody interactions**)
- 246-D: Core epitope aa 591 to 597, a cluster I epitope that does

not bind to either a peptide complex that approximates the core of the fusogenic form of gp41 or the individual peptides N51 and C43 that form this structure – MAbs 181-D and 246-D had similar properties. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)

- 246-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 cluster I anti-gp41 MAbs which showed good cross clade reactivity – 246-D bound strongly or moderately to all 26 HIV-1 group M clades viruses tested and showed the strongest binding of all anti-Env MAbs tested, including the V3 and C5 region MAbs – notes core epitope as LLGI – no neutralizing activity was observed when 246-D was tested with five isolates. Nyambi *et al.* [2000] (**subtype comparisons**)
- 246-D: Mutations in BH10 gp160, W596Y and T605A, as well as deletions of 605-609 (TTAVP) and 597-609 (GCSGKLICTTAVP), abrogate binding of enhancing MAbs 86, 240D, 50-69, and 246-D – 5/6 enhancing MAbs identified to date bind to the immunodominant region 579-613. Mitchell *et al.* [1998] (**antibody binding site definition and exposure**)
- 246-D: This antibody, along with murine MAb D61, can be blocked by any of a group of 8 conformational MAbs (M10, D41, D54, T4, T6, T9, T10 and T35). Earl *et al.* [1997] (**antibody interactions**)
- 246-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D)and cluster II gp41 (98-6) MAbs at higher concentrations and 246-D neutralized 91US056 – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 246-D: No neutralizing activity, both ADCC and viral enhancing activity. Forthal *et al.* [1995] (**complement**, **enhancing activity**)
- 246-D: Virions complexed to gp41 Ab facilitate presentation of p66 RT epitopes to Th cells. Manca *et al.* [1995a]
- 246-D: Ab-mediated activation of complement on HIV+ cells is higher than Ab independent activation—what has been termed "Ab independent" in fact results in part from IgM in normal human serum that is HIV-cross-reactive. Saarloos *et al.* [1995] (**complement**)
- 246-D: Called SZ-246.D. Eddleston *et al.* [1993]
- 246-D: Did not mediate deposition of complement component C3 on HIV infected cells unless cells were pre-incubated with sCD4. Spear *et al.* [1993] (**complement**)
- 246-D: No neutralizing activity, some enhancing activity. Robinson *et al.* [1991] (**enhancing activity**)
- 246-D: Fine mapping indicates core is LLGI. Xu *et al.* [1991] (**antibody binding site definition and exposure**)

No. 725
MAb ID polyclonal
HXB2 Location gp160 (590–607)
Author Location gp41
Epitope `QQLLGIWGCSGKLICTTA`
Subtype B, CRF01_AE
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Parekh *et al.* 2002

- A simple enzyme immunoassay (EIA) that detects increasing levels of anti-HIV IgG after seroconversion can be used for detecting recent HIV-1 infection – longitudinal specimens from 139 incident infections in the US and Thailand were used in the study – the method was generally applicable for HIV-1 subtypes A, B, C, D and E(CRF01). Parekh *et al.* [2002]

No. 726
MAb ID 9G5A
HXB2 Location gp160 (591–594)
Author Location gp41 (596–599 IIIB)
Epitope `QLLG`
Neutralizing
Immunogen anti-idiotype
Species (Isotype) mouse (IgM)
References Beretta & Dalgleish 1994; Lopalco *et al.* 1993

- 9G5A: Anti-idiotype to gp120 C terminus (C5 region) MAb M38. Lopalco *et al.* [1993]

No. 727
MAb ID 181-D (SZ-181.D)
HXB2 Location gp160 (591–597)
Author Location gp41 (591–597 HXB2)
Epitope `qLLGIWg`
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG2κ)
Ab Type gp41 cluster I
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU, NY
References Holl *et al.* 2006a; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Gorny & Zolla-Pazner 2000; Fontenot *et al.* 1995; Forthal *et al.* 1995; Eddleston *et al.* 1993; Robinson *et al.* 1991; Xu *et al.* 1991
Keywords ADCC, antibody binding site definition and exposure, dendritic cells, enhancing activity, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 181-D: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 181-D: This is one of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)

- 181-D: Core epitope aa 591 to 597, a cluster I epitope that does not bind to either a peptide complex that approximates the core of the fusogenic form of gp41 or the individual peptides N51 and C43 that form this structure – MAbs 181-D and 246-D had similar properties. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
- 181-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 cluster I anti-gp41 MAbs which showed good cross clade reactivity – 181-D bound the majority of isolates although binding was moderate to weak. Nyambi *et al.* [2000] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 181-D: No neutralizing, no ADCC, and no viral enhancing activity. Forthal *et al.* [1995] (**ADCC**, **enhancing activity**)
- 181-D: Called SZ-181.D. Eddleston *et al.* [1993]
- 181-D: No enhancing or neutralization activity. Robinson *et al.* [1991] (**enhancing activity**)
- 181-D: Fine mapping indicates core is LLGIW. Xu *et al.* [1991] (**antibody binding site definition and exposure**)

No. 728
MAb ID 240-D (F240)
HXB2 Location gp160 (592–600)
Author Location gp41 (592–600 HXB2)
Epitope LLGIWGCSG
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp41 cluster I
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU, NY
References Vincent *et al.* 2008; Frey *et al.* 2008; Holl *et al.* 2006a; Gorny & Zolla-Pazner 2004; Finnegan *et al.* 2002; Nyambi *et al.* 2000; Mitchell *et al.* 1998; Wisnewski *et al.* 1996; Wisnewski *et al.* 1995; Binley *et al.* 1996; Spear *et al.* 1993; Robinson *et al.* 1991; Xu *et al.* 1991
Keywords antibody binding site definition and exposure, antibody sequence variable domain, binding affinity, complement, dendritic cells, enhancing activity, kinetics, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 240-D: NIH AIDS Research and Reference Reagent Program: 1242.
- 240-D: Molecular mechanism of neutralization by MPER antibodies, 2F5 and 4E10, was studied using preparations of trimeric HIV-1 Env protein in the prefusion, the prehairpin intermediate and postfusion conformations. MAb 240-D was used to analyze antigenic properties of construct 92UG-gp140-Fd, derived from isolate 92UG037.8 and stabilized by a C-terminal foldon tag. 92UG-gp140-Fd trimer binds 240-D. There is also strong binding of 240-D with plasmin cleaved 92UG-gp140-Fd. Frey *et al.* [2008] (**antibody binding site definition and exposure**, **binding affinity**)
- 240-D: 240-D reacted with maltose-binding protein MBP32, containing both HR1 and HR2 domains of gp41, and with MBP37, containing only the HR2 domain, but not with MBP-HR1, containing only the HR1 domain. In addition, 246-D did not react with MBP-HR1/T20, MBP-HR1/H44, and MBP-HR1/C23 complexes. Vincent *et al.* [2008] (**antibody binding site definition and exposure**)
- 240-D: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication by this Ab for macrophages and iDCs occurrs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. It is also suggested that this Ab is directed against epitopes distinct from those recognized by NAbs and that it will not imapair virus entry into PBMCs but that it could participate in the protection of mucosal HIV transmission by preventing the infection of macrophages and iDCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 240-D: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 240-D: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I MAbs 50-69, F240, 240-D,3D6, and 246-D recognize a nonhelical hydrophobic region, positions 598-604, that forms a disulfide loop in the six-helix bundle. Cluster II MAbs 98-6 and 126-6 recognized residues 644-663 of gp41, a portion of the second heptad repeat. These MAbs were found to behave similarly, so 50-69 and 98-6 were used as representatives. Exposure of cluster I and cluster II epitopes required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor. Binding to CD4 exposed hidden cluster I and II epitopes. The MAbs were found to bind to gp120/gp41 complexes, not to gp41 after shedding of gp120, and were localized to at fusing-cell interfaces. Kinetic and binding results indicate that these MAbs are exposed in transitional structures during the fusion process, possibly the prehairpin intermediate prior to co-receptor binding, although other intermediate structures may be involved. They do not bind once syncytia begin to show extensive cyotplasmic mixing. These MAbs failed to inhibit fusion. The NAb 2F5 has a very different behavior in this study. Finnegan *et al.* [2002] (**antibody binding site definition and exposure**, **kinetics**)
- 240-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 cluster I anti-gp41 MAbs which showed good cross clade reactivity – 246-D bound strongly or moderately to 24/26 HIV-1 group M clades viruses tested. Nyambi *et al.* [2000] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 240-D: Mutations in BH10 gp160, W596Y and T605A, as well as deletions of 605-609 (TTAVP) and 597-609 (GCSGK-LICTTAVP), abrogate binding of enhancing MAbs 86, 240D, 50-69, and 246-D – 5/6 enhancing MAbs identified to date bind to the immunodominant region 579-613. Mitchell *et al.* [1998] (**enhancing activity**)
- 240-D: Binds to a linear epitope located in the cluster I region – binding of 50-69 and 240-D inhibited by Fabs A1, A4, M8B,

B Cell

M26B, M12B and T2. Binley *et al.* [1996] (**antibody binding site definition and exposure**)
- 240-D: V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996] (**antibody sequence variable domain**)
- 240-D: Did not mediate deposition of complement component C3 on HIV infected cells. Spear *et al.* [1993] (**complement**)
- 240-D: No neutralizing activity, some enhancing activity. Robinson *et al.* [1991] (**enhancing activity**)
- 240-D: Fine mapping indicates core is IWG. Xu *et al.* [1991] (**antibody binding site definition and exposure**)

No. 729
MAb ID F240
HXB2 Location gp160 (592–606)
Author Location gp41 (592–606 BH10)
Epitope LLGIWGCSGKLICTT
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster I
Research Contact L. Cavacina or M. Posner, Dept. of Med. Harvard Med. School, Boston MA, USA
References Vincent *et al.* 2008; Miranda *et al.* 2007; Holl *et al.* 2006a; Liu *et al.* 2005a; Kalia *et al.* 2005; Gorny & Zolla-Pazner 2004; Finnegan *et al.* 2002; Follis *et al.* 2002; Cavacini *et al.* 2003; Cavacini *et al.* 2002; York *et al.* 2001; Cavacini *et al.* 1998a
Keywords antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, binding affinity, co-receptor, dendritic cells, enhancing activity, isotype switch, neutralization, review, variant cross-recognition or cross-neutralization

- F240: F240 reacted with maltose-binding protein MBP32, containing both HR1 and HR2 domains of gp41, and with MBP37, containing only the HR2 domain, but not with MBP-HR1, containing only the HR1 domain. Vincent *et al.* [2008] (**antibody binding site definition and exposure**)
- F240: F240 Ab was produced in Chinese hamster ovary (CHO)-K1 cells as three different isotypes, F240-IgG1, F240-IgG3, and F240-IgG4. The produced Abs were shown to be equivalently immunoreactive with recombinant gp140 and primary isolate viruses as the parental F240. In contrast to parental F240, F240-IgG1 from CHO cells was able to neutralize the majority of tier 1 and 2 clade B isolates, and two clade C tier 2 isolates. Clade A tier 2 isolates were not neutralized by this Ab. F240-IgG3 isotype was most potent in neutralizing the virus, while F240-IgG4 was less able to neutralize infection. There were no differences found in the sequences of the L and H chain variable regions of all the F240 Abs, but there was an increase in glycans associated with the Abs generated in CHO cells. PNGase F treatment, which removes all types of N-linked glycosylation, did not affect binding properties of CHO-derived F240 Abs, but it significantly abolished the neutralizing activity of F240 with isolate 89.6. PNGase F-treatment had no effect on the neutralization of SF162 and 93MW960 isolates, while it was required to neutralize the 67970 isolate by F240-IgG1 Ab. Miranda *et al.* [2007] (**isotype switch**, **neutralization**, **binding affinity**, **antibody sequence variable domain**)
- F240: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication by this Ab for macrophages and iDCs occurrs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. It is also suggested that this Ab is directed against epitopes distinct from those recognized by NAbs and that it will not imapair virus entry into PBMCs but that it could participate in the protection of mucosal HIV transmission by preventing the infection of macrophages and iDCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- F240: Point mutations in the highly conserved structural motif LLP-2 within the intracytoplasmic tail of gp41 resulted in conformational alternations of both gp41 and gp120. The alternations did not affect virus CD4 binding, coreceptor binding site exposure, or infectivity of the virus, but did result in decreased binding and neutralization by certain MAbs and human sera. F240 showed a decrease in binding to the LLP-2 mutant compared to the wildtype virus, indicating that its epitope was altered by the mutation. Kalia *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)
- F240: Transduction of human CD4+ H9 T cells with both the intracellularly expressed and secreted forms of the single-chain F240 Ab inhibited MN virus production. The secreted form was more potent. Viral replication of HIV-1 primary isolates was not reduced. Liu *et al.* [2005a]
- F240: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- F240: The MAb B4e8 binds to the base of the V3 loop, neutralizes multiple primary isolates and was studied for interaction with other MAbs. Anti-gp41 MAb F240 could inhibit B4e8 neutralization. Cavacini *et al.* [2003] (**antibody interactions**)
- F240: This study examined antibody interactions, binding and neutralization with a B clade R5 isolate (92US660) and R5X4 isolate (92HT593). Abs generally bound and neutralized the R5X4 isolate better than the R5 isolate, with the exception of F240 which bound both equally well, which captured more virus than any other human MAb tested, and didn't neutralize either isolate.F240 enhanced the binding of CD4BS MAbs IgG1b12 and F105 and the gp41 MAb 2F5 for both R5X4 and R5 isolates. F240 binding to gp41 was not affected by the binding of the V3 loop MAb B4a1, but preincubation with F240 could enhance B4a1 binding of the R5 isolate. Synergistic neutralization between F240 and CD4i MAbs 17b and 48d was noted for the R5X4 but not the R5 isolate, and F240 also enhanced neutralization of the R5X4 isolate by 2F5, but had no effect on R5 virus. In contrast, F240 combined with 2G12 demonstrated enhanced neutralization of R5 virus at low Ab concentrations. Cavacini *et al.* [2002] (**antibody interactions**, **co-receptor**)
- F240: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during bind-

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ing and fusion. Cluster I MAbs 50-69, F240, 240-D,3D6, and 246-D recognize a nonhelical hydrophobic region, positions 598-604, that forms a disulfide loop in the six-helix bundle. Cluster II MAbs 98-6 and 126-6 recognized residues 644-663 of gp41, a portion of the second heptad repeat. These MAbs were found to behave similarly, so 50-69 and 98-6 were used as representatives. Exposure of cluster I and cluster II epitopes required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor. Binding to CD4 exposed hidden cluster I and II epitopes. The MAbs were found to bind to gp120/gp41 complexes, not to gp41 after shedding of gp120, and were localized to at fusing-cell interfaces. Kinetic and binding results indicate that these MAbs are exposed in transitional structures during the fusion process, possibly the prehairpin intermediate prior to co-receptor binding, although other intermediate structures may be involved. They do not bind once syncytia begin to show extensive cytoplasmic mixing. These MAbs failed to inhibit fusion. The NAb 2F5 has a very different behavior in this study. Finnegan *et al.* [2002] (**antibody binding site definition and exposure**)

- F240: Alanine mutations were introduced into the N- and C-terminal alpha-helices of gp41 to destabilize interhelical packing interactions in order to study their inhibitory effect on viral infectivity. These mutations were shown to inhibit viral replication though affecting the conformational transition to the fusion-active form of gp41, and allow increased inhibition by gp41 peptides. 2F5 sensitivity is increased in the mutated viruses, presumably because 2F5s neutralization activity is focused on the transition to the fusion active state. No other gp41 MAb against tested, including NC-1, 50-69D, 1281, 98-6D, 246-D and F240, neutralized the parental or the fusion-deficient mutated viruses. Follis *et al.* [2002] (**antibody binding site definition and exposure**)
- F240: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAbs alters some step after binding. York *et al.* [2001] (**variant cross-recognition or cross-neutralization**)
- F240: Distinct from MAb 240-D, an antibody with a similar epitope in the immunodominant region of gp41 – dose-dependent reactivity with HIV isolates RF, SF2, IIIB, and MN was observed – F240 had no neutralizing activity and enhances infection in the presence of complement – reactivity of F240 is enhanced by preincubation of cells with sCD4 or anti-CD4BS MAb F105 – heavy and light chain variable domains were sequenced, and a strong homology to hu MAb 3D6 was observed, as 3D6 binds to the same epitope, these MAbs may define a human Ab clonotype. Cavacini *et al.* [1998a] (**enhancing activity**, **variant cross-recognition or cross-neutralization**, **antibody sequence variable domain**)

No. 730
MAb ID D49
HXB2 Location gp160 (592–608)
Author Location gp41 (597–613)
Epitope LLGIWGCSGKLICTTAV
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* dimeric Env
Species (Isotype) mouse
Ab Type gp41 cluster I
Research Contact Pat Earl
References Nelson *et al.* 2008; Dimitrov *et al.* 2007; Earl *et al.* 1997; Earl *et al.* 1994
Keywords kinetics

- D49: Immobilized D49 was able to capture infectious HIV-1 whole virions in a standard virus capture assay, unlike mAbs 8K8 and D5. Nelson *et al.* [2008]
- D49: In contrast to a decrease of 2F5 and 4E10 binding upon triggering of HIV-1 Env-expressing cells with target cells, binding of D49 to it epitope in the immunodominant loop of gp41 remains unchanged, indicating that the decrease seen for 2F5 and 4E10 is not due to removal of gp41 from the surface. Dimitrov *et al.* [2007] (**kinetics**)
- D49: Binding maps to region 597-613: WGCSGKLICTTAVPWNA – immunodominant region containing two Cys residues. Earl *et al.* [1997]
- D49: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 731
MAb ID D61
HXB2 Location gp160 (592–608)
Author Location gp41 (592–608 HXB2)
Epitope LLGIWGCSGKLICTTAV
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* dimeric Env
Species (Isotype) mouse
Ab Type gp41 cluster I
Research Contact Patricia Earl and Christopher Broder, NIH
References Zhang *et al.* 2008; Wright *et al.* 2008; Golding *et al.* 2002b; Earl *et al.* 1997; Weissenhorn *et al.* 1996; Richardson *et al.* 1996; Earl *et al.* 1994
Keywords antibody binding site definition and exposure, antibody generation, isotype switch, mucosal immunity

- D61: Several IgG MAbs were isotype switched to IgA and tested for their abilities to generate immune complexes with HIV-1 and be excreted from polarized epithelial cells from the basolateral to the apical surface via polymeric Ig receptor (pIgR) binding. Unlike IgA D10, D47, D19, and D25, IgA D61 was not able to excrete HIV. D61 bound weakly to HIV but the produced immune complex failed to associate with pIgR. These results show that some IgA Abs have potential to excrete HIV from mucosal lamina propria thus decreasing the viral burden and access to susceptible cells. Wright *et al.* [2008] (**isotype switch**, **mucosal immunity**)
- D61: D61 did not compete with the newly defined neutralizing mAb m44 for binding to gp41. Zhang *et al.* [2008]

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- D61: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – the preincubation 31.5 C step did not alter the inhibitory activity of neutralizing Abs anti-gp41 2F5, or anti-gp120 2G12, IG1b12, 48d, and 17b – nor did it alter two gp41 MAbs, T9 and D61, inability to inhibit fusion. Golding *et al.* [2002b] (**antibody binding site definition and exposure**)
- D61: Binding maps to region 597-613: WGCSGKLICT-TAVPWNA – immunodominant region containing two Cys residues – this antibody, along with human MAb 246-D, can be blocked by any of a group of 8 conformational MAbs (M10, D41, D54, T4, T6, T9, T10 and T35) – members of this competition group are blocked by sera from HIV-1 + individuals. Earl *et al.* [1997] (**antibody binding site definition and exposure**)
- D61: Linear gp41 epitope in the cluster I region – human sera blocked binding in oligomeric ELISA assay to a similar extent for gp41 MAbs D20, D43, D61, and T4. Richardson *et al.* [1996] (**antibody binding site definition and exposure**)
- D61: Does not precipitate gp41(21-166), but due to a structural difference in the disulfide bonding region near the two cysteines – the authors propose that this region may change conformation during the activation of the membrane fusion state of the HIV-1 glycoprotein. Weissenhorn *et al.* [1996] (**antibody binding site definition and exposure**)
- D61: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994] (**antibody generation**)

No. 732
MAb ID T32
HXB2 Location gp160 (592–608)
Author Location gp41 (597–613)
Epitope `LLGIWGCSGKLICTTAV`
Neutralizing
Immunogen vaccine
Vector/Type: tetrameric Env *HIV component:* Env
Species (Isotype) mouse
Ab Type gp41 cluster I
Research Contact Patricia Earl and Christopher Broder, NIH
References Earl *et al.* 1997; Earl *et al.* 1994

- T32: Binding maps to region 597-613: WGCSGKLICT-TAVPWNA – immunodominant region containing two Cys residues. Earl *et al.* [1997]
- T32: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 733
MAb ID T34
HXB2 Location gp160 (592–608)
Author Location gp41 (597–613)
Epitope `LLGIWGCSGKLICTTAV`
Neutralizing
Immunogen vaccine
Vector/Type: tetrameric Env *HIV component:* Env
Species (Isotype) mouse
Ab Type gp41 cluster I
Research Contact Patricia Earl and Christopher Broder, NIH
References Earl *et al.* 1997; Earl *et al.* 1994

- T34: Binding maps to region 597-613: WGCSGKLICT-TAVPWNA – immunodominant region containing two Cys residues. Earl *et al.* [1997]
- T34: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response – an oligomer with no gp120/gp41 cleavage site was used as the immunogen. Earl *et al.* [1994]

No. 734
MAb ID 115.8
HXB2 Location gp160 (593–604)
Author Location gp41 (598–609)
Epitope `LGLIWGCSGKLIC`
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) mouse (IgM)
References Oldstone *et al.* 1991

- 115.8: Stimulated by immunization with the peptide: LGLI-WGCSGKLIC (aa 598-609) – poor reactivity with CSGKLIC – reacts well with longer HIV-2 peptide NSWGCAFRQVC as well as CAFRQVC – disulfide bond between cysteines required. Oldstone *et al.* [1991]

No. 735
MAb ID M-1
HXB2 Location gp160 (593–604)
Author Location gp41 (598–609)
Epitope `LGIWGCSGKLIC`
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) mouse (IgG1, IgG2b)
References Yamada *et al.* 1991

- M-1: Unlike M-22, did not react to 43-kd protein found in rat and human astrocytes. Yamada *et al.* [1991]

No. 736
MAb ID M-11
HXB2 Location gp160 (593–604)
Author Location gp41 (598–609)
Epitope `LGIWGCSGKLIC`
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) mouse (IgG1)
References Yamada *et al.* 1991

- M-11: Strongly reacted with a cellular 43-kd protein found in rat and human astrocytes as well as with gp41. Yamada *et al.* [1991]

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No. 737
MAb ID M-13
HXB2 Location gp160 (593–604)
Author Location gp41 (598–609)
Epitope LGIWGCSGKLIC
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) mouse (IgG2b)
References Yamada *et al.* 1991

- M-13: Reacted with a cellular 43-kd protein found in rat and human astrocytes as well as with gp41. Yamada *et al.* [1991]

No. 738
MAb ID M-2
HXB2 Location gp160 (593–604)
Author Location gp41 (598–609)
Epitope LGIWGCSGKLIC
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) mouse (IgG2b)
References Yamada *et al.* 1991

- M-2: Strongly reacted with a cellular 43-kd protein found in rat and human astrocytes as well as with gp41. Yamada *et al.* [1991]

No. 739
MAb ID M-22
HXB2 Location gp160 (593–604)
Author Location gp41 (598–609)
Epitope LGIWGCSGKLIC
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) mouse (IgG2b)
References Yamada *et al.* 1991

- M-22: Strongest reaction of 12 anti-HIV-1 gp41 MAbs to a cellular 43-kd protein found in rat and human astrocytes. Yamada *et al.* [1991]

No. 740
MAb ID M-24
HXB2 Location gp160 (593–604)
Author Location gp41 (598–609)
Epitope LGIWGCSGKLIC
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) mouse (IgG1)
References Yamada *et al.* 1991

- M-24: Strongly reacted with a cellular 43-kd protein found in rat and human astrocytes as well as with gp41. Yamada *et al.* [1991]

No. 741
MAb ID M-25
HXB2 Location gp160 (593–604)
Author Location gp41 (598–609)
Epitope LGIWGCSGKLIC
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) mouse (IgG1)
References Yamada *et al.* 1991

- M-25: Reacted with a cellular 43-kd protein found in rat and human astrocytes as well as with gp41. Yamada *et al.* [1991]

No. 742
MAb ID M-28
HXB2 Location gp160 (593–604)
Author Location gp41 (598–609)
Epitope LGIWGCSGKLIC
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) mouse (IgG1)
References Yamada *et al.* 1991

- M-28: Strongly reacted with a cellular 43-kd protein found in rat and human astrocytes as well as with gp41. Yamada *et al.* [1991]

No. 743
MAb ID M-29
HXB2 Location gp160 (593–604)
Author Location gp41 (598–609)
Epitope LGIWGCSGKLIC
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) mouse (IgG1)
References Yamada *et al.* 1991

- M-29: Unlike M-22, did not react to 43-kd protein found in rat and human astrocytes. Yamada *et al.* [1991]

No. 744
MAb ID M-36
HXB2 Location gp160 (593–604)
Author Location gp41 (598–609)
Epitope LGIWGCSGKLIC
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) mouse (IgG1)
References Yamada *et al.* 1991

- M-36: Unlike M-22, did not react to 43-kd protein found in rat and human astrocytes. Yamada *et al.* [1991]

No. 745
MAb ID M-4
HXB2 Location gp160 (593–604)
Author Location gp41 (598–609)

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Epitope LGIWGCSGKLIC
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) mouse (IgG2b)
References Yamada *et al.* 1991

- M-4: Unlike M-22, did not react to 43-kd protein found in rat and human astrocytes. Yamada *et al.* [1991]

No. 746
MAb ID M-6
HXB2 Location gp160 (593–604)
Author Location gp41 (598–609)
Epitope LGIWGCSGKLIC
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) mouse (IgG2b)
References Yamada *et al.* 1991

- M-6: Unlike M-22, did not react to 43-kd protein found in rat and human astrocytes. Yamada *et al.* [1991]

No. 747
MAb ID polyclonal α598-609
HXB2 Location gp160 (594–601)
Author Location gp41 (598–609)
Epitope GIWGCSGK
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Poumbourios *et al.* 1992

- alpha(598-609): Affinity purified from HIV-1 + plasma – immunodominant region, binds oligomer and monomer. Poumbourios *et al.* [1992]

No. 748
MAb ID 1B8.env (1B8)
HXB2 Location gp160 (594–604)
Author Location gp41 (594–605 HXB2)
Epitope GIWGCSGKLIC
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG2λ)
References Gorny & Zolla-Pazner 2004; Enshell-Seijffers *et al.* 2001; Banapour *et al.* 1987
Keywords antibody binding site definition and exposure, review, variant cross-recognition or cross-neutralization

- 1B8B.env: Called 1B8. There are 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 1B8.env: Monoclonal antibodies to this epitope have distinct phenotypes—41-7 and 1B8.env were found to be not neutralizing, 2F11 possibly enhancing, and clone 3 beneficial. Enshell-Seijffers *et al.* [2001]
- 1B8.env: Highly conserved epitope recognized by the majority of HIV-1 infected people – MAb does not neutralize. Banapour *et al.* [1987] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)

No. 749
MAb ID polyclonal
HXB2 Location gp160 (594–609)
Author Location gp41 (601–616)
Epitope GIWGCSGKLICTTAVP
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human
References Petrov *et al.* 1990

- Immunodominant and broadly reactive peptide. Petrov *et al.* [1990]

No. 750
MAb ID polyclonal
HXB2 Location gp160 (595–607)
Author Location gp41 (600–612)
Epitope IWGCSGKLICTTA
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Belliard *et al.* 2003
Keywords rate of progression

- Sera from 101 slow progressors and 42 fast progressors were tested for responses to Tat peptides, and compared to responses to gp41 peptide 600-612, as anti-Tat antibodies had been shown by others to be elevated in slow progressors. Most patient sera react with this peptide, it is used in diagnostics. In this study, overall levels of Tat antibodies were not different in the two groups, however relative levels of antibodies to different Tat peptides and to this gp41 peptide were observed. Belliard *et al.* [2003] (**rate of progression**)

No. 751
MAb ID clone 3 (CL3)
HXB2 Location gp160 (597–606)
Author Location gp41 (597–606)
Epitope GCSGKLICTT
Subtype B
Neutralizing L P
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
Research Contact BioClonetics (Philadelphia)
References Kramer *et al.* 2007; Srivastava *et al.* 2005; Mc Cann *et al.* 2005; Ferrantelli *et al.* 2004a; Gorny & Zolla-Pazner 2004; Enshell-Seijffers *et al.* 2001; Cotropia *et al.* 1996; Cotropia *et al.* 1992; Broliden *et al.* 1989
Keywords antibody binding site definition and exposure, neutralization, rate of progression, responses in children, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- Clone 3: This review summarizes Clone 3 Ab epitope, properties and neutralization activity. Kramer *et al.* [2007] (**review**)

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- Clone 3: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**, **review**)
- Clone 3: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **review**)
- clone 3: Called CL3 here. Nabs against HIV-1 M group isolates were tested for their ability to neutralize 6 randomly selected HIV-1 O group strains. Clone 3 could neutralize some O group strains. CL3 is specific for a linear epitope containing 2 cysteines that generate a loop that could be important during the fusion of the virus with the target cell. This epitope is represented as GCxGxxxCxT HIV-1 group O isolates. Ferrantelli *et al.* [2004a] (**variant cross-recognition or cross-neutralization**)
- clone 3: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. clone 3 neutralized 3 diverse B clade TCLA strains and 3 primary O group strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**, **subtype comparisons**)
- clone 3: Monoclonal antibodies to this epitope have distinct phenotypes—41-7 and 1B8.env were found to be not neutralizing, 2F11 possibly enhancing, and clone 3 beneficial. Enshell-Seijffers *et al.* [2001] (**variant cross-recognition or cross-neutralization**)
- clone 3: Inhibits replication of three diverse HIV-1 laboratory strains, as well as an AZT-resistant isolate. Cotropia *et al.* [1996] (**variant cross-recognition or cross-neutralization**)
- clone 3: Core binding domain gcsgkLIC – lack of serological activity to this region correlates with rapid progression in infants (Broliden *et al.* [1989]) Cotropia *et al.* [1992]. Broliden *et al.* [1989]; Cotropia *et al.* [1992] (**antibody binding site definition and exposure**, **responses in children**, **rate of progression**)

No. 752
MAb ID 4
HXB2 Location gp160 (598–604)
Author Location gp41 (598–609)
Epitope `CSGKLIC`
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) mouse (IgG2b)
References Bizub-Bender *et al.* 1994; Oldstone *et al.* 1991

- There is another MAb with this ID that reacts with integrase. Bizub-Bender *et al.* [1994]; Oldstone *et al.* [1991]
- 4: Stimulated by immunization with the peptide: LGLIWGCSGKLIC (aa 598-609) – poor cross-reactivity with HIV-2 peptide CAFRQVC – slightly more reactive with longer HIV-2 peptide NSWGCAFRQVC. Oldstone *et al.* [1991]

No. 753
MAb ID 41-6
HXB2 Location gp160 (598–604)
Author Location gp41 (598–609)
Epitope `CSGKLIC`
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) mouse (IgG2b)
References Oldstone *et al.* 1991

- 41-6: Stimulated by immunization with the peptide: LGLIWGCSGKLIC (aa 598-609) – poor cross-reactivity with HIV-2 peptide CAFRQVC – slightly more reactive with LGLIWGCSGKLIC and HIV-2 form NSWGCAFRQVC – disulfide bond between cysteines required. Oldstone *et al.* [1991]

No. 754
MAb ID 41-7
HXB2 Location gp160 (598–604)
Author Location gp41 (605–611)
Epitope `CSGKLIC`
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
References Enshell-Seijffers *et al.* 2001; Bugge *et al.* 1990

- 41-7: Monoclonal antibodies to this epitope have distinct phenotypes—41-7 and 1B8.env were found to be not neutralizing, 2F11 possibly enhancing, and clone 3 beneficial. Enshell-Seijffers *et al.* [2001]
- 41-7: Sera from 6/6 HIV-1 positive, but no HIV-2 positive individuals, interfered with 41-7 binding – Ab does not neutralize. Bugge *et al.* [1990]

No. 755
MAb ID 68.1
HXB2 Location gp160 (598–604)
Author Location gp41 (598–609)
Epitope `CSGKLIC`
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) mouse (IgM)
References Oldstone *et al.* 1991

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- 68.1: Stimulated by immunization with the peptide: LGLIWGCSGKLIC (aa 598-609) – cross-reactive with HIV-2 peptide CAFRQVC – more reactive with longer HIV-1 peptide LGLIWGCSGKLIC and HIV-2 peptide NSWGCAFRQVC. Oldstone *et al.* [1991]

No. 756
MAb ID 68.11
HXB2 Location gp160 (598–604)
Author Location gp41 (598–609)
Epitope CSGKLIC
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) mouse (IgM)
References Oldstone *et al.* 1991

- 68.11: Stimulated by immunization with the peptide: LGLIWGCSGKLIC (aa 598-609) – cross-reactive with HIV-2 peptide CAFRQVC – more reactive with longer HIV-1 peptide LGLIWGCSGKLIC and HIV-2 peptide NSWGCAFRQVC. Oldstone *et al.* [1991]

No. 757
MAb ID 75
HXB2 Location gp160 (598–604)
Author Location gp41 (598–609)
Epitope CSGKLIC
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) rat (IgG)
References Oldstone *et al.* 1991

- 75: Stimulated by immunization with the peptide: LGLIWGCSGKLIC (aa 598-609) – poor cross-reactivity with HIV-2 peptide CAFRQVC – more reactive with longer HIV-2 peptide NSWGCAFRQVC. Oldstone *et al.* [1991]

No. 758
MAb ID polyclonal
HXB2 Location gp160 (598–604)
Author Location gp41 (603–609)
Epitope CSGKLIC
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Enshell-Seijffers *et al.* 2001

- Monoclonal antibodies to this epitope have distinct phenotypes – 41-7 and 1B8.env were found to be not neutralizing, 2F11 possibly enhancing, and clone 3 beneficial – isolated mimotope-presenting phages corresponding to the immunodominant gp41 epitope CSGKLIC were used to study the diversity of polyclonal responses in 30 HIV+ sera, and all but one of the patients reacted showing distinctive variable polyclonal recognition patterns. Enshell-Seijffers *et al.* [2001]

No. 759
MAb ID 105-732
HXB2 Location gp160 (599–606)
Author Location gp41 (HAM112, O group)
Epitope KGRLICYT
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* O group HAM112 *HIV component:* gp160
Species (Isotype) mouse (IgG2bκ)
References Scheffel *et al.* 1999

- 105-732: Overlapping peptides based on group O HAM112 Env were tested for MAb reactivity – MAb 105-732 bound to two overlapping peptides. Scheffel *et al.* [1999]

No. 760
MAb ID 3D6 (IAM 41-3D6)
HXB2 Location gp160 (599–613)
Author Location gp41 (604–617 BH10)
Epitope SGKLICTTAVPWNAS
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster I, immunodominant region
Research Contact H. Katinger, Inst. Appl. Microbiol., Vienna, Austria and Viral Testing Systems, Houston, TX
References Gorny & Zolla-Pazner 2004; Finnegan *et al.* 2002; Cavacini *et al.* 1999; Cavacini *et al.* 1998a; Cavacini *et al.* 1998b; Kunert *et al.* 1998; Wisnewski *et al.* 1996; Stigler *et al.* 1995; Sattentau *et al.* 1995; Chen *et al.* 1994b; He *et al.* 1992; Felgenhauer *et al.* 1990
Keywords antibody binding site definition and exposure, antibody sequence variable domain, kinetics, review, structure

- 3D6: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 3D6: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I MAbs 50-69, F240, 240-D,3D6, and 246-D recognize a nonhelical hydrophobic region, positions 598-604, that forms a disulfide loop in the six-helix bundle. Cluster II MAbs 98-6 and 126-6 recognized residues 644-663 of gp41, a portion of the second heptad repeat. These MAbs were found to behave similarly, so 50-69 and 98-6 were used as representatives. Exposure of cluster I and cluster II epitopes required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor. Binding to CD4 exposed hidden cluster I and II epitopes. The MAbs were found to bind to gp120/gp41 complexes, not to gp41 after shedding of gp120, and were localized to at fusing-cell interfaces. Kinetic and binding results indicate that these MAbs are exposed in transitional structures during the fusion process, possibly the prehairpin intermediate prior to co-receptor binding, although other intermediate structures may be involved. They do not bind once syncytia begin to show extensive cyotplasmic mixing. These MAbs failed to inhibit fusion. The NAb 2F5 has a very different behavior in this study. Finnegan

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et al. [2002] (**antibody binding site definition and exposure**, **kinetics**)

- 3D6: Cavacini *et al.* note that both MAbs F223 and 3D6 are anti-HIV-1 Env MAbs that have an autoimmune response and that both use uses VH3 germline genes. Cavacini *et al.* [1999]
- 3D6: Binds to the immunodominant region of gp41 – a strong homology between heavy variable domains of hu MAb 3D6 and MAb F20 was observed, these MAbs may define a human Ab clonotype. Cavacini *et al.* [1998a] (**antibody sequence variable domain**)
- 3D6: The complete V, J and D(H) domain was sequenced – in contrast the sequences of five neutralizing MAbs, 3D6 had very little somatic mutation, with homologies of 97-98% relative to germline genes. Kunert *et al.* [1998] (**antibody sequence variable domain**)
- 3D6: 3D6 is V H3 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996] (**antibody sequence variable domain**)
- 3D6: Called IAM 41-3D6: binding increased after pretreatment of infected cells with sCD4 – binding domain overlaps site that is critical for gp120-gp41 association. Sattentau *et al.* [1995] (**antibody binding site definition and exposure**)
- 3D6: Optimum peptide for binding 3D6 Fab was CSGKLICTTAVPW. Stigler *et al.* [1995] (**antibody binding site definition and exposure**)
- 3D6: This MAb binds to HIV gp41, and to a 43 kd protein found in human T, B and monocyte cell lines, proposed molecular mimicry. Chen *et al.* [1994b]
- 3D6: Fab fragment crystal structure. He *et al.* [1992] (**structure**)
- 3D6: Sequence of cDNA encoding V-regions. Felgenhauer *et al.* [1990] (**antibody sequence variable domain**)

No. 761
MAb ID P1G9
HXB2 Location gp160 (600–610)
Author Location gp41
Epitope `GKLICTTAVPW`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with protein boost
Strain: B clade SF162 *HIV component:* gp140
Species (Isotype) mouse (IgG1κ)
Ab Type gp41 cluster I
Research Contact Nina Derby or Leo Stamatatos, Seattle Biomedical Research Institute, Seattle, WA, USA, leo.stamatotos@sbri.org
References Derby *et al.* 2007
Keywords antibody binding site definition and exposure, binding affinity, kinetics, neutralization, optimal epitope

- P1G9: This Ab recognized trimeric ΔV2gp140 but not monomeric ΔV2gp140, suggesting that the epitope is affected by the state of Env oligomerization. P1G9 did not neutralize homologous SF162, nor viruses lacking V1 or V2 loops. Lack of neutralizing activity of this Ab could not be attributed to its binding kinetics. P1G9 did not neutralize any of the viruses with Envs lacking specific glycosylation sites. Derby *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **optimal epitope**, **kinetics**, **binding affinity**)

No. 762
MAb ID F172-D8 (F172-D8, scFvD8)
HXB2 Location gp160 (604–615)
Author Location gp41 (609–620)
Epitope `CTTAVPWNASWS?`
Neutralizing
Immunogen
Species (Isotype) human
References Kanduc *et al.* 2008; Legastelois & Desgranges 2000

- F172-D8: Similarity level of the F172-D8 binding site pentapeptide PWNAS to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- F172-D8: As an approach to intercellular immunization using a single-chain variable fragment, scFvD8 was constructed based on the MAb F172-D8, directed at a loop in gp41 between the two heptad repeat regions – intracellular scFvD8 expression decreased gp160 expression and a scFvD8 transfected cell line did not support infection by HIV-1 Ba-L or primary isolates. Legastelois & Desgranges [2000]

No. 763
MAb ID P2D2
HXB2 Location gp160 (624–638)
Author Location gp41
Epitope `NNMTWMEWEREREIGNY`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with protein boost
Strain: B clade SF162 *HIV component:* gp140ΔV2
Species (Isotype) mouse (IgG2aκ)
Research Contact Nina Derby or Leo Stamatatos, Seattle Biomedical Research Institute, Seattle, WA, USA, leo.stamatotos@sbri.org
References Derby *et al.* 2007
Keywords antibody binding site definition and exposure, binding affinity, kinetics, neutralization, optimal epitope

- P2D2: This Ab recognized trimeric ΔV2gp140 but not monomeric ΔV2gp140, suggesting that the epitope is affected by the state of Env oligomerization. P2D2 did not neutralize homologous SF162, nor viruses lacking V1 or V2 loops. Lack of neutralizing activity of this Ab could not be attributed to its binding kinetics. P2D2 did not neutralize any of the viruses with Envs lacking specific glycosylation sites. Derby *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **optimal epitope**, **kinetics**, **binding affinity**)

No. 764
MAb ID P3B2
HXB2 Location gp160 (628–633)

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Author Location gp120
Epitope WKEM(D/N)R
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp140ΔV2
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 V1
Research Contact Nina Derby or Leo Stamatatos, Seattle Biomedical Research Institute, Seattle, WA, USA, leo.stamatotos@sbri.org
References Ching *et al.* 2008; Derby *et al.* 2007
Keywords antibody binding site definition and exposure, neutralization, optimal epitope

- P3B2: The study explores how the V1 loop of Env influences the neutralization susceptibilities of heterologous viruses to antibodies elicited by the SF162gp140 immunogen. When the V1 loop of the heterologous isolates was replaced by the V1 loop present on the DF162go140 immunogen, these isolates became susceptible to neutralization by P3B2. Ching *et al.* [2008] (**neutralization**)
- P3B2: Binding of P3B2 is partially dependent on the conformation of V1, while the presence of V3 is not required. This Ab bound equally to the trimeric and monomeric gp140 from both SF162wt and SF162ΔV2, suggesting that the binding does not require presence of the V2 loop. P3B2 neutralized SF162 potently but it did not have any heterologous neutralizing activity. The Ab did not neutralize virus lacking V1. The SF162ΔV2 virus was significantly more susceptible to neutralization by P3B2 than the wildtype virus. Glycans at positions 154 and 195 in V1V2 were involved in regulating P3B2 neutralizing potential. Neutralization by P3B2 was also enhanced strongly by deletion of the V3 glycan at position 299, somewhat less by deletion at position 329, and only slightly or not at all by deletion of the glycan at position 293. Glycans present in the V4-V5 region had only modest effects on the neutralizing potential of this Ab, where their removal resulted in a more neutralization resistant virus. Derby *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **optimal epitope**)

No. 765
MAb ID P3C8
HXB2 Location gp160 (628–633)
Author Location gp120 (SF162)
Epitope WKEM(D/N)R
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp140ΔV2 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 V1
Research Contact Nina Derby or Leo Stamatatos, Seattle Biomedical Research Institute, Seattle, WA, USA, leo.stamatotos@sbri.org
References Ching *et al.* 2008; Derby *et al.* 2007; Kraft *et al.* 2007; Derby *et al.* 2006
Keywords antibody binding site definition and exposure, binding affinity, escape, neutralization, optimal epitope, vaccine antigen design

- P3C8: The study explores how the V1 loop of Env influences the neutralization susceptibilities of heterologous viruses to antibodies elicited by the SF162gp140 immunogen. When the V1 loop of the heterologous isolates was replaced by the V1 loop present on the DF162go140 immunogen, these isolates became susceptible to neutralization by p3C8. Ching *et al.* [2008] (**neutralization**)
- P3C8: The minimal epitope for this Ab is most probably located within the N-terminal portion of the WKEMNRGEIKNCSFN peptide, WKEM(D/N)R. Binding of P3C8 is partially dependent on the conformation of V1, while the presence of V3 is not required. P3C8 neutralized SF162 potently but it did not have any heterologous neutralizing activity. The Ab had potent reactivity with trimeric and monomeric gp140 from both SF162wt and SF162ΔV2. The SF162ΔV2 virus was significantly more susceptible to neutralization by P3C8 than the wildtype virus. P3C8 did not neutralize virus lacking V1 loop. Glycans at positions 154 and 195 in V1V2 were involved in regulating P3C8 neutralizing potential. Neutralization by P3C8 was also enhanced strongly by deletion of the V3 glycan at position 299, somewhat less by deletion at position 329, and only slightly or not at all by deletion of the glycan at position 293. Glycans present in the V4-V5 region had only modest effects on the neutralizing potential of this Ab, where their removal resulted in a more neutralization resistant virus. Derby *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **optimal epitope**, **vaccine antigen design**, **binding affinity**)
- P3C8: Viruses from early and late infection of a macaque with SHIV SF162P4 were resistant to contemporaneous serum that had broadly reactive NAbs. SF162 was highly susceptible to neutralization by anti-V3 MAbs 447D and P3E1, as well as anti-V1 MAb P3C8, while envelopes cloned from this animal at 304 days and at 643 days (time of death) post infection had developed resistance to all three of these antibodies. This is a new anti-V1 loop Ab isolated from mice immunized with ΔV2gp140 SF162. Kraft *et al.* [2007] (**neutralization**, **escape**)
- P3C8: Macaques were immunized with SF162gp140, ΔV2gp140, ΔV2ΔV3gp140 and ΔV3gp140 constructs and their antibody responses were compared to the broadly reactive NAb responses in a macaque infected with SHIV SF162P4, and with pooled sera from humans infected with heterologous HIV-1 isolates (HIVIG). All four gp140 proteins were recognized by P3C8 equally indicating that the P3C8 epitope is well exposed in all constructs. P3C8 neutralized SF162 efficiently while its neutralization potential was reduced by 81% in the presence of V1 peptides. Derby *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**)

No. 766
MAb ID P4D7
HXB2 Location gp160 (628–633)
Author Location gp120
Epitope WKEM(D/N)R
Subtype B

B Cell

Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp140ΔV2
Species (Isotype) mouse (IgG1κ)
Ab Type gp120 V1
Research Contact Nina Derby or Leo Stamatatos, Seattle Biomedical Research Institute, Seattle, WA, USA, leo.stamatotos@sbri.org
References Ching *et al.* 2008; Derby *et al.* 2007
Keywords antibody binding site definition and exposure, neutralization, optimal epitope

- P4D7: The study explores how the V1 loop of Env influences the neutralization susceptibilities of heterologous viruses to antibodies elicited by the SF162gp140 immunogen. When the V1 loop of the heterologous isolates was replaced by the V1 loop present on the DF162go140 immunogen, these isolates became susceptible to neutralization by p4D7. Ching *et al.* [2008] (**neutralization**)
- P4D7: Binding of P4D7 is partially dependent on the conformation of V1, while the presence of V3 is not required. This Ab bound equally to the trimeric and monomeric gp140 from both SF162wt and SF162ΔV2, suggesting that the binding does not require presence of the V2 loop. P4D7 neutralized SF162 potently but it did not have any heterologous neutralizing activity. The Ab did not neutralize virus lacking V1. The SF162ΔV2 virus was significantly more susceptible to neutralization by P4D7 than the wildtype virus. Glycans at positions 154 and 195 in V1V2 were involved in regulating P3B2 neutralizing potential. Neutralization by P3B2 was also enhanced strongly by deletion of the V3 glycan at position 299, somewhat less by deletion at position 329, and only slightly or not at all by deletion of the glycan at position 293. Glycans present in the V4-V5 region had only modest effects on the neutralizing potential of this Ab, where their removal resulted in a more neutralization resistant virus. Derby *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **optimal epitope**)

No. 767
MAb ID P3C5
HXB2 Location gp160 (628–634)
Author Location gp120
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with protein boost *Strain:* B clade SF162 *HIV component:* gp140
Species (Isotype) mouse (IgG2aκ)
Ab Type gp120 V3
Research Contact Nina Derby or Leo Stamatatos, Seattle Biomedical Research Institute, Seattle, WA, USA, leo.stamatotos@sbri.org
References Derby *et al.* 2007
Keywords antibody binding site definition and exposure, binding affinity, neutralization, optimal epitope

- P3C5: P3C5 bound to V3 loop peptides with lower affinity than P3E1. This Ab bound equally to the trimeric and monomeric gp140 from both SF162wt and SF162ΔV2, suggesting that the binding does not require presence of the V2 loop. P3C5 neutralized SF162 with significantly reduced potency and it did not have any heterologous neutralizing activity. The SF162ΔV2 virus was significantly more susceptible to neutralization by P3C5 than the wildtype virus, while neutralization of the virus lacking V1 loop was significantly reduced, suggesting that the positioning of the Ab epitope is affected by the V1 loop. Glycans at positions 154 and 195 in V1V2 were involved in regulating P3C5 neutralizing potential. Neutralization by P3C5 was also enhanced strongly by deletion of the V3 glycan at position 299, somewhat less by deletion at position 329, and only slightly by deletion of the glycan at position 293. Glycans present in the V4-V5 region had only modest effects on the neutralizing potential of this Ab, where their removal resulted in a more neutralization resistant virus. Derby *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **optimal epitope**, **binding affinity**)

No. 768
MAb ID D50
HXB2 Location gp160 (632–655)
Author Location gp41 (642–665)
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* dimeric Env
Species (Isotype) mouse
Ab Type gp41 cluster II
Research Contact Patricia Earl and Christopher Broder, NIH
References Zhang *et al.* 2008; Nelson *et al.* 2008; Haynes & Montefiori 2006; Haynes *et al.* 2005b; de Rosny *et al.* 2004a; de Rosny *et al.* 2004b; Srivastava *et al.* 2002; Yang *et al.* 2000; Earl *et al.* 1997; Richardson *et al.* 1996; Binley *et al.* 1996; Earl *et al.* 1994
Keywords antibody binding site definition and exposure, antibody generation, antibody interactions, review

- D50: D50 was shown to bind to Envs used in typical epitope binding assays, unlike the neutralizing Abs 8K8, DN9, and D5 used in this study. Nelson *et al.* [2008]
- D50: D50 did not compete with the newly defined neutralizing mAb m44 for binding to gp41. Zhang *et al.* [2008]
- D50: This review describes the effectiveness of the current HIV-1 immunogens in eliciting neutralizing antibody responses to different clades of HIV-1. It also summarizes different evasion and antibody escape mechanisms, as well as the most potent neutralizing MAbs and their properties. MAbs reviewed in this article are: 2G12, IgG1b12, 2F5, 4E10, A32, 447-52D and, briefly, D50. Novel immunogen design strategies are also discussed. Haynes & Montefiori [2006] (**antibody binding site definition and exposure**)
- D50: This review summarizes data on the polyspecific reactivities to host antigens by the broadly neutralizing MAbs IgG1b12, 2G12, 2F5 and 4E10. It also hypothesizes that some

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broadly reactive Abs might not be routinely made because they are derived from B cell populations that frequently make polyspecific Abs and are thus subjected to B cell negative selection. Different types of anti-MPER Abs are discussed, including D50. Haynes *et al.* [2005b] (**antibody generation**, **antibody interactions**, **review**)

- D50: The MAb 2F5 binds to the C-heptad and is neutralizing, but the MAb D50 binds to the C-heptad and is not neutralizing. 2F5 binds preferentially to native gp41 prior to receptor activation. D50 prefers the triggered form after receptor activation. Trapped fusion-intermediates suggest 2F5 remains present shortly after gp120 triggering by CD4, but may be lost by the time the six-helix bundle is formed. D50 binds equally to the fusion-intermediate and six-helix bundle. 2F5 neutralization seems to block a later step of the fusion process. de Rosny *et al.* [2004b] (**antibody binding site definition and exposure**)
- D50: The mechanism of 2F5 neutralization was explored, and experiments suggest it is due to interference with a late step in viral entry. sCD4 binding to gp120 triggers conformational changes in gp41 allowing formation of the six helix bundle. The NAb 2F5 preferentially bound native gp41, prior to receptor triggering, while the antibody D50 that also binds to the heptad region, near 2F5, is not neutralizing, and preferentially bound the CD4 triggered gp41. The C and N peptides that can be used to block the formation of the six helix bundle and lock gp41 in the fusion intermediate state after sCD4 triggering enabled 2F5 to bind after sCD4 triggering, while D50 was able to bind to both the peptide-trapped and sCD4 induced six helix bundle equally well, suggesting the D50 epitope is linear and more exposed after sCD4 binding. de Rosny *et al.* [2004a] (**antibody binding site definition and exposure**)
- D50: Oligomeric gp140 (o-gp140) derived from R5 primary isolate US4 was characterized for use as a vaccine reagent – D50 was used to capture the o-gp140 for ELISA to test the antigencity of o-gp140 using a panel of well characterized MAbs. Srivastava *et al.* [2002]
- D50: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) – gp41 MAbs T4, D12, T3, and D50 bound less efficiently to gp140-GNC4 than did pooled sera, but T4 and D12 recognized the gp140-GNC4 timer equivalently to gp140(-), and T3 and D50 recognized the trimer at greater levels than gp140(-). Yang *et al.* [2000] (**antibody binding site definition and exposure**)
- D50: Found to bind to a linear peptide, between Env amino acids 642-655 – can be blocked by the conformation dependent MAbs D16, D17, D31, D36, D37, D40, D44, D55, D59, T37, and T45 – the region is in the immunogenic cluster two region – reactive with 9/10 HIV-1 strains tested, all except HIV-1 ADA, in which the change E659D and E662A may result in the loss of binding (ELLE to DLLA). Earl *et al.* [1997] (**antibody binding site definition and exposure**)
- D50: Thought to be a discontinuous epitope recognizing residues between 649-668 – designated cluster II – Fabs D5, D11, G1, T3, M12, M15, S6, S8, S9, S10 block binding. Binley *et al.* [1996] (**antibody binding site definition and exposure**)
- D50: Richardson suggests this is a linear gp41 epitope. Richardson *et al.* [1996] (**antibody binding site definition and exposure**)
- D50: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994] (**antibody generation**)

No. 769
MAb ID 5-21-3
HXB2 Location gp160 (642–665)
Author Location gp41 (642–665 HXB2)
Epitope `IHSLIEESQNQQEKNEQELLELDK`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* gp41
Species (Isotype) mouse
References Scheffel *et al.* 1999; Hunt *et al.* 1990

- 5-21-3: Binds group M gp41, used as a control in a study of group O MAbs. Scheffel *et al.* [1999]
- 5-21-3: Recognizes a contiguous, conformation-dependent epitope in a hydrophilic region. Hunt *et al.* [1990]

No. 770
MAb ID 120-16 (SZ-120.16)
HXB2 Location gp160 (644–663)
Author Location gp41 (644–663 HXB2)
Epitope `SLIEESQNQQEKNEQELLEL`
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG2κ)
References Wisnewski *et al.* 1996; Forthal *et al.* 1995; Eddleston *et al.* 1993; Robinson *et al.* 1991; Xu *et al.* 1991; Tyler *et al.* 1990; Robinson *et al.* 1990b; Andris *et al.* 1992

- 120-16: 120-16 is V H4 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996]
- 120-16: No neutralizing activity, both ADCC and viral enhancing activity. Forthal *et al.* [1995]
- 120-16: Called SZ-120.16. Eddleston *et al.* [1993]
- 120-16: Synergizes with huMAb 50-69 *in vitro* to enhance HIV-1 infection. Robinson *et al.* [1991]
- 120-16: Less reactive region than AVERY region – most Abs involving this region bound conformational epitopes, this was the only linear one. Xu *et al.* [1991]
- 120-16: Antibody dependent enhancement (ADE) of HIV-1 IIIB infectivity, synergistically enhanced by MAb V10-9. Robinson *et al.* [1990b]
- 120-16: Potent ADCC (in contrast to MAb 98-43, gp41(579-604)). Tyler *et al.* [1990]

No. 771
MAb ID 98-6 (SZ-98.6, 98.6, 98-6D)
HXB2 Location gp160 (644–663)
Author Location gp41 (644–663 HXB2)
Epitope `SLIEESQNQQEKNEQELLEL`

B Cell

Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG2κ)
Ab Type gp41 alpha-helical hairpin intermediate, gp41 cluster II
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU, NY
References Penn-Nicholson *et al.* 2008; Alam *et al.* 2008; Kim *et al.* 2007; Holl *et al.* 2006a; Usami *et al.* 2005; Ling *et al.* 2004; Gorny & Zolla-Pazner 2004; Finnegan *et al.* 2002; Follis *et al.* 2002; Golding *et al.* 2002b; Verrier *et al.* 2001; Taniguchi *et al.* 2000; Nyambi *et al.* 2000; Gorny *et al.* 2000; Gorny & Zolla-Pazner 2000; Nyambi *et al.* 1998; Hioe *et al.* 1997b; Wisnewski *et al.* 1996; Sattentau *et al.* 1995; Manca *et al.* 1995a; Forthal *et al.* 1995; Chen *et al.* 1995; Laal *et al.* 1994; Tani *et al.* 1994; Spear *et al.* 1993; Eddleston *et al.* 1993; Xu *et al.* 1991; Robinson *et al.* 1991; Sattentau & Moore 1991; Andris *et al.* 1992; Tyler *et al.* 1990; Robinson *et al.* 1990b; Till *et al.* 1989; Gorny *et al.* 1989; Pinter *et al.* 1989
Keywords ADCC, antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, binding affinity, complement, dendritic cells, enhancing activity, immunotoxin, kinetics, neutralization, rate of progression, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 98-6: NIH AIDS Research and Reference Reagent Program: 1240.
- 98-6: 98-6 blocked 2F5 and 13H11 binding to gp41 epitopes to variable degrees; the combination of 98-6 and 13H11 completely blocked 2F5 binding. MAb 98-6 showed strong binding to HIV-1-positive infected cells. Alam *et al.* [2008] (**antibody interactions**)
- 98-6: For assessment of gp41 immunogenic properties, five soluble GST-fusion proteins encompassing C-terminal 30, 64, 100, 142, or 172 (full-length) amino acids of gp41 ectodomain were generated from M group consensus env sequence. The three smaller protein fragments were not detected by 98-6, since they do not contain both heptad repeat regions required for coiled-coil structure that contains the 98-6 Ab epitope. GST-gp41-142 and -172 reacted strongly against 98-6, indicating that these protein fragments exist in post-hairpin configuration. Penn-Nicholson *et al.* [2008]
- 98-6: To test the immunogenicity of three molecularly engeneered gp41 variants on the cell surface their reactivity with 98-6 Ab was assessed. The reactivity of 4cSSL24 and gp41d4mt variants was detected while the BAFF-C56 variant was not recognized by this Ab. Kim *et al.* [2007] (**binding affinity**)
- 98-6D: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 98.6: 98.6 was found to bind to both monomeric and oligomeric gp41. Binding of this Ab to H9/IIIB-infected cells gave a strong signal which was increased by sCD4 pretreatment. Binding to H9/MN-infected cells gave no signal regardless of sCD4 pretreatment, indicating that the seven amino acids of the C34, which differ between the MN and IIIB strains, are possibly responsible in determining whether 98.6 binds to gp41 or not. Sera from both long-term survivors and AIDS patients inhibited binding of 98.6 to H9/IIIB-infected cells. Usami *et al.* [2005] (**antibody binding site definition and exposure**, **rate of progression**)
- 98-6: One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have any neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- 98-6: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of 17b and F105 was decreased by trypsin, but increased by thrombin. gp41 MAbs 246D, 98.6, 50-69, were decreased by trypsin, unaltered by thrombin, while NAb 2F5 binding was increased by thrombin. Thrombin may increase HIV-induced cell fusion in blood by causing a conformational activating shift in gp120. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 98-6: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I MAbs 50-69, F240, 240-D,3D6, and 246-D recognize a nonhelical hydrophobic region, positions 598-604, that forms a disulfide loop in the six-helix bundle. Cluster II MAbs 98-6 and 126-6 recognized residues 644-663 of gp41, a portion of the second heptad repeat. These MAbs were found to behave similarly, so 50-69 and 98-6 were used as representatives. Exposure of cluster I and cluster II epitopes required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor. Binding to CD4 exposed hidden cluster I and II epitopes. The MAbs were found to bind to gp120/gp41 complexes, not to gp41 after shedding of gp120, and were localized to at fusing-cell interfaces. Kinetic and binding results indicate that these MAbs are exposed in transitional structures during the fusion process, possibly the prehairpin intermediate prior to co-receptor binding, although other intermediate structures may be involved. They do not bind once syncytia begin to show extensive cyotplasmic mixing. These MAbs failed to inhibit fusion. The NAb 2F5 has a very different behavior in this study. Finnegan *et al.* [2002] (**antibody binding site definition and exposure**, **kinetics**)
- 98-6: Called 98-6D. Alanine mutations were introduced into the N- and C-terminal alpha-helices of gp41 to destabilize interhelical packing interactions in order to study their inhibitory effect on viral infectivity. These mutations were shown to inhibit viral replication though affecting the conformational transition to the fusion-active form of gp41, and allow increased inhibition by gp41 peptides. 2F5 senstivity is increased in the mutated viruses, presumably because 2F5s neu-

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tralization activity is focused on the transition to the fusion active state. No other gp41 MAb against tested, including NC-1, 50-69D, 1281, 98-6D, 246-D and F240, neutralized the parental or the fusion-deficient mutated viruses. Follis *et al.* [2002] (**antibody binding site definition and exposure**)

- 98-6: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – 98-6 binds to a C-HR hairpin epitope and blocks fusion when added to a 2 hour E/T preincubation at 31.5 C, but if added after 1 hour, doesn't inhibit – this is in contrast to six-helix bundle Abs 167-D and 1281 that inhibit more efficiently when added after one hour of incubation. Golding *et al.* [2002b] (**antibody binding site definition and exposure**)
- 98-6: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6—six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D, while six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001] (**antibody interactions**, **variant cross-recognition or cross-neutralization**)
- 98-6: 98-6 and 2F5 both bind to a peptide N51-C43 complex trimer of heterodimers that approximates the core of the fusogenic form of gp41, and to C43 alone but not to N51 alone – 98-6 and 2F5 have comparable affinities for C43, but 98-6 has a higher affinity for the complex and the binding of 98-6 is not inhibited by N51. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**, **binding affinity**)
- 98-6: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, but gp41 MAb 50-69 bound with a 5 fold preference for the oligomer, while other gp41 MAbs (1367, 98-6, 167-D, 1281, 1342, and 1379) did not show a preference. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)
- 98-6: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 cluster II anti-gp41 MAbs – of these 2F5, 167-D, 126-6, and 1281 bound across clades, but usually weakly, while 98-6 and 1342 had poor cross reactivity – Clade D isolates bound most consistently to cluster II MAbs – no neutralizing activity was observed when tested against 5 isolates, but 98-6 did not bind to these isolates. Nyambi *et al.* [2000] (**subtype comparisons**)
- 98-6: The fusogenic form of gp41 is recognized by 98-6, and the epitope is a conformational epitope formed by the interaction of two regions of gp41 which form an alpha-helical bundle. Taniguchi *et al.* [2000] (**antibody binding site definition and exposure**)
- 98-6: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – anti-gp41 Abs 98-6, 1367 and 1342 were not able to bind detectably with any of the viruses from any clade. Nyambi *et al.* [1998] (**variant cross-recognition or cross-neutralization**)
- 98-6: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D)and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 98-6: 98-6 is V H4 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996] (**antibody sequence variable domain**)
- 98-6: One of several anti-gp41 MAbs that bind to a gp41-maltose binding fusion protein designed to study the leucine zipper domain of gp41, showing that the construct has retained aspects of normal gp41 conformation. Chen *et al.* [1995] (**antibody binding site definition and exposure**)
- 98-6: No neutralizing activity, positive ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995] (**ADCC**, **enhancing activity**)
- 98-6: Virions complexed to gp41 Ab facilitate presentation of p66 RT epitopes to Th cells. Manca *et al.* [1995a]
- 98-6: Preferentially recognizes oligomeric form of gp41 – enhanced binding to HIV-1 infected cells at 37 degrees relative to 4 degrees – addition of sCD4 enhances binding. Sattentau *et al.* [1995] (**antibody binding site definition and exposure**)
- 98-6: Epitope described as cluster II, 644-663, conformational – does not neutralize IIIB or synergize neutralization by anti-V3 MAb 447-52D or by CD4 BS MAbs. Laal *et al.* [1994] (**antibody binding site definition and exposure**, **antibody interactions**, **variant cross-recognition or cross-neutralization**)
- 98-6: This MAb was expressed as a surface anti-gp41 monoclonal antibody receptor for gp41 on a CD4-negative B-cell line. Transfected cells could bind HIV Envelope, but could not be infected by HIV-1. When CD4 delivered by retroviral constructs was expressed on these cells, they acquired the ability to replicate HIV-1, and sIg/gp41 specifically enhanced viral replication. Tani *et al.* [1994]
- 98-6: Called SZ-98.6 – binds to a conformational domain within aa 644-663 of gp41, and reacts with astrocytes, as do 167-7 and ND-15G1. Eddleston *et al.* [1993] (**antibody binding site definition and exposure**)
- 98-6: Did not mediate deposition of complement component C3 on HIV infected cells, binding enhanced by sCD4. Spear *et al.* [1993] (**complement**)
- 98-6: No neutralizing or enhancing activity. Robinson *et al.* [1991] (**enhancing activity**)
- 98-6: Two fold increase in binding to gp120 in the presence of bound sCD4. Sattentau & Moore [1991] (**antibody binding site definition and exposure**)

- 98-6: Appeared to be specific for a conformational or discontinuous epitope. Xu *et al.* [1991] (**antibody binding site definition and exposure**)
- 98-6: No neutralizing or enhancing activity for HIV-1 IIIB. Robinson *et al.* [1990b] (**enhancing activity**)
- 98-6: Serves as target for antibody-dependent cellular cytotoxicity, ADCC. Tyler *et al.* [1990] (**ADCC**)
- 98-6: Kills HIV-infected cells when coupled to deglycosylated ricin A chain. Gorny *et al.* [1989] (**immunotoxin**)
- 98-6: Reacts preferentially with gp160 oligomer, compared to gp41 monomer. Pinter *et al.* [1989] (**antibody binding site definition and exposure**)
- 98-6: Toxic to HIV-infected T cells (H9) and monocytes (U937) when coupled to deglycosylated A chain of ricin. Till *et al.* [1989] (**immunotoxin**)

No. 772
MAb ID 167-7 (SZ-167.7)
HXB2 Location gp160 (644–663)
Author Location gp41 (644–663)
Epitope `SLIEESQNQQEKNEQELLEL`
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG2λ)
Ab Type gp41 cluster II
References Eddleston *et al.* 1993; Xu *et al.* 1991

- 167-7: Called SZ-167.7 – binds to a conformational domain within aa 644-663 of gp41, and reacts with astrocytes, as do 98-6 and ND-15G1. Eddleston *et al.* [1993]
- 167-7: Specific for a conformational epitope. Xu *et al.* [1991]

No. 773
MAb ID ND-15G1 (ND-15GI)
HXB2 Location gp160 (644–663)
Author Location gp41 (644–663 HXB2)
Epitope `SLIEESQNQQEKNEQELLEL`
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster II
References Gorny & Zolla-Pazner 2004; Eddleston *et al.* 1993
Keywords antibody binding site definition and exposure, review

- ND-15G1: One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- ND-15G1: Mapped to the conformational epitope within aa 644-663, and reacts with astrocytes, as do 98-6 and 167-7. Eddleston *et al.* [1993] (**antibody binding site definition and exposure**)

No. 774
MAb ID 167-D (167)
HXB2 Location gp160 (644–663)
Author Location gp41 (644–663 HXB2)
Epitope `SLIEESQNQQEKNEQELLEL`
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp41 cluster II, gp41six-helix bundle
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU, NY
References Alam *et al.* 2008; Holl *et al.* 2006a; Gorny & Zolla-Pazner 2004; Golding *et al.* 2002b; Nyambi *et al.* 2000; Gorny *et al.* 2000; Gorny & Zolla-Pazner 2000; Manca *et al.* 1995a; Forthal *et al.* 1995; Spear *et al.* 1993
Keywords ADCC, antibody binding site definition and exposure, antibody interactions, complement, dendritic cells, enhancing activity, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 167-D: 167-D blocked 2F5 and 13H11 binding to gp41 epitopes to variable degrees. MAb 167-D showed strong binding to HIV-1-positive infected cells. Alam *et al.* [2008] (**antibody interactions**)
- 167-D: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 167-D: Called 167. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- 167-D: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – 98-6 binds to a C-HR hairpin epitope and blocks fusion when added to a 2 hour E/T preincubation at 31.5 C, but if added after 1 hour, doesn't inhibit – this is in contrast to six-helix bundle Abs 167-D and 1281 that inhibit more efficiently when added after one hour of incubation. Golding *et al.* [2002b] (**antibody binding site definition and exposure**)
- 167-D: This cluster II MAb binds to a conformational epitope in the region 644-663 – like most cluster II MAbs (126-6, 167-D, 1281, 1342, and 1379 all reacted similarly) it binds to a peptide N51-C43 complex trimer of heterodimers that approximates the core of the fusogenic form of gp41, but not to C43 nor to N51 alone. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
- 167-D: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, but gp41 MAb 50-69 bound with a 5 fold preference for the oligomer, while other gp41 MAbs (1367, 98-6, 167-D, 1281, 1342, and 1379) did not show a preference. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)
- 167-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 cluster II anti-gp41 MAbs – of these 2F5, 167-D, 126-6, and 1281 bound across clades, but usually weakly, while 98-6 and 1342 had poor cross reac-

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tivity – Clade D isolates bound most consistently to cluster II MAbs. Nyambi *et al.* [2000] (**subtype comparisons**)

- 167-D: No neutralizing activity, no ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995] (**ADCC**, **enhancing activity**, **variant cross-recognition or cross-neutralization**)
- 167-D: Virions complexed to gp41 Ab facilitate presentation of p66 RT epitopes to Th cells. Manca *et al.* [1995a]
- 167-D: Did not mediate deposition of complement component C3 on HIV infected cells – complement mediated virolysis of MN and IIIB in the presence of sCD4. Spear *et al.* [1993] (**complement**)

No. 775
MAb ID polyclonal
HXB2 Location gp160 (659–670)
Author Location gp41 (659–670)
Epitope `ELLELDKWASLW`
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade *HIV component:* gp41 *Adjuvant:* QS21
Species (Isotype) guinea pig
References McGaughey *et al.* 2003
Keywords antibody binding site definition and exposure, binding affinity, vaccine antigen design

- 2F5: Cyclic peptides ELLELDKWASLW that adopt constrained beta-turn conformation of the 2F5 epitope beta-turn in the complexed crystal structure were synthesized and optimize 2F5 binding affinity. This peptide elicits high titer peptide-specific immune responses in guinea pigs that do not neutralize; the authors propose this may be the result of a short CDR3 loop in guinea pigs and additional recessed contact points between 2F5 and gp41. McGaughey *et al.* [2003] (**antibody binding site definition and exposure**, **vaccine antigen design**, **binding affinity**)

No. 776
MAb ID 18F11
HXB2 Location gp160 (662–667)
Author Location gp41
Epitope `ELDKWA`
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* Other *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse (IgG)
Ab Type gp41 MPER (membrane proximal external region)
References Zhang *et al.* 2005a
Keywords antibody binding site definition and exposure, binding affinity, neutralization, vaccine antigen design

- 18F11: The new ELDKWA-specific MAb was obtained from mice immunized with four copies of ELDKWA-epitope with spacers between the epitopes. 18F11 was shown to react with the ELDKWA epitope on native gp41. It inhibited syncytium formation, however, less efficiently then 2F5. 18F11 was as potent as 2F5 in neutralization of primary isolate 92US657 but was ineffective against the laboratory-adapted HIV-1 IIIB strain. 18F11 did not neutralize group O primary isolate BCF02. Zhang *et al.* [2005a] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **binding affinity**)

No. 777
MAb ID 7E10
HXB2 Location gp160 (662–667)
Author Location gp41
Epitope `ELDKWA`
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* Other *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse (IgG)
Ab Type gp41 MPER (membrane proximal external region)
References Zhang *et al.* 2005a
Keywords antibody binding site definition and exposure, binding affinity, neutralization, vaccine antigen design

- 7E10: The new ELDKWA-specific MAb was obtained from mice immunized with four copies of ELDKWA-epitope with spacers between the epitopes. 7E10 was shown to react with the ELDKWA epitope on native gp41. It inhibited syncytium formation, however, less efficiently then 2F5. 7E10 was as potent as 2F5 in neutralization of primary isolate 92US657 but was ineffective against the laboratory-adapted HIV-1 IIIB strain. 7E10 did not neutralize group O primary isolate BCF02. Zhang *et al.* [2005a] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **binding affinity**)

No. 778
MAb ID polyclonal
HXB2 Location gp160 (662–667)
Author Location gp41 (662–667)
Epitope `ELDKWA`
Neutralizing no
Immunogen vaccine
HIV component: gp41
Species (Isotype) guinea pig
Ab Type gp41 MPER (membrane proximal external region)
References Joyce *et al.* 2002

- 2F5: DP178 is a peptide derived from the C-term heptad repeat of gp41 that is a potent inhibitor of viral-mediated fusion – it contains ELDKWA but fails to stimulate 2F5-like NAbs upon immunization – the peptide was extended to force an increase in helicity, and the modified peptide had a increase in affinity for 2F5, but upon guinea pig immunization although high peptide-specific Ab titers were achieved the sera were incapable of viral neutralization – the authors propose that 2F5 may be a low affinity maturation intermediate, which may account for its breadth and why it is hard to recreate the NAb response, but also suggests that the high concentrations required for neutralization are not relevant *in vivo*. Joyce *et al.* [2002]

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No. 779
MAb ID polyclonal
HXB2 Location gp160 (662–667)
Author Location gp41
Epitope ELDKWA
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) mouse
References Liu *et al.* 2005b
Keywords vaccine antigen design, vaccine-specific epitope characteristics

- A peptide containing eight copies of the MAb 2F5's ELDKWA-epitope separated by aa spacers GSGGGGS, RS, and GS was used to test the impact of spacers on eliciting antibody responses to peptides. Both GSGGGGS and GS induced high titers of ELDKWA peptide-specific Abs in BALB/c mice, which reacted with rsgp41. Liu *et al.* [2005b] (**vaccine antigen design**, **vaccine-specific epitope characteristics**)

No. 780
MAb ID polyclonal
HXB2 Location gp160 (662–667)
Author Location
Epitope ELDKWA
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* Other *Adjuvant:* Keyhole Limpit Haemocyanin (KLH)
Species (Isotype) goat (IgA, IgG)
References Dorosko *et al.* 2008
Keywords neutralization, vaccine antigen design

- Two goats were immunized with HIV-1 MPR 649-684 peptide to evaluate induction of MPR 649-684-specific Abs in goat colostrum and mature milk. Observable levels of MPR 649-684-specific IgA were detected in the colostrum of one animal, while the colostrum of both animals contained MPR 649-684-specific IgG Abs. IgG levels were higher than IgA levels. There were no MPR 649-684-specific Abs in the mature milk of the vaccinated animals, suggesting a rapid decline in Ab titers. Immunoprecipitated IgG and IgA showed varying and low level neutralization of free virus. Dorosko *et al.* [2008] (**neutralization**, **vaccine antigen design**)

No. 781
MAb ID 5B2
HXB2 Location gp160 (662–667)
Author Location Env (669–674 IIIB)
Epitope ELDKWA
Neutralizing
Immunogen vaccine
Vector/Type: peptide keyhole limpet hemocyanin (KLH) conjugate *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse (IgG)
Ab Type C-domain
References Tian *et al.* 2001

- 5B2: There is an RT specific Ab Szilvay *et al.* [1992] and a gp41 specific Ab Tian *et al.* [2001] both called 5B2. Tian *et al.* [2001]
- 5B2: Peptides GPGRAFY and ELDKWA were conjugated to keyhole limpet hemocyanin and used to raise mouse MAbs – MAb hybridomas were generated with defined specificity – 5B2 and 9G11 bind to the peptide and to rgp41. Tian *et al.* [2001]

No. 782
MAb ID 9G11
HXB2 Location gp160 (662–667)
Author Location Env (669–674 IIIB)
Epitope ELDKWA
Neutralizing
Immunogen vaccine
Vector/Type: peptide keyhole limpet hemocyanin (KLH) conjugate *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse (IgG)
Ab Type C-domain
References Tian *et al.* 2001

- 9G11: Peptides GPGRAFY and ELDKWA were conjugated to KLH and used to raise mouse monoclonal Ab—MAb hybridomas were generated with defined specificity—5B2 and 9G11 bind to the peptide and to rgp41. Tian *et al.* [2001]

No. 783
MAb ID TH-Ab1
HXB2 Location gp160 (662–667)
Author Location gp41 (669–674)
Epitope ELNKWA
Neutralizing L P
Immunogen vaccine
Vector/Type: peptide keyhole limpet hemocyanin (KLH) conjugate *Strain:* B clade TH936705 *HIV component:* gp41 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) rabbit (IgG1)
Ab Type C-domain
References Dong *et al.* 2001; Xiao *et al.* 2000a

- TH-Ab1: ELNKWA is an escape variant not recognized by the broadly neutralizing MAb 2F5, which recognizes the core epitope ELDKWA—Abs were raised against the peptide escape variant CGELNKWAGELNKWA linked to KLH carrier—these polyclonal antibodies, like the MAb TH-Ab1 also raised to ELNKWA, could recognize ELDKWA and escape mutant peptide epitopes ELEKWA and ELDEWA. Dong *et al.* [2001]

No. 784
MAb ID polyclonal
HXB2 Location gp160 (662–667)
Author Location gp41
Epitope ELDKWA
Neutralizing L P
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41

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Species (Isotype) rabbit
Ab Type C-domain
References Liao *et al.* 2000

- Low levels of anti-ELDKWA antibodies are observed in HIV-1 + individuals, so a C-domain P2 peptide linked to a carrier was used to immunize mice and rabbits, and stimulated a high-level anti-ELDKWA response in mice and rabbits – vaccine was C-TSLIHSLIEESQNQQEKNEQELLELDKWA linked to carrier peptide K/G [(KGGG)_7-K]. Liao *et al.* [2000]

No. 785
MAb ID polyclonal
HXB2 Location gp160 (662–667)
Author Location gp41 (669–674)
Epitope ELDKWA
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* Env *Adjuvant:* BSA
Species (Isotype) rabbit, mouse
Ab Type C-domain, gp41 MPER (membrane proximal external region)
References Xiao *et al.* 2000b

- Strong epitope-specific neutralizing antibody responses were induced using a Env peptide bound to BSA, C(ELDKWAG)_4-BSA, but not full gp160. Xiao *et al.* [2000b]

No. 786
MAb ID polyclonal
HXB2 Location gp160 (662–667)
Author Location gp41 (662–667 BH10)
Epitope ELDKWA
Neutralizing L
Immunogen vaccine
Vector/Type: influenza *Strain:* B clade BH10 *HIV component:* gp41
Species (Isotype) mouse (IgA, IgG)
Ab Type C-domain
References Muster *et al.* 1995; Muster *et al.* 1994

- Sustained ELDKWA specific IgA response in mucosa of immunized mice. Muster *et al.* [1995]

No. 787
MAb ID polyclonal
HXB2 Location gp160 (662–667)
Author Location gp120 (669–674)
Epitope ELDKWA
Neutralizing
Immunogen vaccine
Vector/Type: protein, polyepitope *HIV component:* gp160 *Adjuvant:* BSA
Species (Isotype) rabbit
Ab Type C-domain
References Lu *et al.* 2000b; Lu *et al.* 2000c

- High titer response to ELDKWA and RILAVERYLKD was observed upon vaccination with multiple-epitope vaccine CG-GPGRAFY-G-ELDKWA-G-RILAVERYLKD conjugated to BSA, with a weak response to GPGRAFY – immunization with CG-(ELDKWA-GPGRAFY)_2-K was also tried, yielding a strong Ab response to both ELDKWA and GPGRAFY – gp160 vaccination yielded strong Ab response but not to any of the peptides studied here. Lu *et al.* [2000c,b]

No. 788
MAb ID 14D9
HXB2 Location gp160 (662–667)
Author Location gp41 (669–674 MVP5180)
Epitope ELDEWA
Subtype B, CRF01_AE, O
Neutralizing
Immunogen vaccine
Vector/Type: peptide keyhole limpet hemocyanin (KLH) conjugate *Strain:* natural variants *HIV component:* gp41 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse (IgG1)
Ab Type gp41 adjacent to cluster II, C-term, gp41 MPER (membrane proximal external region)
References Kanduc *et al.* 2008; Huang *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, subtype comparisons, variant cross-recognition or cross-neutralization

- 14D9: Similarity level of the 14D9 binding site pentapeptide ELDEW to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 14D9: This mouse MAb was raised against a variant of ELDKWA core epitope of the NAb 2F5, eldEwa, derived from the 2F5 neutralization resistance variant MVP5180. The eldEwa peptide was conjugated to the carrier protein keyhole limpet hemocyanin (KLH) and adminstered to BALB/c mice and 14D9 was prepared using standard hybridoma methods. 2F5 does not bind to the variants eldEwa, elNkwa (B.TH.TH936705) or elEkwa, while 14D9 binds only to eldEwa and not ELDKWA. The eldEwa variant is common in the HIV-1 O group. Huang *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 789
MAb ID 2F5 (IAM 2F5, IAM-41-2F5, IAM2F5, c2F5)
HXB2 Location gp160 (662–667)
Author Location gp41 (662–667 BH10)
Epitope ELDKWA
Neutralizing L P
Immunogen HIV-1 infection
Species (Isotype) human (IgG3κ)
Ab Type gp41 adjacent to cluster II, C-term, gp41 MPER (membrane proximal external region)

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References Huarte *et al.* 2008b; Utachee *et al.* 2009; Zhang *et al.* 2008; Yamamoto & Matano 2008; Willey & Aasa-Chapman 2008; Vincent *et al.* 2008; van Montfort *et al.* 2008; Chong *et al.* 2008; Floss *et al.* 2008; Tomaras *et al.* 2008; Tasca *et al.* 2008; Sun *et al.* 2008; Srivastava *et al.* 2008; Sadler *et al.* 2008; Pugach *et al.* 2008; Polonis *et al.* 2008; Peters *et al.* 2008b; Perdomo *et al.* 2008; Penn-Nicholson *et al.* 2008; Patel *et al.* 2008; Pacheco *et al.* 2008; Nora *et al.* 2008; Nelson *et al.* 2008; Matoba *et al.* 2008; Keele *et al.* 2008; Kanduc *et al.* 2008; Julien *et al.* 2008; Huarte *et al.* 2008a; Hrin *et al.* 2008; Haynes & Shattock 2008; Gustchina *et al.* 2008; Crooks *et al.* 2008; Dorosko *et al.* 2008; Dey *et al.* 2008; Chen *et al.* 2008a; Bryson *et al.* 2008; Blish *et al.* 2008; Frey *et al.* 2008; Gach *et al.* 2008b; Gach *et al.* 2008a; Coutant *et al.* 2008; Binley *et al.* 2008; Alam *et al.* 2008; Gustchina *et al.* 2007; Zhang *et al.* 2006a; Yuste *et al.* 2006; Ye *et al.* 2006; Yang *et al.* 2006; Pahar *et al.* 2006; Li *et al.* 2006c; Wang *et al.* 2006a; Veiga & Castanho 2006; Sánchez-Martínez *et al.* 2006a; Sánchez-Martínez *et al.* 2006b; Ou *et al.* 2006; Lorizate *et al.* 2006b; Lorizate *et al.* 2006a; Zhang & Dimitrov 2007; van Montfort *et al.* 2007; Kim *et al.* 2007; Bunnik *et al.* 2007; Vcelar *et al.* 2007; Schweighardt *et al.* 2007; Phogat *et al.* 2007; Mehandru *et al.* 2007; Gao *et al.* 2007; Dunfee *et al.* 2007; Derby *et al.* 2007; Chen *et al.* 2007b; Blay *et al.* 2007; Beddows *et al.* 2007; Gray *et al.* 2006; Joos *et al.* 2006; Braibant *et al.* 2006; Davis *et al.* 2006; Cham *et al.* 2006; Choudhry *et al.* 2006; Holl *et al.* 2006a; Jiang *et al.* 2006; Herrera *et al.* 2006; Sack *et al.* 2007; Quakkelaar *et al.* 2007b; Quakkelaar *et al.* 2007a; Nelson *et al.* 2007; McKnight & Aasa-Chapman 2007; Lin & Nara 2007; Law *et al.* 2007; Kraft *et al.* 2007; Huang *et al.* 2007b; 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dows *et al.* 1999; Poignard *et al.* 1999; Montefiori & Evans 1999; Frankel *et al.* 1998; Kunert *et al.* 1998; Geffin *et al.* 1998; Parren *et al.* 1998b; Jiang *et al.* 1998; Li *et al.* 1998; Takefman *et al.* 1998; Ernst *et al.* 1998; Fouts *et al.* 1998; Trkola *et al.* 1998; Yang *et al.* 1998; Parren *et al.* 1998a; Connor *et al.* 1998; Mondor *et al.* 1998; Andrus *et al.* 1998; Gorny *et al.* 1997; Earl *et al.* 1997; Burton & Montefiori 1997; Ugolini *et al.* 1997; Turbica *et al.* 1997; Stamatatos *et al.* 1997; Mascola *et al.* 1997; Moore & Trkola 1997; Kessler II *et al.* 1997; Li *et al.* 1997; Mo *et al.* 1997; D'Souza *et al.* 1997; Schutten *et al.* 1997; Purtscher *et al.* 1996; Stoiber *et al.* 1996; McKeating *et al.* 1996; Pincus *et al.* 1996; Conley *et al.* 1996; Sattentau 1996; Poignard *et al.* 1996b; McKeating 1996; Calarota *et al.* 1996; Kessler *et al.* 1995; Neurath *et al.* 1995; Moore & Ho 1995; Sattentau *et al.* 1995; Trkola *et al.* 1995; D'Souza *et al.* 1995; Beretta & Dalgleish 1994; Muster *et al.* 1994; McGaughey *et al.* 2004; Chen *et al.* 1994b; Thali *et al.* 1994; Conley *et al.* 1994b; D'Souza *et al.* 1994; Dacheux *et al.* 2004; Buchacher *et al.* 1994; Laal *et al.* 1994; Purtscher *et al.* 1994; Klasse *et al.* 1993a; Allaway *et al.* 1993; Muster *et al.* 1993; Buchacher *et al.* 1992

Keywords acute/early infection, adjuvant comparison, anti-idiotype, antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, assay development, assay standardization/improvement, autoantibody, autologous responses, binding affinity, brain/CSF, co-receptor, complement, dendritic cells, drug resistance, enhancing activity, escape, HAART, ART, HIV exposed persistently seronegative (HEPS), immunoprophylaxis, immunotherapy, immunotoxin, isotype switch, kinetics, macrophage, mimics, mimotopes, mother-to-infant transmission, mucosal immunity, neutralization, optimal epitope, rate of progression, responses in children, review, SIV, structure, subtype comparisons, supervised treatment interruptions (STI), therapeutic vaccine, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization, viral fitness and reversion

- 2F5: UK Medical Research Council AIDS reagent: ARP3063.
- 2F5: NIH AIDS Research and Reference Reagent Program: 1475.
- 2F5: Neutralization susceptibility of CRF01_AE Env-recombinant viruses, derived from blood samples of Thai HIV-1 infected patients in 2006, was tested to 2F5. Approximately 40% of viruses tested showed high susceptibility to 2F5, including viruses with and without conserved 2F5 epitopes, suggesting that the susceptibility of CRF01_AE to 2F5 is not determined by the conservation of the core epitope sequence. Several X4R5 viruses were less susceptible to 2F5 compared with X4 or R5 viruses. There was no correlation observed between virus neutralization susceptibility to 2F5 and viral infectivity, the length of the gp120 variable regions, or the number of PNLG sites. Utachee *et al.* [2009] (**co-receptor**, **neutralization**, **subtype comparisons**)
- 2F5: 2F5 binding to gp41 was partially blocked by murine MAbs 5A9 and 13H11. 13H11 and the three cluster II human MAbs 98-6, 126-6 and 167-D blocked 2F5 binding to gp41 epitopes to variable degrees; the combination of 98-6 and 13H11 completely blocked 2F5 binding. MAb 2F5 showed strong binding to HIV-1-positive infected cells. Alam *et al.* [2008] (**antibody interactions**, **kinetics**, **binding affinity**)
- 2F5: 24 broadly neutralizing plasmas from HIV-1 subtype B an C infected individuals were investigated using a series of mapping methods to identify viral epitopes targeted by NAbs. Three different assays were used to analyze gp41-directed neutralizing activity. MAb 2F5 was shown to neutralize equivalently in the standard and post-CD4/CCR5 assay. Weak post-CD4/CCR5 neutralization was detected in five subtype B and two subtype C plasmas. 2F5 was shown to neutralize two of the MPER-engrafted mutant viruses, but the subtype B plasmas did not exactly recapitulate this activity. Neutralization of four subtype B plasmas was not inhibited by a 2F5 peptide. These results indicated that the anti-gp41 activity of the plasmas was probably not due to the presence of 2F5-like Abs. Binley *et al.* [2008] (**neutralization**, **subtype comparisons**)
- 2F5: This study explored features of Env that would enhance exposure of conserved HIV-1 epitopes. The changes in neutralization susceptibility, mediated by two mutations, T569A (in the HR1) and I675V (in the MPER), were unparalleled in their magnitude and breadth on diverse HIV-1 Env proteins. The variant with both TA and IV mutations was 2.8-fold more susceptible to b12, >180-fold more susceptible to 4E10, >780-fold more susceptible to sCD4 and resulted in 18-fold enhanced susceptibility to autologous plasma and >35-fold enhanced susceptibility to the plasma pool. It was also >360-fold more susceptible to 2F5. Mutant with only one IV mutation was >27-fold more susceptible to 2F5. Blish *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**)
- 2F5: Crystal structure of the heterodimeric complex of Ab2/3H6 Fab, an anti-idiotypic Ab, and 2F5 Fab, showed that the contacts between the Abs are predominantly made between the heavy chains of the two molecules. Mainly CDR-H3 of Ab2/3H6 forms contacts to 2F5 although residues from all three heavy-chain loops contribute to binding, interacting with a single linear ten amino acid sequence on the surface of 2F5. There is only a limited overlap between the parts of 2F5 recognized by Ab2/3H6 and those interacting with peptides derived from the linear gp41 epitope, but this overlap is sufficient to lead to steric competition between Ab2/3H6 and gp41. The results indicate that Ab2/3H6 is an anti-idiotypic Ab of the Ab2γ class, an Ab that does not carry the internal image of the linear primary gp41 2F5 epitope. Bryson *et al.* [2008] (**anti-idiotype**, **structure**)
- 2F5: Three constructs of the outer domain (OD) of gp120

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of subtype C, fused with Fc, were generated for immunization of mice: OD(DL3)-Fc (has 29 residues from the centre of the V3 loop removed), OD(2F5)-Fc (has the same deletion reconstructed to contain the sequence of 2F5 epitope), and the parental OD-Fc molecule. Only OD(2F5)-Fc construct reacted with 2F5. Sera from mice immunized with OD(2F5)-Fc showed low Ab titers, and no significant neutralization activity. Chen *et al.* [2008a] (**neutralization**, **vaccine antigen design**)

- 2F5: The goal of the study was to measure NAb responses in patients infected with HIV-1 prevalent subtypes in China. g160 genes from plasma samples were used to establish a pseudovirus-based neutralization assay. 2F5 neutralized 67% of subtype B clones and all subtype AE clones, but not subtype BC clones. Chong *et al.* [2008] (**neutralization**, **subtype comparisons**)
- 2F5: NMR structure of P1, a minimal MPER region that permits interaction with the mucosal galactosyl ceramide HIV-receptor, was analyzed in interaction with 2F5 at different pH. The best fit between NMR P1 and crystal structures of the Ab was at pH 6 and 5. The binding of 2F5 to P1 inserted into the liposomes of different compositions mimicking various biological membranes revealed 5- to 10-fold higher affinity of 2F5 to P1 in the lipid environment compared to aqueous environment, suggesting that specific lipid environment stabilizes the appropriate structure of the HIV-1 peptide. Coutant *et al.* [2008] (**kinetics**, **binding affinity**, **structure**)
- 2F5: The study compared Ab neutralization against the JR-FL primary isolate and trimer binding affinities judged by native PAGE. There was direct quantitative relationship between monovalent Fab-trimer binding and neutralization, implying that neutralization begins as each trimer is occupied by one Ab. In BN-PAGE, neutralizing Fabs, 2F5 in particular, and sCD4 were able to shift JR-FL trimers, In contrast, most non-neutralizing Fabs bound to monomer, but their epitopes were conformationally occluded on trimers, confirming the exclusive relationship of trimer binding and neutralization. Crooks *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- 2F5: Five amino acids in the gp41 N-terminal region that promote gp140 trimerization (I535, Q543, S553, K567 and R588) were considered. Their influence on the function and antigenic properties of JR-FL Env expressed on the surfaces of pseudoviruses and Env-transfected cells was studied. Various non-neutralizing antibodies bind less strongly to the Env mutant, but neutralizing antibody binding is unaffected. There was no difference in 2F5 binding to wild type and mutant JR-FL, and 2F5 inhibited infection of the two pseudoviruses with comparable potencies. Dey *et al.* [2008] (**binding affinity**)
- 2F5: Neutralization of HIV-1 BAL by 2F5 Ab was compared to neutralization capabilities of immunoprecipitated IgG and IgA Abs from the colostrum of two goats immunized with HIV-1 MPR 649-684 peptide. Immunoprecipitated IgG and IgA showed varying and low level neutralization of free virus, while the highest percent neutralization achieved by 2F5 was 24.9%. Dorosko *et al.* [2008] (**neutralization**)
- 2F5: The study examined whether elastin-like peptide (ELP) fusion technology is compatible with the production of MAb 2F5, which is a complex heteromultimeric pharmaceutical protein. ELP fusion to the light chain, heavy chain of both chains of a plant-derived antibody had no adverse effects on protein quality, but had a positive impact on the yield. Floss *et al.* [2008]
- 2F5: Molecular mechanism of neutralization by MPER antibodies, 2F5 and 4E10, was studied. Preparations of trimeric HIV-1 Env protein in the prefusion, the prehairpin intermediate and postfusion conformations were used. The epitopes for 2F5 and 4E10 were found to be exposed only on a form designed to mimic an prehairpin intermediate state during viral entry, which helps to explain the rarity of 2F5- and 2E10-like antibody responses. Frey *et al.* [2008] (**antibody binding site definition and exposure**, **binding affinity**)
- 2F5: This study describes an expression, purification and in vivo administration in guinea pigs of an anti-idiotypic HIV-1 vaccine based on murine anti-idiotypic MAb Ab2/3H6, which mimics the antigen recognition site of 2F5. Gach *et al.* [2008a] (**anti-idiotype**, **mimics**, **vaccine antigen design**)
- 2F5: This study describes the molecular features of murine anti-idiotypic MAb Ab2/3H6, which mimics the antigen recognition site of 2F5. Mice immunization with AB2/3H6 Fab variants elicited a specific 2F5-like humoral immune response. Gach *et al.* [2008b] (**anti-idiotype**, **mimics**, **vaccine antigen design**, **structure**)
- 2F5: The IC50 for 2F5 in a standard neutralization assay is 3.8nM but is increased 20-fold in the postattachment neutralization assay to 72nM. The neutralization half-life for 2F5 is 15 minutes but is increased 3-fold to 44 minutes in the presence of N36Mut(e,g), peptide, which is a class 3 inhibitor that prolongates temporal window of neutralization by disrupting trimerization of the N-heptad repeat (N-HR) in the prehairpin intermediate by sequestering the N-HR into N-HR/N36Mut(e,g) heterodimers. HXB2 was neutralized synergistically by 2F5 and N36Mut(e,g), where the formation of N-HR/N36Mut(e,g) heterodimers enhances the probability of 2F5 binding and the binding of 2F5 enhances the probability of N-HR/N36Mut(e,g) heterodimer formation, greatly diminishing the probability of 6-helix bundle formation. Gustchina *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **kinetics**)
- 2F5: This review summarizes the obstacles that stand in the way of making a successful preventive HIV-1 vaccine, such as masked or transiently expressed Ab epitopes, polyclonal B-cell class switching, and inefficient, late, and not sufficiently robust mucosal IgA and IgG responses. Possible reasons why HIV-1 envelope constructs expressing 2F5 epitope fail to induce broadly neutralizing Abs are discussed. Haynes & Shattock [2008] (**vaccine antigen design**, **review**)
- 2F5: Synergy of 2F5 with MAbs 2G12, D5, and peptide C34 was examined. 2F5 exhibited synergy in inhibition of HIV-1 89.6 with MAb 2G12, D5 and peptide C34. In combination with a matured D5 variant (2-75), the synergistic effect was increased. D5 and 2F5 contributed equally to the observed synergy. It is suggested that 2F5 and D5 have complementary roles, binding to distinct but adjacent Env trimers on the same virion, thereby synergistically preventing formation of fusion pores. Hrin *et al.* [2008] (**antibody interactions**)
- 2F5: A MPER peptide, AISpreTM, overlapping 2F5 and 4E10 epitope sequences, was capable of breaching the permeabil-

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ity barrier of lipid vesicles. 2F5 blocked the peptide bilayer-destabilizing activity, whether the lipid composition contained cholesterol or sphingomyelin raft-lipids, indicating that the lipid composition of the membrane has a less pronounced effect on the 2F5 inhibitory activity. The 2F5 epitope appears to remain anchored to the water-membrane interface and is more accessible for Ab binding under different membrane lipid conditions. Huarte *et al.* [2008a] (**antibody binding site definition and exposure**)

- 4E10: The study compared the in-membrane recognition and blocking activity of the 2F5 and 4E10 MAbs, using solution-diffusing, unstressed phospholipid vesicles with sizes that approximate to that of the HIV virion, and an MPER-derived sequences that combines the full length 2F5 and 4E10 epitopes. 2F5 MAb had lower affinity for membrane-bound species than 4E10 MAb, as defined by inhibition data together with direct electron microscopy and flow cytometry determination of the vesicle-antibody association. Huarte *et al.* [2008b]
- 2F5: Eight 2F5 Fab' crystal structures, free and in complex with various gp41 peptide epitopes, revealed several key features of Ab-antigen interaction. The extended complementarity-determining region (CDR) H3 loop is mobile, both in ligand-free and epitope-bound forms. The interaction between 2F5 and the ELDKWA epitope core is critical, and there are also close and specific contacts with residues located N-terminal to the core, while the residues located at the C-terminus of the core do not interact as tightly with the Ab. In the presence of a larger peptide, these C-terminus residues adopt a conformation consistent with the start of an α helix. At the base of the CDR H3, a sulfate ion is present near residue Arg100H, that might be mimicking the negatively charged phosphate of a lipid headgroup representing a possible site of interaction between 2F5 and the phospholipid bilayer. Julien *et al.* [2008] (**antibody binding site definition and exposure**, **structure**)
- 2F5: Similarity level of the 2F5 binding site pentapeptide LDKWA to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 1 time, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 2F5: A mathematical model was developed and used to derive transmitted or founder Env sequences from individuals with acute HIV-1 subtype B infection. All of the transmitted or early founder Envs were sensitive to neutralization by 2F5, but there was a modest heightened resistance of acute Envs compared to chronic Envs to neutralization by 2F5. Keele *et al.* [2008] (**neutralization**, **acute/early infection**)
- 2F5: CTB-MPR649-684 (cholera toxin subunit B and residues 649-684 of gp41 MPER region) peptide was developed for vaccine studies in rabbits. 2F5 affinity to the CTB-MPR peptide was equivalent to 2F5 affinity toward an MPR peptide, indicating that the fusion peptide presented antigenically competent MPR. Sera from immunized rabbits displayed no neutralizing activity, but could inhibit epithelial transcytosis of virus, indicating elicitation of non-neutralizing Abs capable of stopping mucosal transmission and infection of target cells. Matoba *et al.* [2008] (**binding affinity**)
- 2F5: Transmission of HIV-1 by immature and mature DCs to CD4+ T lymphocytes was significantly higher for CXCR4- than for CCR5-tropic strains. In addition, 2F5 inhibited transmission of CCR5-tropic viruses while transmission of 2F5-neutralized X4 variants increased, indicating that X4 HIV-1 has an advantage over R5 in transmission when neutralized with 2F5. The increase in transmission of X4 viruses is probably mediated by increase in capture, as X4 HIV-1 capture increased twofold upon 2F5 neutralization, while neutralization by 2F5 had no effect on capture of R5 viruses. Capture analysis of different HIV-1 molecular clones showed that neutralization by 2F5 increased transmission of only X4 and late R5X4 variants with a higher V3 charge. van Montfort *et al.* [2008] (**co-receptor**, **neutralization**, **dendritic cells**)
- 2F5: 2F5 was shown to bind to Envs used in typical epitope binding assays, unlike the neutralizing Abs 8K8, DN9, and D5 used in this study. Nelson *et al.* [2008]
- 2F5: Contemporaneous biological clones of HIV-1 were isolated from plasma of chronically infected patients and tested for their functional properties. The clones showed striking functional diversity both within and among patients, including differences in infectivity and sensitivity to inhibition by 2F5. There was no correlation between clonal virus infectivity and sensitivity to 2F5 inhibition, indicating that these properties are dissociable. The sensitivity to 2F5 inhibition was, however, a property shared by viruses from a given patient, suggesting that the genetic determinants that define this sensitivity may lie in regions that are not necessarily subject to extensive diversity. Nora *et al.* [2008] (**neutralization**)
- 2F5: Two HIV-1 isolates, NL4-3 and KB9, were adapted to replicate in cells using the common marmoset receptors CD4 and CXCR4. The adaptation resulted in a small number of changes of env sequences in both isolates. The adapted NL4-3 variants were equally sensitive to neutralization by 2F5 as the adapted KB9 variants. Some of the NL4-3 and KB9 variants exhibited increased sensitivity to neutralization by 2F5 compared to the wildtype isolates. Pacheco *et al.* [2008] (**neutralization**)
- 2F5: To examine sequence and conformational differences between subtypes B and C, several experiments were preformed with 11 MAbs regarding binding and neutralization. Both binding and neutralization studies revealed that the 11 MAbs could be divided in three different groups, and that the most differences between the subtypes were located in the stem and turn regions of V3. 2F5 was used as control in neutralization assays, and was able to neutralize JR-FL isolate, and with lower potency, SF162. A chimeric SF162 variant with a JR-FL-like V3 sequence was hypersensitive to neutralization by this Ab. Patel *et al.* [2008] (**neutralization**)
- 2F5: For assessment of gp41 immunogenic properties, five soluble GST-fusion proteins encompassing C-terminal 30, 64, 100, 142, or 172 (full-length) amino acids of gp41 ectodomain were generated from M group consensus Env sequence. All five protein fragments were equally recognized by 2F5 indicating that the 2F5 epitope is conformationally similar and equally exposed. Patients considered as slow progressors generally exhibited greater Ab reactivity against the 30aa fragment, indicating that these Abs target MPER region and exhibit 2F5- and 4E10-like properties. Plasma from these pa-

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tients also exhibited broader and more potent neutralizing activity against several HIV-1 isolates. Plasma from 8 of 44 patients reacted with peptides that bind 2F5, indicating that these patients mounted 2F5-like Ab response. Penn-Nicholson *et al.* [2008] (**rate of progression**)

- C2F5: Neutralization of HIV-1 IIIB LAV isolate by 2F5 was within the same range as the neutralization of the virus by natural antibodies from human sera against the gal(α1,3)gal disaccaride linked to CD4 gp120-binding peptides, indicating that the activity of natural antibodies can be re-directed to neutralize HIV-1. Perdomo *et al.* [2008] (**neutralization**)
- 2F5: The sensitivity of R5 envelopes derived from several patients and sevaral tissue sites, including brain tissue, lymph nodes, blood, and semen, was tested to a range of inhibitors and Abs targeting CD4, CCR5, and various sites on the HIV envelope. All but one envelope from brain tissue were macrophage-tropic while none of the envelopes from the lymph nodes were macrophage-tropic. Macrophage-tropic envelopes were also less frequent in blood and semen. There was no clear correlation between macrophage-tropism and neutralization sensitivity to 2F5, indicating that variation in macrophage tropism is not caused by variation in the membrane proximal region of Env. Peters *et al.* [2008b] (**brain/CSF**, **macrophage**, **neutralization**)
- 2F5: This minireview summarizes data on differences in neutralizing activities of MAbs and pooled human sera using a traditional primary cell neutralization assay and the more standardized TZM-bl reporter cell line assay. Also, suggestions are made on how to improve and standardize neutralization assays for comparable use in different laboratories. 2F5 neutralization was tested against a panel of 60 HIV-1 primary isolates (10 each from clades A-D, CRF01_AE and CRF02_AG) in the two assays. 13 viruses from the PBMC assay and 9 viruses from the TZM-assay were not neutralized by this Ab (including subtype C in both assays). In total, the assay discordances were shown to be bi-directional and not attributable to assay sensitivity. Polonis *et al.* [2008] (**neutralization**, **review**, **subtype comparisons**, **assay standardization/improvement**)
- 2F5: In order to assess whether small molecule CCR5 inhibitor resistant viruses were more sensitive to neutralization by NAbs, two escape mutant viruses, CC101.19 and D1/85.16, were tested for their sensitivity to 2F5, compared to the sensitivity of CC1/85 parental isolate and the CCcon.19 control isolate. The CC101.19 escape mutant has 4 sequence changes in V3 while the D1/85.16 has no sequence changes in V3 and relies on other sequence changes for its resistance. D1/85.16 isolate was moderately (6-fold) more sensitive to 2F5 neutralization than the parental isolate, while CC101.19 was not. As D1/85.16 escape mutant had a polymorphism in the first position of the 2F5 epitope (Aldkwas), this sequence change might be responsible for its modest increase in the 2F5 neutralization sensitivity. Overall, the study suggests that CCR5 inhibitor-resistant viruses are likely to be somewhat more sensitive to neutralization than their parental viruses. Pugach *et al.* [2008] (**co-receptor**, **neutralization**, **escape**)
- 2F5: Quaternary structure of gp41 helical domains N-HR and C-HR was mimicked by 3α N-HR and 3α C-HR mimetic proteins consisting of covalently linked trimeric coiled-coil bundle, which is a truncated version of the gp41 prehairpin. The 3α mimetics were immunogenic and elicited Abs in guinea pigs specific for gp41. The sera from immunized animals neutralized viral R5 and X4-tropic viruses at 31.5 degrees C, but not under standard assay conditions, in which 2F5 blocked HIV-1 infection. Sadler *et al.* [2008] (**neutralization**)
- 2F5: Trimeric envelope glycoproteins with a partial deletion of the V2 loop derived from subtype B SF162 and subtype C TV1 were compared. 2F5 recognized both B and C trimers, indicating that the 2F5 epitope was exposed and preserved in the subtype C trimers. Subtype C trimer had many biophysical, biochemical, and immunological characteristics similar to subtype B trimer, except for a difference in the three binding sites for CD4, which showed cooperativity of CD4 binding in subtype C but not in subtype B. Srivastava *et al.* [2008] (**binding affinity**, **subtype comparisons**)
- 2F5: The MPER region was shown to have an L-shaped structure, with the conserved C-terminal residues immersed in the membrane and the variable N-terminal residues exposed to the aqueous phase. The specific binding of 2F5 to the MPER was comparable to that of 4E10, with little or no binding to the membrane alone. It is suggested that 2F5, like 4E10, extracts its epitope from the viral membrane, and that the key requirement for neutralization is induction of structural rearrangement of the MPER hinge by the Ab. It is also suggested that exposure of the membrane-embedded residues of the MPER region to the immune system in their native L-shaped form may elicit neutralizing Abs. Sun *et al.* [2008] (**antibody binding site definition and exposure**)
- 2F5: The neutralization profile of early R5, intermediate R5X4, and late X4 viruses from a rhesus macaque infected with SHIV-SF162P3N was assessed. 2F5 neutralized the late X4 virus, and to some extent the parental R5 virus, but did not neutralize the R5X4 intermediate. A K to N mutation within the 2F5 epitope in the R5X4 intermediate accounted for its neutralization resistance. Tasca *et al.* [2008] (**co-receptor**, **neutralization**, **escape**)
- 2F5: To investigate B-cell responses immediately following HIV-1 transmission, env-specific Ab responses to autologous and consensus Envs in plasma donors were determined. Broadly neutralizing Abs with specificity similar to 2F5 did not appear during the first 40 days after plasma virus detection. Tomaras *et al.* [2008] (**acute/early infection**)
- 2F5: 2F5 reacted with maltose-binding proteins MBP30 and MBP32, containing both HR1 and HR2 domains of gp41, and with MBP37 and MBP44, containing only the HR2 domain, but not with MBP-HR1, containing only the HR1 domain. Vincent *et al.* [2008] (**antibody binding site definition and exposure**)
- 2F5: The various effects that neutralizing and non-neutralizing anti-envelope Abs have on HIV infection are reviewed, such as Ab-mediated complement activation and Fc-receptor mediated activities, that both can, through various mechanisms, increase and decrease the infectivity of the virus. The importance of these mechanisms in vaccine design is discussed. The unusual features of the 2F5 MAb, and its neutralizing activities, are described. Willey & Aasa-Chapman [2008] (**neutralization**, **review**)
- 2F5: Current insights into CTLs and NAbs, and their possible protective mechanisms against establishment of persistent

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HIV/SIV infection are discussed. Pre- and post-infection sterile and non-sterile protection of NAbs against viral challenge, and potential role of NAbs in antibody-mediated antigen presentation in modification of cellular immunity, are reviewed. Use of 2F5 in immunization experiments and its in vivo antiviral activity in suppression of viral rebound in HIV-1 infected humans undergoing structured treatment interruptions are described. Yamamoto & Matano [2008] (**immunotherapy**, **supervised treatment interruptions (STI)**, **review**)

- 2F5: The newly detected mAb m44 was shown to neutralize a subtype C SHIV strain more potently than 2F5. In binding assays, 2F5 did not bind to 5Hb region. 2F5 did not compete with m44 for binding. A fusion protein of gp41 constructed for alanine-scanning mutagenesis bound to 2F5, indicating that its antigenic structure was intact. Five alanine mutations in the C-HR region (M94, W96, M97, R101, and I103) affected binding of 2F5 to gp41. 2F5 bound to self antigens in lipid binding assays. Zhang *et al.* [2008] (**neutralization**, **binding affinity**)
- 2F5: The autoantibody nature of the two membrane proximal HIV-1 neutralizing antibodies, 2F5 and 4E10, was evaluated by comparison to human anti-cardiolipin MAbs derived from a primary antiphospholipid syndrome patient. Both 2F5 and 4E10 bound specifically to cardiolipin. CDR3 sequence similarities between 2F5, 4E10 and anti-cardiolipin MAbs were observed. Both 2F5 and 4E10 binding to the peptide-lipid conjugate was best fit by a two-step conformational change model. These results suggest that these MAbs share binding and structural similarities with human autoantibodies and their induction by vaccines or natural infection therefore might be limited by immune tolerance mechanisms. Alam *et al.* [2007] (**antibody sequence variable domain**)
- 2F5: Sera from rabbits immunized with either monomeric gp120, trimeric cleavage-defective gp140 or disulfide-stabilized soluble trimeric gp140 were tested for neutralization of chimeric SIVmac239 viruses expressing epitope for this Ab. Little or no neutralization was observed indicating that little or no Ab activity in these rabbit sera was directed against the gp41 region. Beddows *et al.* [2007] (**neutralization**, **vaccine antigen design**)
- 2F5: Pseudoviruses derived from gp120 env variants that evolved in multiple macaques infected with SHIV 89.6P displayed a range of degrees of virion-associated Env cleavage. Pseudoviruses with higher amount of cleaved Env were more resistant to neutralization by 2F5. The gp41 sequence was the same in all pseudoviruses, indicating that changes in gp120 can mediate sensitivity of gp41 to neutralization. Blay *et al.* [2007] (**neutralization**)
- 2F5: 7/15 and 9/15 subtype A HIV-1 envelopes from samples taken early in infection were neutralized by MAbs 4E10 and 2F5, respectively, and the potency was generally modest. Mutational patterns in the MAb binding sites did not readily explain the observed patterns of sensitivity and resistance. Blish *et al.* [2007] (**neutralization**, **variant cross-recognition or cross-neutralization**, **acute/early infection**, **subtype comparisons**)
- 2F5: No differences in neutralization sensitivity between (R5)X4 and R5 viruses obtained early and late after X4 emergence were observed. Bunnik *et al.* [2007] (**co-receptor**, **neutralization**)
- 2F5: Spread of HIV-1 through formation of virological synapses (VS) between infected and uninfected T-cells was shown to require Env-CD4 receptor interactions. Treatment of cells with 2F5 did not block VS-mediated transfer, indicating that VS-mediated transfer is not dependent on activation of viral membrane fusion. 2F5 at the same or lower concentrations blocked cell-free infection. Chen *et al.* [2007b] (**neutralization**)
- 2F5: 2F5, 4E10, and m46 neutralization was more potent when tested in a HeLa cell line expressing low CCR5 than in a HeLa cell line expressing high CCR5 levels. PBMC tend to have low CCR5 expression. Choudhry *et al.* [2007] (**co-receptor**, **neutralization**, **assay standardization/improvement**)
- 2F5: 2F5 bound with slower on-rates and faster off-rates to the SF162gp140 and ΔV2gp140 proteins than the anti-gp41MAbs P4A3 and P4C2, but in contrast to the anti-gp41 MAbs, it neutralized the SF162 virus. Thus, differences in neutralization potency could not be explained by differing kinetics. Derby *et al.* [2007] (**neutralization**, **kinetics**, **binding affinity**)
- 2F5: SOSIP Env proteins are modified by the introduction of a disulfide bond between gp120 and gp41 (SOS), and an I559P (IP) substitution in gp41, and form trimers. The KNH1144 subtype A virus formed more stable trimers than did the prototype subtype B SOSIP Env, JRFL. The stability of gp140 trimers was increased for JR-FL and Ba-L SOSIP proteins by substituting the five amino acid residues in the N-terminal region of gp41 with corresponding residues from KNH1144 virus. b12, 2G12, 2F5, 4E10 and CD4-IgG2 all bound similarly to the WT and to the stabilized JRFL SOSIP timers, suggesting that the trimer-stabilizing substitutions do not impair the overall antigenic structure of gp140 trimers. Dey *et al.* [2007a] (**vaccine antigen design**)
- 2F5: Chimeric SIV viruses containing 2F5 and 4E10 epitopes were not neutralized by broadly neutralizing sera from two clade B and one clade A infected asymptomatic individuals, indicating that MPER NAb epitopes did not account for the broad neutralizing activity observed. Dhillon *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**)
- 2F5: Kinetics experiments of 2F5 binding to MPER region during viral fusion showed that the 2F5 kinetics resembled those of the six-helix bundle formation and fusion blocker C34, indicating that the function of MPER in the fusion cascade is still in effect at a late stage in the fusion reaction. Binding of 2F5 was shown to decrease upon triggering HIV-1 Env-expressing cells with appropriate target cells and addition of C34 did not counteract this loss, suggesting that changes in exposure of MPER occur independently of the six-helix bundle formation. Dimitrov *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **kinetics**, **binding affinity**)
- 2F5: A D386N change in the V4 region, which results in restoration of N-glycosylation at this site, did not have any impact on the neutralization of a mutant virus by 2F5 compared to wildtype. Also, there was no association between increased

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sensitivity to 2F5 neutralization and enhanced macrophage tropism. Dunfee *et al.* [2007] (**neutralization**)

- 2F5: Newborn macaques were challenged orally with the highly pathogenic SHIV89.6P and then treated intravenously with a combination of IgG1b12, 2G12, 2F5 and 4E10 one and 12 hours post-virus exposure. All control animals became highly viremic and developed AIDS. In the group treated with mAbs 1 hour post-virus exposure, 3/4 animals were protected from persistent systemic infection and one was protected from disease. In the group treated with mAbs 12 hour post-virus exposure, one animal was protected from persistent systemic infection and disease was prevented or delayed in two animals. IgG1b12, 2G12, and 4E10 were also given 24 hours after exposure in a separate study; 4/4 treated animals become viremic, but with delayed and lower peak viremia relative to controls. 3/4 treated animals did not get AIDS during the follow up period, and 1 showed a delayed progression to AIDS, while the 4 untreated animals died of AIDS. Thus the success of passive immunization with NAbs depends on the time window between virus exposure and the start of immunoprophylaxis. Ferrantelli *et al.* [2007] (**immunoprophylaxis**)
- 2F5: An anti-idiotypic mouse Ab (Ab2/3H6) against MAb 2F5 was partially humanized, expressed and characterized for its interactions with 2F5. The recombinantly expressed variants of Ab2/3H6 were able to bind to the paratope of 2F5 and also significantly inhibit binding of 2F5 to its epitope. All recombinant Ab2/3H6 were also able to inhibit the neutralization of HIV-1 isolate RF by 2F5. Gach *et al.* [2007] (**anti-idiotype**, **neutralization**, **binding affinity**)
- 2F5: This review summarizes data on the development of HIV-1 centralized genes (consensus and ancestral) for induction of neutralizing antibody responses. Functionality and conformation of native epitopes in proteins based on the centralized genes was tested and confirmed by binding to 2F5 and other MAbs. Antibodies induced by immunization with these centralized proteins did not, however, have the breadth and potency compared to that of 2F5 and other broadly neutralizing MAbs. 2F5 physical characteristics of autoantibodies as a possible reason for lack of 2F5 broad production is also discussed. Gao *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **review**)
- 2F5: The potency of 2F5 was 25-fold higher than the potency of new neutralizing Fab 3674 in neutralization of laboratory and primary strains of HIV-1 subtypes A, B and C. Gustchina *et al.* [2007] (**neutralization**, **subtype comparisons**)
- 2F5: Using sychronously infected cell cultures, the binding of b12, 2F5 and 2G12 to the cell-free virus interferes with a step of infection subsequent to cell attachment. HIV escape from b12 ocurred 30 and 10 min before escape from 2F5 for IIIB infection of HeLa cells and JRFL infection of Cf2Th-CD4/CCR5 cells, respectivelly, indicating that neutralization efficiency is determined by the time frames during which Ab can bind to the receptor-activated envelope proteins during the entry phase. 2F5 neutralization was enhanced by a decreasing the rate of coreceptor CXCR4 engagement, presumably by increasing the time the CD4 bound Env was available and slowing viral entry kinetics. Haim *et al.* [2007] (**co-receptor**, **kinetics**)
- 2F5: HIV-1 env clones resistant to cyanovirin (CV-N), a carbohydrate binding agent, showed amino acid changes that resulted in deglycosylation of high-mannose type residues in the C2-C4 region of gp120. Compared to their parental virus HIV-1 IIIB, these resistant viruses maintained similar sensitivity to 2F5. Hu *et al.* [2007] (**neutralization**, **escape**)
- 2F5: Binding of 2F5 to gp41 was not significantly affected by the small molecule HIV-1 entry inhibitor IC9564. IC9564 induces conformational change of gp120 to allow CD4i antibody 17b to bind, but inhibits CD4-induced gp41 conformational changes. Huang *et al.* [2007b] (**antibody binding site definition and exposure**)
- 2F5: This review summarizes current knowledge on the various functional properties of antibodies in HIV-1 infection, including 2F5 mAb, in vivo and in vitro activity of neutralizing Abs, the importance and downfalls of non-neutralizing Abs and antibodies that mediate antibody-dependent cellular cytotoxicity and the complement system, and summarizes data on areas tht need future investigation on Ab-mediated immune control. Huber & Trkola [2007] (**review**)
- 2F5: To test the immunogenicity of three molecularly engeneered gp41 variants on the cell surface their reactivity with 2F5 was assessed. The reactivity of 4cSSL24 variant was comparable to gp160 while the other two variants showed somewhat lower expression levels. When guinea pigs were immunized with the three variants, the level of the specific anti-gp41 Ab responses was low with the anti-gp41 response preferentially directed to the C-helical domain, away from the MPER region. Kim *et al.* [2007] (**vaccine antigen design**, **binding affinity**)
- 2F5: A new high throughput method was developed for neutralization analyses of HIV-1 env genes by adding cytomegalovirus (CMV) immediate enhancer/promoter to the 5' end of the HIV-1 rev/env gene PCR products. The PCR method eliminates cloning, transformation, and plasmid DNA preparation steps in the generation of HIV-1 pseudovirions and allows for sufficient amounts of pseudovirions to be obtained for a large number of neutralization assays. Pseudovirions generated with the PCR method showed similar sensitivity to 2F5 Ab, indicating that the neutralization properties are not altered by the new method. Kirchherr *et al.* [2007] (**assay development**, **neutralization**)
- 2F5: Four consensus B Env constructs: full length gp160, uncleaved gp160, truncated gp145, and N-linked glycosylation-site deleted (gp160-201N/S) were compared. All were packaged into virions, and all but the fusion defective uncleaved version mediated infection using the CCR5 co-receptor. Primary isolate Envs varied between completely resistant or somewhat sensitive to neutralization by membrane proximal Nabs 4E10 and 2F5. The most sensitive Con B construct was the truncated version of Con B Env with a stop codon immediately following the membrane spanning domain, suggesting that truncation of the gp41 cytoplasmic domain facilitates greater accessibility of the MPER region. The Con B gp160 was quite resistant, and the gp160-201N/S more sensitive, to 4E10 and 2F5. Kothe *et al.* [2007] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**)
- 2F5: Viruses from 304 days and at 643 days (time of death) post-infection of a macaque infected with SHIV SF162P4

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were resistant to contemporaneous serum that had broadly reactive NAbs. While resistance to anti-V3, b12, and anti-V1 MAbs developed over time, viruses remained senstitive to 2F5 and 2G12. Kraft *et al.* [2007] (**neutralization**, **escape**)

- 2F5: This review summarizes 2F5 Ab epitope, properties and neutralization activity. 2F5 use in passive immunization studies in primates and possible mechanisms explaining protection against infection are discussed. Also, 2F5 autoreactivity and its implications for active immunizations are discussed. Kramer *et al.* [2007] (**immunotherapy**, **review**)
- 2F5: High levels of gp120-specific Abs were elicited when mice and rabbits were immunized by DNA priming and protein boosting with G1 and G2 grafts, consisting of 2F5 and 4E10 epitopes, respectivelly, engrafted into the V1/V2 region of gp120. A consistent NAb response against the homologous JR-FL virus was detected in rabbits but not in mice. 4E10 bound to the engrafted construct, but embedding the MPER epitopes in the immunogenic V1/V2 region did not result in eliciting anti-MPER antibodies in mice or rabbits. 2F5 bound to the Graft1 antigen consisting of 2F5 and 4E10 epitopes engrafted into the immunogenic V1/V2 region of gp120 much more weakly than to gp41 suggesting that the 2F5 epitope might be hidden or folded incorrectly in this construct. Law *et al.* [2007] (**vaccine antigen design**)
- 2F5: 2F5 structure, binding, neutralization, and strategies that can be used for vaccine antigen design to elicit anti-gp41 Abs, are reviewed in detail. The effect of the autoreactivity of 2F5 on vaccine antigen design is discussed. Lin & Nara [2007] (**vaccine antigen design**, **review**, **structure**)
- 2F5: This review summarizes data on possible vaccine targets for elicitation of neutralizing Abs and discusses whether it is more practical to design a clade-specific than a clade-generic HIV-1 vaccine. Development of a neutralizing Ab response in HIV-1 infected individuals is reviewed, including data that show no apparent division of different HIV-1 subtypes into clade-related neutralization groups. Also, a summary of the neutralizing activity of mAb 2F5 in different HIV-1 clades is provided. McKnight & Aasa-Chapman [2007] (**variant cross-recognition or cross-neutralization**, **review**)
- 2F5: Three MAbs, 2G12, 4E10 and 2F5, were administered to ten HIV-1 infected individuals treated with ART during acute and early infection, in order to prevent viral rebound after interruption of ART. MAb infusions were well tolerated with essentially no toxicity. Viral rebound was not prevented, but was significantly delayed in 8/10 patients. 2G12 activity was dominant among the MAbs used. Antiviral activity of 2F5 was not clearly demonstrated. Development of resistance to 2F5 was not observed despite ongoing viral replication. Plasma HIV-1 RNA levels did not increase following cessation of Ab infusion. Plasma viremia was essentially identical between patients not receiving MAb therapy and patients receiving 4E10 and 2F5 in the face of 2G12 resistance. 2F5 also failed to accumulate with repeated infusions in patient plasma. Long-term suppression of viremia was achieved in 3/10 patients. Mehandru *et al.* [2007] (**escape**, **immunotherapy**, **supervised treatment interruptions (STI)**)
- 2F5: HIV-1 neutralized with 2F5 was shown to be more efficiently captured by immature monocyte-derived DCs (iMDDCs) and DC-SIGN-expressing Raji cells than nonneutralized virus. 2F5-neutralized virus captured by these cells was successfully released and transferred to CD4+ T lymphocytes. The released virus could be re-neutralized by 2F5 before infecting CD4+ T cells, indicating that Ab-HIV-1 complex is separated upon capture by DC-SIGN cells. Capture of 2F5-neutralized virus was inhibited by blocking Fc receptors and DC-SIGN on iMDDCs, indicating significant role of DC-SIGN, and a partial role of Fc receptors, in the Ab-enhanced capture of HIV-1. van Montfort *et al.* [2007] (**enhancing activity**, **neutralization**, **dendritic cells**)
- 2F5: Z13e1, a high affinity variant of Fab Z13, was identified through targeted mutagenesis and affinity selection against gp41 and an MPER peptide. Z13e1 showed 100-fold improvement in binding affinity for MPER antigens over Z13, but was still less potent than 4E10 at neutralizing several pseudotyped Envs. Neutralization assays of HIV-1 JR2 MPER alanine mutants showed that mutants W666A and W672A were completely resistant to neutralization by 2F5. Nelson *et al.* [2007] (**antibody binding site definition and exposure**)
- 2F5: This review provides information on the HIV-1 glycoprotein properties that make it challenging to target with neutralizing Abs. 2F5 structure and binding to HIV-1 envelope and current strategies to develop versions of the Env spike with functional trimer properties for elicitation of broadly neutralizing Abs, such as 2F5, are discussed. In addition, approaches to target cellular molecules, such as CD4, CCR5, CXCR4, and MHC molecules, with therapeutic Abs are reviewed. Phogat *et al.* [2007] (**review**)
- 2F5: The ability of 2F5 to neutralize recently transmitted viruses was examined in four homosexual and two parenteral transmission pairs. The vast majority of recently transmitted viruses from 3/4 homosexual recipients were sensitive to neutralization by 2F5, although viruses isolated later in the course of infection showed increased sensitivity to 2F5 in the patient with early viruses resistant to 2F5 neutralization. In the parenteral transmission, one of the recipients had early viruses resistant to 2F5 neutralization, and one had viruses sensitive to 2F5 neutralization. The neutralization sensitivity patterns of recipient viruses to 2F5 did not correlate to the neutralization sensitivity patterns of their donors in the homosexual couples, while the HIV-1 variants from the parenteral pairs were similarly resistant/sensitive to neutralization by 2F5. Despite variations in 2F5 sensitivity, none of the viruses had mutations in the crucial DKW residues of the 2F5 epitope. Quakkelaar *et al.* [2007b] (**neutralization**, **acute/early infection**, **mother-to-infant transmission**)
- 2F5: This study found that, contrary to expectations, the viruses resistant to b12, 4E10, 2G12 and 2F5 neutralization did not have lower replication kinetics than viruses sensitive to neutralization. Viruses from early infection tended to have relatively low replications rates. Quakkelaar *et al.* [2007a] (**viral fitness and reversion**, **acute/early infection**, **escape**)
- 2F5: 2F5 was produced in transgenic tobacco BY2 suspension cell cultures. The plant derived antibody was efficiently assembled and intact. When compared to CHO-derived 2F5, the plant derived 2F5 showed similar kinetic properties and 89% of the binding capacity of the CHO-derived Ab. However, it was only 33% as efficient in HIV-1 RF neutralization assay. Sack *et al.* [2007] (**neutralization**, **binding affinity**)

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- 2F5: A reference panel of recently transmitted Tier 2 HIV-1 subtype B envelope viruses was developed representing a broad spectrum of genetic diversity and neutralization sensitivity. The panel includes viruses derived from male-to-male, female-to-male, and male-to-female sexual transmissions, and CCR5 as well as CXCR4 using viruses. The envelopes displayed varying degrees of neutralization sensitivity to 2F5, with 14 of 19 enevlopes sensitive to neutralization by this Ab. Schweighardt *et al.* [2007] (**neutralization**, **assay standardization/improvement**)
- 2F5: Infusion of a MAb cocktail (4E10, 2G12 and 2F5) into HIV-1 infected subjects was shown to be associated with increased levels of serum anti-cardiolipin and anti-phosphatidylserine Ab titers, and increased coagulation times. In the absence or in the presence of adult and neonate plasma, 2F5 exhibited low binding to phosphatidylserine, did not bind to cardiolipin, and did not induce significant prolongations of clotting times in human plasma, indicating that infusion of 2F5 was not responsible for autoreactivity and prolonged clotting times. Vcelar *et al.* [2007] (**antibody interactions**, **autoantibody**, **binding affinity**, **immunotherapy**)
- 2F5: Novel approaches based on sequential (SAP) and competitive (CAP) antigen panning methodiologies, and use of antigens with increased exposure of conserved epitopes, for enhanced identification of broadly cross-reactive neutralizing Abs are reviewed. Previously known broadly neutralizing human mAbs are compared to Abs identified by these methods. Zhang & Dimitrov [2007] (**review**)
- 2F5: This review summarizes current knowledge of HIV-1 lipid-protein interactions and antibodies to liposomal phospholipids and cholesterol. A potential use of Abs to lipids to neutralize HIV-1 and a potential role of the broadly neutralizing HIV-1 Abs, mainly 2F5 and 4E10, in binding to phospholipids is discussed. Alving *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**, **review**)
- 2F5: Inhibition of 2F5 binding to gp160 by 2F5-like Abs in sera from long-term non-progressors (LTNP) was determined. 2F5-like Abs were present in almost all sera from LTNPs but at a lower levels than b12. No statistically significant correlation was found for the specificity of this Ab comparing sera able to neutralize all four HIV-1 strains and sera that could not. Braibant *et al.* [2006] (**enhancing activity**, **neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2F5: The majority of broadly cross-reactive neutralizing (BCN) Envs were neutralized at lower concentrations of 2F5 than the non-BCN Envs. Amino acid variability of the 2F5 epitope was examined. The presence of T at position 662 was associated with increased sensitivity to neutralization by 2F5 while the K665N mutation resulted in resistance to 2F5 Cham *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **escape**, **subtype comparisons**)
- 2F5: Neutralization of HIV-1 primary isolates of different HIV-1 clades (A, B, C, D, E) by 2F5 was determined in cells expressing high or low surface concentrations of CD4 and CCR5 receptors. CD4 cell surface concentration had no effect on the inhibitory activity of this Ab while the CCR5 surface concentration had a significant effect decreasing the 50% inhibitory concentration of 2F5 in cell lines with low CCR5. Choudhry *et al.* [2006] (**co-receptor**, **neutralization**, **variant cross-recognition or cross-neutralization**)
- 2F5: Neutralization rates and rate constants for the neutralization of clade B primary isolates SF33, SF162 and 89.6 by this Ab were determined. Statistically significant neutralization was not observed for isolates SF162 and 89.6. It was shown that neutralization sensitivity is not associated with neutralization of cell-associated or free virus. Davis *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **kinetics**)
- 2F5: Macaques were immunized with SF162gp140, ΔV2gp140, ΔV2ΔV3gp140 and ΔV3gp140 constructs and their antibody responses were compared to the broadly reactive NAb responses in a macaque infected with SHIV SF162P4, and with pooled sera from humans infected with heterologous HIV-1 isolates (HIVIG). 2F5 recognized all four gp140 proteins equally. 2F5 was found to equally neutralize SF162 and Δ2F5.4E10, which is a virus with mutations in the 2F5 and 4E10 epitopes and is resistant to neutralization by 2F5 and 4E10. This indicates that 2F5-like Abs were not present in sera from the gp140-immunized animals nor in the SHIV-infected and in the HIVIG sera. Derby *et al.* [2006] (**antibody binding site definition and exposure**, **antibody generation**, **neutralization**)
- 2F5: Genetic variability and co-variation of the mAb 2F5, 4E10 and Z13 epitopes in B and non B clades was investigated. A significant shift in the predominant sequence patterns over time was observed for all three epitopes. Also, significant inter-subtype genetic variability of the three epitopes was detected. However, the 4E10 epitope displayed a more similar variability within B clade and non-B clades, concurring with the cross-clade neutralizing activity of this mAb. Epitope co-variation was also noted, as one third of the recently isolated HIV-1 strains displayed simultaneous epitope variants. Dong & Chen [2006] (**antibody binding site definition and exposure**, **subtype comparisons**)
- 2F5: Env-pseudotyped viruses were constructed from the gp160 envelope genes from seven children infected with subtype C HIV-1. 2F5 failed to neutralize any of the seven viruses, correlating with the replacement of the crucial lysine at the position 665 of the 2F5 epitope on these viruses. When this Ab was mixed with IgG1b12 and 2G12, the neutralization was similar as to IgGb12 alone, indicating that the majority of the pool activity was due to IgG1b12. When 4E10 was added to this mix, all isolates were neutralized. Gray *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **responses in children**, **mother-to-infant transmission**)
- 2F5: This review describes the effectiveness of the current HIV-1 immunogens in eliciting neutralizing antibody responses to different clades of HIV-1. It also summarizes different evasion and antibody escape mechanisms, as well as the most potent neutralizing MAbs and their properties. MAbs reviewed in this article are: 2G12, IgG1b12, 2F5, 4E10, A32, 447-52D and, briefly, D50. Novel immunogen design strategies are also discussed. Haynes & Montefiori [2006] (**antibody binding site definition and exposure**, **neutralization**, **optimal epitope**, **escape**, **review**, **subtype comparisons**, **structure**)

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- 2F5: Viruses with cleavage-competent 2G12-knockout Env and cleavage-defective Env able to bind 2G12 were constructed. 2F5 was shown to bind more to the cleavage-defective Envs than to the cleavage-competent Envs. More 2F5 binding was detected to cells co-expressing wildtype and leavage-defective Env than to a mixture of cells expressing either, suggesting that uncleaved Env proteins have an enhancing effect of the binding of 2F5 to the heterotrimer or that fewer than three Abs can bind per trimer and that 2F5 has a higher affinity for the uncleaved Env. Env pseudotyped virions bearing either Wt3.2P(+)gp140δct Env or a mixture of the wildtype and cleavage-defective Env had similar sensitivities to neutralization by 2F5. Herrera *et al.* [2006] (**neutralization**, **binding affinity**)
- 2F5: Inhibition of R5 HIV replication by monoclonal and polyclonal IgGs and IgAs in iMDDCs was evaluated.The neutralizing activity of 2F5 was observed to be higher in iMDDCs than in PBLs and PHA-stimulated PBMCs. Furthermore, the kinetics of Ab addition showed that this mAb inerfered with the first events of HIV-1 entry in iMDDCs. High concentrations of 2F5 triggered a non-HIV-related maturation of target cells. Blockade of FcγRII on iMDDCs decreased the anti-HIV acitvity of 2F5 while increased expression of FcγRI increased inhibition of HIV by 2F5, suggesting the involvment of these receptors in the HIV-inhibitory activity of this Ab. Holl *et al.* [2006b] (**neutralization**, **kinetics**, **dendritic cells**)
- 2F5: The ability of this Ab to inhibit viral growth was increased when macrophages and immature dendritic cells (iDCs) were used as target cells instead of PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication by this Ab for macrophages and iDCs can occur by two distinct mechanisms, neutralization of infectivity involving only the Fab part of the IgG, and, an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**dendritic cells**)
- 2F5: 2F5 was shown to interact with cells transiently transfected by VSV-gp120 expressing vector and stained with sera from mice immunized intranasally with VSV vector expressing HIV-1 HXB2 gp120, indicating that VSV-HXB2 immunization produced anti-HIV-1 Abs. Jiang *et al.* [2006] (**vaccine antigen design**)
- 2F5: Pharmacokinetic properties of this Ab were studied in HIV infected patients infused with high doses of 2G12. The Ab did not elicit an endogenous immune response and had distribution and systemic clearance values similar to other Abs. The elimination half-life was measured to 4.3 days. Joos *et al.* [2006] (**kinetics**, **immunotherapy**)
- 2F5: 2 of 18 subtype C env-pseudotyped clones derived from individuals in acute/early stage of HIV-1 infection were neutralized by this Ab, both of them had a DKW motif reported to be a requirement for 2F5recognition. The sensitivity of clones to a mix of Abs IgG1b12, 2G12 and 2F5 was tracked to IgG1b12. Li *et al.* [2006c] (**neutralization**, **variant cross-recognition or cross-neutralization**, **acute/early infection**, **subtype comparisons**)
- 2F5: The gp140δCFI protein of CON-S M group consensus protein and gp140CFI and gp140CF proteins of CON6 and WT viruses from HIV-1 subtypes A, B and C were expressed in recombinant vaccinia viruses and tested as immunogens in guinea pigs. 2F5 was shown to bind specifically to CON6, CON-S and subtype B recombinant proteins but not to subtype A and C recombinant proteins or to the two subtype B gp120 proteins. The specific binding of 2F5 to CON-S indicated that its conformational epitope was intact. Liao *et al.* [2006] (**antibody binding site definition and exposure**, **vaccine antigen design**, **subtype comparisons**)
- 2F5: PreTM peptide lacks the complete epitope sequence required for efficient recognition of this Ab. Thus, 2F5 was not able to arrest the leakage process and pore-formation at the viral membrane surface indicating that blocking of membrane destabilization depends on specific 4E10 epitope recognition. Lorizate *et al.* [2006a]
- 2F5: This Ab recognized AIS (amphipathic-at-interface sequence)-FP (fusion peptide) hybrid sequence with higher affinity than the linear AIS, indicating that the hybrid sequence better emulates the native gp41 2F5 epitope. Lorizate *et al.* [2006b] (**antibody binding site definition and exposure**, **binding affinity**)
- 2F5: gp41 and p15E of the porcine endogenous retrovirus (PERV) share structural and functional similarities, and epitopes in the membrane proximal region of p15E are able to elicit NAbs upon immunization with soluble p15E. Rabbits immunized with a VSV recombinant expressing an HIV-1 membrane-proximal external region (MPER) fused to PERV p15E, with a fusion p15E-HIV MPER protein boost, elicited HIV specific NAbs. The MPER contains the 2F5 epitope, and the 2F5 MAb was used as a positive control for neutralization in this study, and could bind to the vaccine construct. Luo *et al.* [2006] (**vaccine antigen design**)
- 2F5: In addition to gp120-gp41 trimers, HIV-1 particles were shown to bear nonfunctional gp120-gp41 monomers and gp120-depleted gp41 stumps on their surface. 2F5 effectively neutralized wildype virus particles, however, it did not capture virus efficiently. 2F5 was found to bind to both nonfunctional monomers and to gp120-gp41 trimers. Binding of 2F5 to trimers correlated with its neutralization of wildtype virus particles. Monomer binding did not correlate with neutralization, but it did correlate with virus capture. It is hypothesized that the nonfunctional monomers on the HIV-1 surface serve to divert the Ab response, helping the virus to avoid neutralization. Moore *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- 2F5: The effect of epitope position on 2F5 neutralization was examined by inserting the 2F5 epitope into MLV proline rich region Env surface protein (SU) or into MLV Env TM comparable to its natural position. 2F5 was shown to block cell fusion and virus infection with the SU-located 2F5 epitope while MLV with HA epitope at the same position was not neutralized by anti-HA. 2F5 was shown to block Env-mediated cell fusion in MLV with TM-located 2F5 epitope. Epitope position was also shown to have effect on neutralization by 2F5, where inhibition of cell fusion was more than 10-fold lower when the 2F5 epitope was in SU than in TM. Ou *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**)
- 2F5: SHIV SF162p4 virus used as challenge in ISCOM vaccinated macaques was shown to be highly sensitive to neutralization by this Ab. Pahar *et al.* [2006] (**neutralization**)

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- 2F5: This Ab is shown to have the capacity to penetrate into the membrane interfaces and recognize isolated peptide-epitope sequence embeded into the membrane, however, 2F5 recognizes its epitope with lower affinity when immersed into the membrane interface. This lower affinity is suggested to result from a differently oriented epitope residues in the membrane-bound state. Sánchez-Martínez *et al.* [2006b] (**antibody binding site definition and exposure**)
- 2F5: The capacity of different soluble lysoderivatives to inhibit 2F5 binding to immobilized HIV-1 peptide epitope were compared and it was shown that only dilysocardiolipin resulted in effective blocking. Dilysocardiolipin was also shown to compete with native-functional gp41 for 2F5 recognition indicating that specific cardiolipin recognition by 2F5 involves the epitope-binding site. Sánchez-Martínez *et al.* [2006a] (**antibody binding site definition and exposure**)
- 2F5: Interaction of this Ab with membrane model systems revealed that 2F5 does not significantly interact with model viral or target cell membranes indicating that it does not use membrane interaction prior to gp41 docking. Veiga & Castanho [2006] (**antibody binding site definition and exposure**)
- 2F5:A fusion protein (FLSC R/T-IgG1) that targets CCR5 was expressed from a synthetic gene linking a single chain gp120-CD4 complex containing an R5 gp120 sequence with the hinge-Ch2-Ch3 portion of human IgG1. The fusion protein did not activate the co-receptor by binding. In PBMC assays, FLSC R/T-IgG1 neutralized primary R5 HIV-1 isolates more potently than 2F5, while in cell-line based assays they were comparable. Vu *et al.* [2006] (**neutralization**)
- 2F5: This Ab was used as a positive control in the neutralization assay. At the highest Ab concentrations, 2F5 was able to neutralize several primary isolates but not all, with a neutralization pattern similar to that of rabbit sera immunized with monovalent and polyvalent DNA-prime/protein-boost Env from different HIV-1 subtypes. At a reduced concentrations, 2F5 showed much weaker neutralizing activities. Wang *et al.* [2006a] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2F5: Viruses with wild-type HIV-1JR-FL Envs and HIV-1 hXBc2 Envs were neutralized by this Ab at much lower concentrations than HIV-1 YU2 Env viruses. Viruses bearing inserted artificial epitopes of FLAG in the V4 region were as sensitive to neutralization by this Ab as the parental viruses. A clear relationship between neutralization potency and the affinity of the anti-FLAG antibody for its cognate epitope was observed. Yang *et al.* [2006] (**neutralization**, **binding affinity**)
- 2F5: Significant levels of 2F5 were shown to bind to HA/gp41 expressed on cell surfaces and this Ab did stain cells expressing HA/gp41 in a fluorescence assay. However, a much smaller percentage of the HIV 89.6 Env expressing cells were stained with this Ab than with 2G12, indicating that this Ab recognition site on gp41 is masked by the gp120 subunit in the HIV Env protein and that it is more easily accessible on the HA/gp41 chimeric protein. Ye *et al.* [2006] (**antibody binding site definition and exposure**, **binding affinity**)
- 2F5: The epitope recognition sequence for this Ab was introduced into the corresponding region of SIVmac239 but the replication of this viral variant (SIVmac239/2F5) was delayed in comparison to the parental virus. SIVmac239/2F5 was specifically neutralized by MAb 2F5. Yuste *et al.* [2006] (**neutralization**, **SIV**)
- 2F5: Competition of free gp120 89.6 with immobilized gp140 89.6 for binding to 2F5 was assesed. The binding of this Ab to coated gp140 was not affected by an increase in the gp120 concentration. Zhang *et al.* [2006a] (**binding affinity**)
- 2F5: The major infectivity and neutralization differences between a PBMC-derived HIV-1 W61D strain and its T-cell line adapted counterpart were conferred by the interactions of three Env amino acid substitutions, E440G, D457G and H564N. Chimeric Env-pseudotyped virus Ch5, containing all three of the mutations, was only marginally more neutralization sensitive to 2F5 than Ch2, which did not contain any of these mutations. Env-pseudotyped viruses containing D457G mutation alone, or in combination with E440G or H564N, were also more sensitive to neutralization by 2F5 than Ch2. Beddows *et al.* [2005b] (**neutralization**)
- 2F5: Circular dichroism and NMR were used to analyze the structure of the HIV-1 inhibitor peptide T-20 (gp41 HXB2 aa 638-673) that contains the full 2F5 and partial 4E10 epitope. T-20 was unstructured towards the N terminus, and helical in the central and C-terminal regions. The 2F5 epitope sequence (gp41 HXB2 657-670) forms an intrinsic helical structure, which is stable in water. Biron *et al.* [2005] (**structure**)
- 2F5: A panel of 60 HIV-1 isolates, with complete genome sequences available, was formed for neutralization assay standardization. It comprises of 10 isolates from each of the subtypes A, B, C, D, CRF01_AE and CRF02AG, with majority of the viruses being of R5 phenotype and few of X4 phenotype. Neutralization profile of each isolate was assessed by measuring neutralization by sCD4, a cocktail of MAbs including 2G12, 2F5 and IgG1b12, and a large pool of sera collected from HIV-1 positive patients. The MAb cocktail neutralized with >50% a large portion of the isolates (51/60) including: 10 subtype A isolates, 8 subtype B isolates, 8 subtype C isolates, 9 subtype D isolates, 7 CRF-01_AE isolates, and 9 CRF_02AG isolates. Brown *et al.* [2005] (**neutralization**, **subtype comparisons**, **assay standardization/improvement**)
- 2F5: Four primary isolates (PIs), Bx08, Bx17, 11105C and Kon, were tested for binding and neutralization by 2F5. 2F5 was able to neutralize Bx08, Bx17 and 11105C with various efficiencies, but bound inefficiently to all four PIs. There was no direct correlation between binding and neutralization of the four PIs by 2F5. CD4-induced gp120 shedding had no effect on binding of 2F5 to Bx08. Burrer *et al.* [2005] (**neutralization**, **binding affinity**)
- 2F5: The structure of the 2F5 MAb, particularly its CDRH3 region's binding mechanisms to the MPER region of gp41, and possibly the cellular membrane as well, are reviewed. Engineering of Abs based on revealed structures of broadly neutralizing MAbs is discussed. Burton *et al.* [2005] (**antibody binding site definition and exposure**, **review**, **structure**)
- 2F5: Guinea pigs were immunized with a hybrid HXB2/BaL Env (HIV HXB/BaL gp140δCFI, clade B) in which the tip of the V3 loop (GPGRA) was replaced with the 2F5 epitope LELDKWAS. 2F5 bound to the Env that carried the V3-replacement 2F5 epitope, but antibodies against this construct

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only neutralized the X4-tropic lab adapted HIV strain IIIB, and not CCR5-HIV BaL or SF162 isolates. Chakrabarti *et al.* [2005] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

- 2F5: 2F5 was investigated in differnt neutralization formats, including the standard format that measures activity over the entire infection period and several formats that emphasize various stages of infection. 2F5 showed modest neutralization in the standard format, which was increased with the gp41 tail truncation and/or addition of a disulfide bridge linking gp120 and gp41. 2F5 was also able to neutralize in all the other neutralization formats analyzed, suggesting that it binds Env trimers at various stages of infection. None of the analyzed HIV-1 + human plasmas neutralized in the post-CD4/CCR5 format indicating absence of 2F5 and 4E10 - like Abs. Crooks *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **assay standardization/improvement**)
- 2F5: 2F5 recognizes the epitope ELDKWA, but does not neutralize viruses carrying the commonly found mutated epitope variants: ELDeWA, ELDsWA, ELDnWA, ELDqWA, ELDtWA, or ELnKWA. Peptide cocktails containing ELDKWA, ELnKWA, ELDeWk,and ELeKWA elicit polyclonal antibodies in rabbits that can bind to all of the natural variants that are escape variants for 2F5 expressed in gp41 via Western blotting, as well as ELDrWA. Dong *et al.* [2005a] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **escape**)
- 2F5: Trimeric gp140CF protein synthesized from an artificial group M consensus Env gene (CON6) bound well to 2F5, indicating correct exposure of the 2F5 epitope. Gao *et al.* [2005a] (**antibody binding site definition and exposure**)
- 2F5: 2F5 neutralized viral isolates HXBc2, SF162, 89.6, BaL, ADA, and YU2. Neutralization was concentration dependent, as higher MAb concentration resulted in higher % of neutralization. Grundner *et al.* [2005] (**neutralization**)
- 2F5:2F5 and 4E10 both bind to membrane proximal regions of gp41, and have long hydrophobic CDR3 regions characteristic of polyspecific autoreactive antibodies. Of 35 Env-specific MAbs tested, only 2F5 and 4E10 were reactive with phospholipid cardiolipin. Vaccine induction of antibodies that react with these gp41 membrane proximal regions may be rare because of elimination due to autoantigen mimicry. 2F5 also reacted with centromere B and histone autoantigens, and both 4E10 and 2F5 reacted with HEp-2 cells with diffuse cytoplasmic and nuclear patterns indicating polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)
- 2F5: This review summarizes data on the polyspecific reactivities to host antigens by the broadly neutralizing MAbs IgG1b12, 2G12, 2F5 and 4E10. It also hypothesizes that some broadly reactive Abs might not be routinely made because they are derived from B cell populations that frequently make polyspecific Abs and are thus subjected to B cell negative selection. Haynes *et al.* [2005b] (**antibody generation**, **antibody interactions**, **review**)
- 2F5: Furin co-transfection did not have an effect on the reactivity of Δ140ct HXBc2 and 3.2P pseudoviruses with 2F5, or on their neutralization sensitivity. Presence or absence of sialic acid residues did not affect Env reactivity with 2F5. A cleavage-competent form of 3.2P reacted poorly with 2F5, while its cleavage-defective counterpart showed higher level of MAb reactivity. Both cleavage-competent and cleavage-defective HXBc2 showed higher levels of reactivity to 2F5. DDT-induced dissociation of SOS gp140 and the estimate of cleavage was scored higher when 2F5 was used as detection Ab than when B13 MAb was used. Herrera *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- 2F5: In an attempt to elicit 2F5-like antibodies, the 2F5 epitope ELDKWAS was constrained in the beta-turn sites of the immunoglobulin heavy chain, or alternatively was attached at the C-terminal ends of the immunoglobulin light chain. The constrained heavy chain inserted epitopes bound to 2F5 with 10-fold higher affinity than the light chain unconstrained versions, and when used as an immunogen, elicited epitope-specific antibodies in rabbits, but these antibodies could not neutralize the virus. Ho *et al.* [2005] (**vaccine antigen design**, **vaccine-specific epitope characteristics**)
- 2F5: Why broadly neutralizing Abs, such as 2G12, 2F5 and 4E10, are extremely rare, and their protective abilities and potential role in immunotherapy are discussed. Jülg & Goebel [2005] (**neutralization**, **immunotherapy**, **review**)
- 2F5: Point mutations in the highly conserved structural motif LLP-2 within the intracytoplasmic tail of gp41 resulted in conformational alternations of both gp41 and gp120. The alternations did not affect virus CD4 binding, coreceptor binding site exposure, or infectivity of the virus, but did result in decreased binding of certain MAbs and increased neutralization resistance to MAbs as well as to human polyclonal HIV-Ig and pooled human sera. 2F5 MAb, however, effectively neutralized both the LLP-2 mutant and wildtype viruses, and also exhibited similar levels of binding to both the LLP-2 mutant and the wildtype virus. Kalia *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- 2F5: A series of genetically modified Env proteins were generated and expressed in both insect and animal cells to be monitored for their antigenic characteristics. For 2F5, most of the modified proteins expressed in insect cells containing the 3G mutation (mutations in 3 glycosylation sites) showed higher levels of binding to the MAb than the wildtype did. Additional presence of a glycosylation mutation 1G, close to the 2F5 epitope, increased binding of 2F5 compared to the binding to Env without the mutation. The highest binding to 2F5 was observed for the dV1V2 mutant. When expressed in animal cells, the 3G mutant was the one that displayed increased binding to 2F5 compared to other mutants. Kang *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)
- 2F5: A trimeric recombinant gp140 construct was developed for immunization studies. Its structural integrity was assessed by a panel of MAbs. The trimeric recombinant gp140 lacked the membrane proximal ectodomain segment of gp41, but the 2F5 Ab did bind efficiently to the gp140 trimers containing the entire gp41 ectodomain. Kim *et al.* [2005] (**antibody binding site definition and exposure**)
- 2F5: Sera from subtype A infected individuals from Cameroon have antibodies that react strongly with subtype A and subtype B V3 loops in fusion proteins, and neutral-

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ize SF162 pseudotypes, while sera from 47 subtype B infected individuals reacted only with subtype B V3s. Sera from Cameroon did not neutralize primary A or B isolates, due to indirect masking by the V1/V2 domain rather than due to loss of the target epitope. Neutralization by Cameroonian sera MAbs was blocked by Clade A and B V3 loop fusion proteins, while NAbs to non-V3 epitopes, 2F5, 2G12, and b12, were not blocked. Krachmarov *et al.* [2005] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

- 2F5: A trimeric gp41 construct comprising the env transmembrane domain and the extracellular C-terminal region (gp41ctm) was incorporated into liposomes. 2F5 bound to the liposome-incorporated gp41ctm, indicating that its extracellular region is accessible to this Ab. Sera from mice immunized with either gp41ctm alone or with gp41ctm-liposome did not show any significant neutralization activity, indicating that the construct might not properly expose its 2F5 epitope. Lenz *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**)
- 2F5: Full-length gp160 clones were derived from acute and early human HIV-1 infections and used as env-pseudotyped viruses in neutralization assays for their characterization as neutralization reference agents. 13 out of 19 pseudoviruses were neutralized by 2F5, but few required higher concentration of the Ab for neutralization. MN, SF162.LS and IIIB strains were highly sensitive for neutralization by 2F5. Resistance to neutralization by 2F5 was associated with mutations in the DKW motif, or elsewhere in the 2F5 epitope. A mixture of IgG1b12, 2F5 and 2G12 (TriMab) exhibited potent neutralizing activity against all Env-pseudotyped viruses except one. 8 out of 12 Env-pseudotyped viruses were more sensitive to neutralization by 2F5 than their uncloned parental PBMC-grown viruses. Li *et al.* [2005a] (**neutralization**, **assay standardization/improvement**)
- 2F5: A peptide containing eight copies of the ELDKWA-epitope separated by aa spacers GSGGGGS, RS, and GS was used to test the impact of spacers on eliciting antibody responses to peptides. Both GSGGGGS and GS induced high titers of ELDKWA peptide-specific Abs in BALB/c mice, which reacted with rsgp41. 2F5 served as a positive control in a Western Blot to determine whether epitope-specific Abs bound to recombinant protein rsgp41. Liu *et al.* [2005b] (**vaccine antigen design**, **vaccine-specific epitope characteristics**)
- 2F5: Pseudoviruses expressing HIV-1 envelope glycoproteins from BL01, BR07 and 89.6 strains were compared in neutralization assays to replication competent clone derived from transfection of 293T cells (IMC-293T) and to the IMC-293T derived from a single passage through PBMC (IMC-PBMC). The neutralization responses of pseudoviruses and corresponding IMC-293T to 2F5 were similar, while a significant decrease in viral neutralization sensitivity to 2F5 was observed for all three IMC-PBMC viruses. The decrease was associated with an increase in average virion envelope glycoprotein content on the PBMC-derved virus. Louder *et al.* [2005] (**neutralization**, **assay standardization/improvement**)
- 2F5: Nine anti-gp41 bivalent Fabs that interacted with either or both of the 6-helix bundle and the internal coiled-coil of N-helices of gp41 were selected from a non-immune human phage display library. The IC50 range for the inhibition of LAV ENV-mediated cell-fusion was 6-61 ug/ml. For context, 2F5 and 2G12 (IC50s of 0.5-1.5 ug/ml) were about an order of magnitude more potent in this assay than the best Fabs generated here. Louis *et al.* [2005] (**neutralization**)
- 2F5: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **antibody interactions**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **immunotherapy**, **review**)
- 2F5: Viruses containing substitutions at either L568 or K574 of the gp41 hydrophobic pocket were resistant to D5-IgG1 but were as sensitive to 2F5 as the wildtype virus. 2F5 neutralized more isolates than D5-IgG1 and was shown to be more potent. 2F5 did not, however, neutralize some of the isolates neutralized by D5-IgG1. Miller *et al.* [2005] (**neutralization**)
- 2F5: This short review summarizes recent findings of the role of neutralizing Abs in controlling HIV-1 infection. Certain neutralizing MAbs and their potential role in immunotherapy and vaccination, as well as the reasons for their poor immunogenicity, are discussed. Montefiori [2005] (**antibody binding site definition and exposure**, **therapeutic vaccine**, **escape**, **immunotherapy**)
- 2F5: A short review of studies on 2F5 interaction with autoantigens, epitope accessibility, structure, and neutralizing capability. The reasons why 2F5 appears infrequently in nature are discussed. Nabel [2005] (**antibody binding site definition and exposure**, **antibody generation**, **neutralization**, **immunotherapy**, **review**)
- 2F5: Passive immunization of 8 HIV-1 infected patients with 4E10, 2F5 and 2G12 (day 0, 4E10; days 7, 14 and 21 4E10+2G12+2F5; virus isolated on days 0 and 77) resulted in 0/8 patients with virus that escaped all three NAbs. No viruses fully escaped 2F5, although 5/8 developed a more than 2-fold increase in 2F5 IC50 concentrations at day 77. No changes in the 2F5 epitope were observed in the 77 day study period, although 3 patients had unusual 2F5 epitope sequences to start with (not A/ELDKWA but SLNNWN, ALDTWE, or KFD-NWA); all viruses were susceptible to 2F5 neutralization, although to varying degrees. In a companion in vitro study, resistance to a single MAb emerged in 3-22 weeks, but triple combination resistance was slower and characterized by decreased viral fitness. In the core of the 2F5 epitope, LDKW, the L and W were completely conserved in the in vitro study, but 9/13 cases had a D->N change, 1/13 a K->N, and 1/13 a K->Q. The lack of resistance to the combination of MAbs in vivo and the reduced fitness of the escape mutants selected in vitro suggests passive immunotherapy may be of value in HIV infection. Nakowitsch *et al.* [2005] (**escape**, **immunotherapy**)

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- 2F5: This study is about the V2 MAb C108g, that is type-specific and neutralizes BaL and HXB2. JR-FL is a neutralization resistant strain; modification of JRFL at V2 positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potently neutralize the modified JR-FL. The modification in V2 also increased neutralization sensitivity to V3 MABs 4117c, 2219, 2191, and 447-52D, but only had minor effects on neutralization by CD4BS MAb 5145A, and broadly neutralizing MAbs IgG1b12, 2G12, and 2F5. Pinter *et al.* [2005] (**antibody binding site definition and exposure**)
- 2F5: Escape mutations in HR1 of gp41 that confer resistance to Enfuvirtide reduced infection and fusion efficiency and also delayed fusion kinetics of HIV-1. The mutations also conferred increased neutralization sensitivity of virus to 2F5. Enhanced neutralization correlated with reduced fusion kinetics, indicating that the mutations result in Env proteins remaining in the CD4-triggered state for a longer period of time. Reeves *et al.* [2005] (**antibody binding site definition and exposure**, **drug resistance**, **neutralization**, **escape**, **HAART, ART**)
- 2F5: The antibody M2 is specific for a peptide flag inserted into the V4 loop of YU-2, a neutralization resistant variant with a short V4 loop. IgG1b12 and 2F5 could neutralize both the WT YU-2 and the modified variant. The high diversity of V4 suggests it does not play a direct role in receptor binding or viral entry, yet M2, specific for the peptide insert tag, can neutralize the modified virus, demonstrating that neutralizing activity doesn't have to block functionality of the virus. Ren *et al.* [2005] (**neutralization**)
- 2F5: More that 90% of viruses from both acutely and chronically infected HIV-1 patients were inhibited by this Ab, however, viruses from acute patients were significantly more sensitive to 2F5 than viruses from chronic patients. The epitope of this Ab was highly conserved among all isolates tested suggesting that the higher susceptibility of acute viruses may be due to better epitope accessibility. The sensitivity of viruses to 2F5 was also highly correlated to their sensitivities to 4E10. Rusert *et al.* [2005] (**antibody binding site definition and exposure**, **antibody interactions**, **autologous responses**, **neutralization**, **acute/early infection**)
- 2F5: Ab titers to the 2F5 binding peptide ELDKWA were tested by peptide ELISA in sera from Thais infected with CRF01 virus who were asymptomatic versus those who had AIDS, and antibody titers were found to be significantly lower in AIDS patients. The frequency of recognition of this peptide was low overall (15-35%) in CRF01 infections, as well as infections with clades A-G. Srisurapanon *et al.* [2005] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**, **rate of progression**)
- 2F5: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **binding affinity**, **immunotherapy**, **mother-to-infant transmission**, **review**, **structure**)
- 2F5: This review summarizes data on 447-52D and 2219 crystallographic structures when bound to V3 peptides and their corresponding neutralization capabilities. 2F5, like 447-52D and like other HIV-1 neutralizing Abs, was shown to have long CDR H3 loop, which is suggested to help Abs access recessed binding sites on the virus. Stanfield & Wilson [2005] (**antibody binding site definition and exposure**, **review**, **structure**)
- 2F5: Six acutely and eight chronically infected patients were passively immunized with a mix of 2G12, 2F5 and 4E10 neutralizing Abs during treatment interruption. Two chronically and four acutely infected individuals showed evidence of a delay in viral rebound during Ab treatment suggesting that NAbs can contain viremia in HIV-1 infected individuals. All subjects with virus sensitive to 2G12 developed Ab escape mutants resulting in loss of viremia and failure to treatment while no escape was observed for 4E10 and 2F5. Plasma levels of 2G12 were substantially higher than those of 2F5 and 4E10, and the 2G12 levels exceeded the in vitro required 90% inhibitory doses by two orders of magnitude in subjects that responded to Ab treatment. No such differences were observed for 2F5 or 4E10, suggesting that high levels of NAbs are required for inhibition in vivo, and that the in vivo concentrations of 4E10 and 2F5 might have been to low to control viremia and exert a selective pressure. Trkola *et al.* [2005] (**acute/early infection**, **escape**, **immunotherapy**, **HAART, ART**, **supervised treatment interruptions (STI)**)
- 2F5: This Ab recognized the gp41 epitope ALDKWQ from the 92/BR/025.9 strain. HIV-1 infected patients treated with T20 showed decreased reactivity of their sera to a peptide containing the 2F5 epitope. The Ab titer to this peptide recovered after cessation of T20 therapy. It is indicated that 2F5 may interfere with the T20-HR1 interaction. Vincent *et al.* [2005] (**antibody interactions**)
- 2F5: A multi-epitope ELDKWA/ELDEWA string in a glutathione S-transferase (GST) backbone elicited Abs in mice and rabbits that could bind to gp41 carrying either the 2F5 susceptible ELDKWA variant, or the ELDEWA escape variant. Vaccinations with only the ELDKWA epitope or the ELDEWA embedded-peptide constructs yielded type specific Abs. Wang *et al.* [2005c] (**vaccine antigen design**, **vaccine-specific epitope characteristics**, **escape**)
- 2F5: Ab neutralization of viruses with mixtures of neutralization-sensitive and neutralization-resistant envelope glycoproteins was measured. It was concluded that binding of a single Ab molecule is sufficient to inactivate function of an HIV-1 glycoprotein trimer. The inhibitory effect of the Ab was similar for neutralization-resistant and -sensitive viruses indicating that the major determinant of neutralization potency of an Ab is the efficiency with which it binds to the trimer. It was also indicated that each functional trimer on the virus surface supports HIV-1 entry independently, meaning that every trimer on the viral surface must be bound by an Ab for neutralization of the virus to be achieved. Yang *et al.* [2005c] (**neutralization**)
- 2F5: A substantial fraction of soluble envelope glycoprotein trimers contained inter-subunit disulfide bonds. Reduction of these disulfide bonds had little effect on binding of the 2F5 to the glycoprotein, indicating that the inter-S-S bonds had no

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impact on the exposure of 2F5 epitope. Yuan *et al.* [2005] (**antibody binding site definition and exposure**)

- Two ELDKWA-specific MAbs were obtained from mice immunized with four copies of ELDKWA-epitope with spacers between the epitopes. The two Abs inhibited syncytium formation less efficiently then 2F5 but were as potent as 2F5 in neutralization of primary isolate 92US657. The two murine MAbs were ineffective against the laboratory-adapted HIV-1 IIIB strain while 2F5 neutralized successfully. Neither 2F5 nor the two new MAbs neutralized group O primary isolate BCF02. Zhang *et al.* [2005a] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**)
- 2F5: Alanine scanning mutations of the 21 amino acid region between positions 660-680 showed that only Ala substitutions in the DKW at the core of the epitope reduced binding, positions llelDKWanlwnwfdisnwlw. No single Ala mutation was resistant to both 2F4 and 4E10. Ala substitutions in 12 of the 20 positions enhanced neutralization sensitivity, LLeLdkwanLWNWFdIsnWLW.2F5 inhibits the neutralization activity of peptide T20. Zwick *et al.* [2005] (**antibody binding site definition and exposure**, **escape**)
- 2F5: 93 viruses from different clades were tested for their neutralization cross-reactivity using a panel of HIV antibodies. 2F5 was cross-reactive with A, B, and E subtype viruses, some D, and no C clade viruses. DKW was defined as the core motif, and was found in only 25% of C clade sequences in the database. It was found in C clade viruses in a country specific manner – common in Burundi, Brazil and Ethiopia, rare in Botswana, India, and S. Africa. The potency of the neutralizing activity was somewhat context-dependent. DQW is a common D clade variant from Uganda, and all D viruses in this study were Ugandan. Binley *et al.* [2004] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2F5: Env sequences were derived from 4 men at primary infection and four years later; the antigenicity in terms of the ability to bind to 2G12, 2F5 and IgG1b12 was determined. 2G12 bound primarily to late clones in 3 of the 4 patients, and to both early and late in the other patient. Neither 2F5 nor IgG1b12 showed a difference in binding affinity to early or late envelopes. Dacheux *et al.* [2004] (**antibody binding site definition and exposure**, **acute/early infection**, **kinetics**)
- 2F5: Neonatal rhesus macaques were exposed orally to a pathogenic SHIV, 89.6P. 4/8 were given an intramuscular, passive immunization consisting of NAbs 2G12, 2F5 and 4E10, each given at a different body sites at 40 mg/kg per Ab, at one hour and again at 8 days after exposure to 89.6P. The four animals that were untreated all died with a mean survival time of 5.5 weeks, the four animals that got the NAb combination were protected from infection. This model suggests antibodies may be protective against mother-to-infant transmission of HIV. Ferrantelli *et al.* [2004b] (**mother-to-infant transmission**)
- 2F5: Nabs against HIV-1 M group isolates were tested for their ability to neutralize 6 randomly selected HIV-1 O group strains. IgG1b12 could neutralize some O group strains when used on its own, and quadruple combination of b12, 2F5, 2G12, and 4E10, could neutralize the six Group O viruses tested between 62-97%. The 2F5 epitope in the O group viruses was : ELDEWA. Ferrantelli *et al.* [2004a] (**variant cross-recognition or cross-neutralization**)
- 2F5: This paper reviews MAbs that bind to HIV-1 Env. 2F5 binds to a region of gp41 proximal to cluster II (aa 662-676), neighboring the binding site of the broadly neutralizing MAb 4E10 and of neutralizing Fab Z13. 2F5 is broadly neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
- 2F5: A set of oligomeric envelope proteins were made from six primary isolates for potenial use as vaccine antigens: 92/UG/037 (clade A), HAN2/2 (clade B), 92/BR25/025 (clade C), 92/UG/021 (clade D), 93/BR/029 (clade F) and MVP5180 (clade O). This was one of a panel of MAbs used to explore folding and exposure of well characterized epitopes. The clade C isolate BR25 is apparently misfolded, as conformation-dependent antibodies did not bind to it. 2F5 bound to clade A, B, D and F HIV-1 primary isolates. Polyclonal sera raised in rabbits against these antigens cross-bound the other antigens, but none of the sera had neutralizing activity. Jeffs *et al.* [2004]
- 2F5: 2F5 was used as a positive control in a study that showed that A32-rgp120 complexes open up the CCR5 co-receptor binding site, but did not induce neutralizing antibodies with greater breadth among B subtype isolates than did uncomplexed rgp120 in vaccinated guinea pigs. Liao *et al.* [2004]
- 2F5: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of 17b and F105 was decreased by trypsin, but increased by thrombin. gp41 MAbs 246D, 98.6, 50-69, were decreased by trypsin, unaltered by thrombin, while NAb 2F5 binding was increased by thrombin. Thrombin may increase HIV-induced cell fusion in blood by causing a conformational activating shift in gp120. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 2F5: Mice susceptible to MV infection were intraperitoneally immunized with native HIV-1 89.6 env gp160 and gp140 and δV3 HIV-1 89.6 mutants expressed in live attenuated Schwarz measles vector (MV). The gp160ΔV3 construct raised more cross-reactive NAbs to primary isolates. The constructs had an additional 2F5 MAb epitope, ELDKWAS, but responses were not directed towards this epitope. A HIVIG/2F5/2G12 combination was used as a positive control and could neutralize all isolates. Lorin *et al.* [2004] (**vaccine antigen design**)
- 2F5: Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The loss of the glycan within the V3 loop (GM299 V3) and adjacent to the C-terminal end of the V3 loop (GM329 C3) did not alter neutralization susceptibility to 2F5, but the loss of glycans in C2 (GM292 C2), C4 (GM438 C4), or V5 (GM454 V5) increased 2F5 neutralization susceptibility. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater

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access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure**, **vaccine antigen design**)

- 2F5: This review summarizes properties of 2F5 and its binding to the prefusogenic membrane proximal region of gp41. The linear core epitope does not stimulate cross-reactive NAbs when placed outside the context of gp41, suggesting its presentation in a highly specific moleuclar framework is critical. McGaughey *et al.* [2004] (**vaccine antigen design**, **review**)
- 2F5: 2F5 was used for screening of phage-displayed peptide libraries. 2F5 requires the DKW core for synthetic and phage-displayed peptide recognition, but is multispecific for amino acid residues flanking C-terminally the DKW core epitope. Three clones from the AADKW-X12 library had high affinity for 2F5, but did not share obvious holomogy with gp41 or each other; Ala substitution showed each bound to 2F5 with a different mechanism. Menendez *et al.* [2004] (**antibody binding site definition and exposure**, **mimotopes**)
- 2F5: A set of HIV-1 chimeras that altered V3 net charge and glycosylation patterns in V1V2 and V3, involving inserting V1V2 loops from a late stage primary isolate taken after the R5 to X4 switch, were studied with regard to phenotype, co-receptor usage, and MAb neutralization. The loops were cloned into a HXB2 envelope with a LAI viral backbone. It was observed that the addition of the late-stage isolate V1V2 region and the loss of V3-linked glycosylation site in the context of high positive charge gave an X4 phenotype. R5X4, R5, and X4 viruses were generated, and sCD4, 2G12 and b12 neutralization resistance patterns were modified by addition of the late stage V1V2, glycosylation changes, and charge in concert, while neutralization by 2F5 was unaffected. Nabatov *et al.* [2004] (**antibody binding site definition and exposure**, **co-receptor**)
- 2F5: An antigen panel representing different regions of gp41 was generated, and sera from 23 individuals were screened. Anti-gp41 titers were very high, and sera bound to many regions of gp41, there were no immunologically silent regions. Many individuals had broad responses to diverse regions. High titer responses tended to focus on the N-heptad, C-heptad and 2F5-4E10 regions, but there was no correlation between neutralization capacity of sera and the particular peptides recognized. 2F5 responded to the four antigens that carried the minimal EDLKWA epitope. 2F5 did not bind to the minimal epitope embedded in an alpha helix, supporting that the 2F5 conformation of EDLKWA is embedded in a beta sheet. 2F5 bound better to a synthetic peptide containing the proximal regions than to the native gp41. Opalka *et al.* [2004] (**assay standardization/improvement**)
- 2F5: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neturalization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 2F5: A primary isolate, CC1/85, was passaged 19 times in PBMC and gradually acquired increased sensitivity to FAb b12 and sCD4 that was attributed to changes in the V1V2 loop region, in particular the loss of a potential glycosylation site. The affinity for sCD4 was unchanged in the monomer, suggesting that the structural impact of the change was manifested at the level of the trimer. The passaged virus, CCcon19, retained an R5 phenotype and its neutralization susceptibility to other Abs was essentially the same as CC1/85. The IC50 for 2F5 was greater than 50 for CC1/85, and was 35 for CCcon19, so the passaged virus was weakly neutralized by 2F5. Pugach *et al.* [2004] (**variant cross-recognition or cross-neutralization**, **viral fitness and reversion**)
- 2F5: The MAb 2F5 binds to the C-heptad and is neutralizing, but the MAb D50 binds to the C-heptad and is not neutralizing. 2F5 binds preferentially to native gp41 prior to receptor activation. D50 prefers the triggered form after receptor activation. Trapped fusion-intermediates suggest 2F5 remains present shortly after gp120 triggering by CD4, but may be lost by the time the six-helix bundle is formed. D50 binds equally to the fusion-intermediate and six-helix bundle. 2F5 neutralization seems to block a later step of the fusion process, but it does not inhibit binding of NC-1, a MAb specific for the six-helix bundle, so it does not prevent formation of the six-helix bundle. The results are most consistent with 2F5 inhibiting a post-fusion-intermediate step. de Rosny *et al.* [2004b] (**antibody binding site definition and exposure**, **antibody interactions**)
- 2F5: The mechanism of 2F5 neutralization was explored, and experiments suggest it is due to interference with a late step in viral entry. sCD4 binding to gp120 triggers conformational changes in gp41 allowing formation of the six helix bundle. The NAb 2F5 preferentially bound native gp41, prior to receptor triggering, while the antibody D50 that also binds to the heptad region, near 2F5, is not neutralizing, and preferentially bound the CD4-triggered gp41. The C and N peptides that can be used to block the formation of the six helix bundle and lock gp41 in the fusion intermediate state after sCD4 triggering enabled 2F5 to bind after sCD4, while D50 was able to bind to both the peptide-trapped and sCD4 induced six helix bundle equally well. The peptide-trapping studies suggest that 2F5 does not fix Env in the native conformation, but interferes with entry after the initial conformation changes occur. Nor does it block six-helix bundle formation, as 2F5 prebinding does not inhibit NC-1 binding, a MAb that binds specifically to the six-helix bundle. de Rosny *et al.* [2004a]
- 2F5: This review discusses research presented at the Ghent Workshop of prevention of breast milk transmission and immunoprophylaxis for HIV-1 in pediatrics (Seattle, Oct. 2002), and makes the case for developing passive or active immunoprophylaxis in neonates to prevent mother-to-infant transmission. Macaque studies have shown that passive transfer of NAb combinations (for example, IgG1b12, 2G12, 2F5, and 4E10; or 2G12 and 2F5) can confer partial or complete protection to infant macaques from subsequent oral SHIV challenge. Safrit *et al.* [2004] (**immunoprophylaxis**, **mother-to-infant transmission**)
- 2F5: A complex of the epitope peptide ELDKWAS bound to 2F5 was crystalized, and the peptide was found to interact with

amino acids near the base of the very long (22 residue) CDR 3H region of the Ab. Ala substitution of the CDR H3 region confirmed the importance of these sites near the base of the H3 loop for interaction with the epitope in the context of intact gp41 as well as the peptide. A Phe at the apex of the loop was not located directly in the binding site, however binding of 2F5 to the epitope was very sensitive to non-conservative substitutions in this position (F100G, F100H, and F100R); these diminished both binding affinity and 2F5 neutralization, suggesting a role for the very long CDR 3H region. The authors suggest that particularly long CDR H3 regions may be a common feature of HIV-1 NAbs, based on the 22 residues in H3 of 2F5, the 18 H3 residues in b12, and the 22 H3 residues in X5. They express concern that because small animals like mice are unable to elicit Ab responses with such long H3s, they may be poor model systems for HIV vaccine studies. Zwick *et al.* [2004] (**antibody binding site definition and exposure**, **antibody interactions**, **antibody sequence variable domain**, **structure**)

- 2F5: The SOS mutant envelope protein introduces a covalent disulfide bond between gp120 surface and gp41 transmembrane proteins into the R5 isolate JR-FL by adding cysteines at residues 501 and 605. Pseudovirions bearing this protein bind to CD4 and co-receptor bearing cells, but do not fuse until treatment with a reducing agent, and are arrested prior to fusion after CD4 and co-receptor engagement. gp41 NAbs 2F5 and 4E10 are able to potently neutralize the SOS pseudovirion post-attachment, although 2F5 performed relatively poorly in the pre-attachment assay, a further support for previous studies that indicated it does not bind well to native Env, and may bind best after the virus is attached to cells. Binley *et al.* [2003] (**vaccine antigen design**)
- 2F5: A sCD4-17b single chain chimera was made that can bind to the CD4 binding site, then bind and block co-receptor interaction. This chimeric protein is a very potent neutralizing agent, more potent than IgG1b12, 2G12 or 2F5 against Ba-L infection of CCR5-MAGI cells. It has potential for prophylaxis or therapy. Dey *et al.* [2003]
- 2F5: Four newborn macaques were challenged with pathogenic SHIV 89.6 and given post exposure prophylaxis using a combination of NAbs 2F5, 2G12, 4E10 and IgG1b12. 2/4 treated animals did not show signs of infection, and 2/4 macaques maintained normal CD4+ T cell counts and had a lower delayed peak viremia compared to the controls. Ferrantelli *et al.* [2003] (**antibody interactions**, **immunoprophylaxis**, **mother-to-infant transmission**)
- 2F5: This study investigates the effects of glycosylation inhibitors on the binding between HIV-1 gp120 and mannose-binding lectin (MBL). Mannosidase I inhibitor deoxymannojirimycin (dMM) inhibits formation of complex and hybrid N-linked saccharides and yields virus with more mannose residues. dMM added during viral production significantly enhanced the binding 2F5 and 2G12, but not IgG1b12 in a viral capture assay. Hart *et al.* [2003] (**antibody binding site definition and exposure**)
- 2F5: MAbs IgG1b12, 2G12, 2F5 and 4E10 were tested for their ability to neutralize two primary HIV-1 clade A isolates (UG/92/031 and UG/92/037) and two primary HIV-1 clade D isolates (UG/92/001 and UG/92/005). 4E10 demonstrated the most potent cross-neutralization activity. Quadruple administration of MAbs IgG1b12, 2G12, 2F5, and 4E10 induced strong synergistic neutralization of 4 clade A isolates (UG/92/031, UG/92/037, RW/92/020 and RW/92/025) as well as 5 clade D isolates (UG/92/001,UG/9/005, /93/086/RUG/94/108, UG/94/114). The authors note this combination of 4 MAbs neutralizes primary HIV A, B, C, and D isolates. Kitabwalla *et al.* [2003] (**antibody interactions**, **immunoprophylaxis**, **variant cross-recognition or cross-neutralization**, **mother-to-infant transmission**, **subtype comparisons**)
- 2F5: This review dicusses the importance and function of protective antibody responses in animal model studies in the context of effective vaccine development. SHIV models have shown protection using high levels of MAbs can prevent infection, and partial protection that can influence disease course can be obtained from modest levels of NAbs. SHIV challenges studies conducted with infusions of combinations of MAbs b12, 2G12, and 2F5 are reviewed. Mascola [2003] (**immunoprophylaxis**, **review**)
- 2F5: Infusions of 2F5 and 2G12 intravenously administered 24h prior to vaginal SHIV-89.P challenge are able to protect macaques from infections. Animals that recieve a IL-2 adjuvanted DNA immunization SIV Gag and HIV Env have T-cell responses and lower viral loads, but were not protected. Suboptimal levels of 2F5 and 2G12 were not able to confer sterile protection in combination with the T-cell responses stimulated by DNA immunizations. Mascola *et al.* [2003] (**adjuvant comparison**, **vaccine-specific epitope characteristics**)
- 2F5: Cyclic peptides ELLELDKWASLW that adopt constrained beta-turn conformation of the 2F5 epitope beta-turn in the complexed crystal structure were synthesized and optimize 2F5 binding affinity. This peptide elicits high titer peptide-specific immune responses in guinea pigs that do not neutralize; the authors propose this may be the result of a short CDR3 loop in guinea pigs. McGaughey *et al.* [2003] (**antibody binding site definition and exposure**, **vaccine antigen design**, **binding affinity**, **structure**)
- 2F5: AC10 is a subject who was given treatment early after infection, and had a viral rebound after cessation of therapy, which then declined to a low level. The polyclonal sera from AC10 could potently neutralize the rebound virus, and NAb escape followed with a neutralizing response against the escape variant and subsequent escape from that response. Viral loads remained low in this subject despite escape. The rebound isolate that was potently neutralized by autologous sera was not particularly neutralization sensitive, as it resisted neutralization by sCD4 and MAbs IgG1b12, 2G12 and 2F5, and was only moderately sensitive to sera from other HIV+ individuals that had high titers of NAbs to TCLA strains. Montefiori *et al.* [2003] (**acute/early infection**, **escape**)
- 2F5: Env genes derived from uncultured brain biopsy samples from four HIV-1 infected patients with late-stage AIDS were compared to env genes from PBMC samples. Brain isolates did not differ in the total number or positions of N-glycosylation sites, patterns of coreceptor usage, or ability to be recognized by gp160 and gp41 MAbs. 2F5 recognized most variants from 3/4 individuals by gp41 WB; the 4th individual had the ELDKWA variant Aldkwa in all three isolates.

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The other single Env that was not recognized carried eldRwa. Ohagen *et al.* [2003] (**brain/CSF**, **escape**)

- 2F5: Most plasma samples of patients from early infection had NAb responses to early autologous viruses, and NAbs against heterologous strains tended to be delayed. Serial plasma samples were tested against serial isolates, and neutralization escape was shown to be rapid and continuous throughout infection. Autologous neutralization-susceptible and resistant viruses from four patients were tested for susceptability to neutralizing Ab responses using MAbs 2G12, IgG1b12 and 2F5. No correlation was established, all viruses tested were susceptible to at least one of the neutralizing MAbs. Two patients that did not have an autologous NAb response also did not evolve changes in susceptibility to these MAbs, while one patient with a pattern of autologous neutralization and escape acquired a 2G12 sensitive virus at month 6, and lost IgG1b12 sensitivity at month 21. Richman *et al.* [2003] (**autologous responses**, **acute/early infection**, **escape**)
- 2F5: Review of current neutralizing antibody-based HIV vaccine candidates and strategies of vaccine design. Strategies for targeting of the epitopes for NAbs 2F5, 2G12, 4E10, b12, and Z13 are described. Wang [2003] (**vaccine antigen design**, **review**)
- 2F5: The broadly neutralizing antibodies 2F5 and 2G12 were class-switched from IgG to IgA and IgM isotypes. Neutralizing potency was increased with valence for 2G12 so the IgM form was most potent, but for 2F5 the IgG form was most potent. Eight primary isolates were tested including two subtype A isolates. The polymeric IgM and IgA Abs, but not the corresponding IgGs, could interfere with HIV-1 entry across a mucosal epithelial layer, although they were limited in a standard neutralization assay. All isotypes could interact with activated human sera, presumably through complement, to inhibit HIV replication. Wolbank *et al.* [2003] (**complement**, **isotype switch**, **variant cross-recognition or cross-neutralization**, **mucosal immunity**, **subtype comparisons**)
- 2F5: A combination of MAbs 2F5 and 2G12 given in multiple infusions was found to be safe and well tolerated even in high doses in a phase I study of seven HIV-1 infected healthy volunteers—the median elimination half-life was 7.94 days for 2F5, and 16.48 for 2G12—no anti-2F5 or anti-2G12 IgM or IgG responses were detected—although there was some transient increases, overall plasma viral RNA levels decreased in 6/7 volunteers, by a median of 0.62 $\log_{10}$. Armbruster *et al.* [2002] (**immunotherapy**)
- 2F5: IgG1b12 neutralized many South African (5/8) and Malawian (4/8) clade C primary HIV-1 isolates, being more effective than 2F5 which neutralized only two Malawian and no South African isolates. 2G12 did not neutralize any of the 16 isolates. Bures *et al.* [2002] (**subtype comparisons**)
- 2F5: This study examined antibody interactions, binding and neutralization with a B clade R5 isolate (92US660) and R5X4 isolate (92HT593). Abs generally bound and neutralized the R5X4 isolate better than the R5 isolate, with the exception of F240 which bound both equally well, which captured more virus than any other human MAb tested, and didn't neutralize either isolate. F240 enhanced the binding of CD4BS MAbs IgG1b12 and F105 and the gp41 MAb 2F5 for both R5X4 and R5 isolates. F240 also enhanced neutralization of the R5X4 isolate by 2F5, but had no effect on R5 virus. Anti-V3 MAb B4a1 did not impact 2F5 neutralization. Cavacini *et al.* [2002] (**antibody binding site definition and exposure**, **antibody interactions**, **co-receptor**)
- 2F5: A modified gp140 (gp140deltaCFI), with C-term mutations intended to mimic a fusion intermediate and stabilize trimer formation, retained antigenic conformational determinants as defined by binding to CD4 and to MAbs 2F5, 2G12, F105, and b12, and enhanced humoral immunity without diminishing the CTL response in mice injected with a DNA vaccine. Chakrabarti *et al.* [2002] (**vaccine antigen design**)
- 2F5: Six sera from HIV-exposed uninfected individuals(EU) had IgA neutralizing activity dominated by recognition of a distinctive epitope within gp41, QARILAV – sera of QAFILAV-immunized BALB/c mice was neutralizing with the dose-dependent behavior similar to 2F5. Clerici *et al.* [2002a] (**HIV exposed persistently seronegative (HEPS)**)
- 2F5: Review of NAbs that notes that 2F5 alone or in combination with other MAbs can protect some macaques against SHIV infection, that it is safe and well tolerated in humans, and that illustrates gp41's conformational change and exposure of the 2F5 epitope in the transient pre-hairpin form. Ferrantelli & Ruprecht [2002] (**immunoprophylaxis**, **review**)
- 2F5: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I and Cluster II MAbs required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor, binding to a fusion intermediate. 2F5 behaved very differently than these non-neutralizing antibodies: it bound to Env in the absence of target cells, and it was distributed evenly all over the cell surface, not localized in fusion domains. It did not interact with cells that exhibited cytoplasmic mixing. 2F5 was unusual in that it exhibited temperature dependence, and did not interact below 19 degrees C, in contrast to 2G12, M77 98-6 and IgG1b12 which bound strongly at temperatures ranging between 4-37 degrees. The authors suggest the temperature dependence of 2F5 may be due to encreased flexibility of the Envelope spike at warmer temperatures facilitating epitope exposure. Finnegan *et al.* [2002] (**antibody binding site definition and exposure**, **kinetics**)
- 2F5: Alanine mutations were introduced into the N- and C-terminal alpha-helices of gp41 to destabilize interhelical packing interactions in order to study their inhibitory effect on viral infectivity. These mutations were shown to inhibit viral replication though affecting the conformational transition to the fusion-active form of gp41, and allow increased inhibition by gp41 peptides. 2F5 senstivity is increased in the mutated viruses, presumably because 2F5s neutralization activity is focused on the transition to the fusion active state. No other MAb against gp41 tested, including NC-1, 50-69D, 1281, 98-6D, 246-D and F240, neutralized the parental or the fusion-deficient mutated viruses. Follis *et al.* [2002] (**antibody binding site definition and exposure**)
- 2F5: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-

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helix bundles form prior to fusion – the preincubation 31.5 C step did not alter the inhibitory activity of neutralizing Abs anti-gp41 2F5, or anti-gp120 2G12, IG1b12, 48d, and 17b. Golding *et al.* [2002b]

- 2F5: UK1-br and MACS2-br are R5 isolates derived from brain tissue samples from AIDS patients with dementia and HIV-1 encephalitis; both are neurotropic, but only UK1-br induced neuronal apoptosis and high levels of syncytium formation in macrophages. UK1-br Env had a greater affinity for CCR5 than MACS-br, and required low levels of CCR5 and CD4 for cell-to-cell fusion and single round infection. PBMC infected with UK1-br and MACS2-br virus isolates were resistant to neutralization by MAb 2G12. UK1-br was more sensitive than MACS2-br to IgG1b12, 2F5 and CD4-IgG2 neutralization. This pattern of Ab reactivity was similar to the to CD4-independent varient ADA197N/K, and thought to result from conformational changes which better expose the CCR5 binding regions, although the loss of the particular N-linked glycosylation site in the V1V2 stem region of ADA was experimentally shown to not be responsible for the the CD4-independent phenotype of UK1-br. Gorry *et al.* [2002] (**brain/CSF**, **co-receptor**)
- 2F5: HIV-1 gp160ΔCT (cytoplasmic tail-deleted) proteoliposomes (PLs) containing native, trimeric envelope glycoproteins from R5 strains YU2 and JRFL, and X4 strain HXBc2, were made in a physiologic membrane setting as candidate immunogens for HIV vaccines—2F5 bound to gp160ΔCT with a reconstituted membrane ten-fold better than the same protein on beads (except for the YU2 form that doesn't bind 2F5)—anti-CD4BS MAbs IgG1b12 and F105, A32 (C1-C4), C11 (C1-C5), and 39F (V3) MAbs bound gp160ΔCT PLs indistinguishably from gp160ΔCT expressed on the cell surface. Grundner *et al.* [2002] (**vaccine antigen design**)
- 2F5: ELDKWAS was embedded into a beta-turn-like conformational site on a framework of an antibody specific for human leukocyte antigen HLA-DR – this construct was recognized by 2F5, and is suggested as an adjuvant-independent vaccine candidate. Ho *et al.* [2002] (**vaccine antigen design**)
- 2F5: A mouse MAb was raised against a variant of ELDKWA core epitope of the NAb 2F5, eldEwa, derived from the 2F5 neutralization resistant variant MVP5180. 2F5 does not bind to the variants eldEwa, elNkwa (B.TH.TH936705) or elEkwa, while 14D9 binds only to eldEwa and not ELDKWA. The eldEwa variant is common in the HIV-1 O group. Huang *et al.* [2002] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2F5: DP178 is a peptide derived from the C-term heptad repeat of gp41 that is a potent inhibitor of viral-mediated fusion—it contains the 2F5 epitope but fails to stimulate 2F5-like NAbs upon immunization—the peptide was extended to force an increase in helicity, and the modified peptide had a increase in affinity for 2F5, but upon guinea pig immunization although high peptide-specific Ab titers were achieved the sera were incapable of viral neutralization—the authors propose that 2F5 may bind with low affinity to a maturation intermediate, which may account for its breadth and why it is hard to recreate the epitope, but also suggests that the high concentrations required for neutralization are not relevant *in vivo*. Joyce *et al.* [2002] (**antibody binding site definition and exposure**)
- 2F5: A 2F5 anti-idiotype murine MAb Ab2/3H6 was developed that blocks 2F5 binding to a synthetic epitope peptide and to gp160 in an ELISA competition assay – Ab2/3H6 diminished the neutralizing potency of 2F5 – Ab2/3H6 Fab fragments were capable of inducing neutralizing Abs and 2F5-epitope specific responses in immunized B6D2F1 mice. Kunert *et al.* [2002] (**vaccine antigen design**)
- 2F5: A polyepitope vaccine was designed based on three repeats of the 2F5 core epitope ELDKWA combined with the V3 region peptide GPGRAFY. Abs raised in mice could recognize the peptides, sgp41, and CHO-WT cells that expressed HIV-1 Env on their surface. Li *et al.* [2002] (**vaccine antigen design**)
- 2F5: Review of NAbs that discusses mechanisms of neutralization, passive transfer of NAbs and protection in animal studies, and vaccine strategies. Liu *et al.* [2002] (**immunoprophylaxis**, **vaccine antigen design**, **review**)
- 2F5: Rhesus macaques were better protected from vaginal challenge with SHIV89.6D (MAb 2G12, 2/4; MAbs 2F5/2G12, 2/5; and HIVIG/2F5/2G12, 4/5 infected) than from intravenous challenge (MAb 2G12, 0/3; MAbs 2F5/2G12, 1/3; and HIVIG/2F5/2G12, 3/6 infected)– the animals that were infected by vaginal challenge after Ab infusion had low or undetectable viral RNA levels and modest CD4 T-cell decline. Mascola [2002] (**immunoprophylaxis**)
- 2F5: ELDKWAS co-crystallized bound to the Fab' 2F5 fragment showed the epitope peptide in a type I beta-turn conformation. Pai *et al.* [2002] (**structure**)
- 2F5: Ab binding characteristics of SOS gp140 were tested using SPR and RIPA – SOS gp140 is gp120-gp41 bound by a disulfide bond – NAbs 2G12, 2F5, IgG1b12, CD4 inducible 17b, and 19b bound to SOS gp140 better than uncleaved gp140 (gp140unc) and gp120 – non-neutralizing MAbs 2.2B (binds to gp41 in gp140unc) and 23A (binds gp120) did not bind SOS gp140 – SOS gp140-2F5-IgG1b12 formed multiple ring structures composed of two SOS gp140 proteins bridged by two Ab molecules, while 2F5 and 2G12 formed extended chains rather than closed rings. Schulke *et al.* [2002] (**vaccine antigen design**)
- 2F5: Oligomeric gp140 (o-gp140) derived from R5 primary isolate US4 was characterized for use as a vaccine reagent – antigen capture ELISA was used to compare the antigenicity of gp120 and o-gp140 using a panel of well characterized MAbs – 2F5 recognized o-gp140. Srivastava *et al.* [2002] (**vaccine antigen design**)
- 2F5: The antiviral response to intravenously administered MAbs 2F5 and 2G12 was evaluated in 7 HAART-naive asymptomatic HIV-1 infected patients during a treatment period of 28 days. MAb therapy reduced plasma HIV RNA in 3/7 patients during the treatment period, and transiently reduced viral load in two more. CD4 counts were up in 3/7 through day 28, and transiently increased in three more. Vigorous complement activation was observed after 48/56 Ab infusions. Before treatment, 2F5 neutralized isolates from five patients and no escape was observed during treatment. Stiegler *et al.* [2002] (**complement**, **variant cross-**

recognition or cross-neutralization, **escape**, **immunotherapy**)

- 2F5: Expanding the minimal epitope ELDKWA to an end-capped, linear nonapeptide, Ac-LELDKWASL-amide attained maximal affinity within a set of native gp41-sequence peptides – scanning single residue substitutions confirmed that essential recognition requirements were the central DKW core sequence and the importance of the terminal Leu residues for high-affinity binding – high specificity binding pockets at central Lys and Trp side-chains and an absolute requirement for the carboxylate group of the Asp side chain were found – the nine residue fragment flanked by pairs of Ser and constrained by a disulfide bridge had high affinity for 2F5. Tian *et al.* [2002] (**antibody binding site definition and exposure**)
- 2F5: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91 was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b]
- 2F5: Passive immunization of neonate macaques with a combination of F105+2G12+2F5 conferred complete protection against oral challenge with SHIV-vpu+ or – the combination b12+2G12+2F5 conferred partial protection against SHIV89.6 – such combinations may be useful for prophylaxis at birth and against milk born transmission – the synergistic combination of IgG1b12, 2G12, 2F5, and 4E10 neutralized a collection of HIV clade C primary isolates. Xu *et al.* [2002] (**antibody interactions**, **immunoprophylaxis**, **subtype comparisons**)
- 2F5: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002]
- 2F5: ELNKWA is an escape variant not recognized by the broadly neutralizing MAb 2F5, which recognizes the core epitope ELDKWA – Abs were raised against the peptide escape variant CGELNKWAGELNKWA linked to KLH carrier – these polyclonal antibodies, like the monoclonal antibody TH-Ab1 also raised to ELNKWA, could recognize ELDKWA and escape mutant peptide epitopes ELEKWA and ELDEWA. Dong *et al.* [2001] (**variant cross-recognition or cross-neutralization**)
- 2F5: A combination of MAbs IgG1b12, 2F5, and 2G12 was given postnatally to four neonates macaques that were then challenged with highly pathogenic SHIV89.6P – one of the four infants remained uninfected after oral challenge, two infants had no or a delayed CD4(+) T-cell decline. Hofmann-Lehmann *et al.* [2001] (**immunoprophylaxis**)
- 2F5: Mutations in two glcosylation sites in the V2 region of HIV-1 ADA at positions 190 and 197 (187 DNTSYRLINCNTS 199) cause the virus to become CD4-independent and able to enter cells through CCR5 alone – these same mutations tended to increase the neutralization sensitivity of the virus, including to antibody 2F5. Kolchinsky *et al.* [2001] (**variant cross-recognition or cross-neutralization**)
- 2F5: Review of studies in macaques that have shown immune control of pathogenic SHIV viremia, improved clinical outcome, and protection, and the implications of the observations for HIV vaccines. Mascola & Nabel [2001] (**review**)
- 2F5: Moore and colleagues review the data concerning the lack of a clear relationship between genetic subtype and serotype – 2F5 is considered in some detail, as it represents a rare vulnerability from the neutralizing antibody perspective, although while it is apparently linear, attempts to present the peptide to the immune system have failed to elicit neutralizing Abs. Moore *et al.* [2001] (**review**, **subtype comparisons**)
- 2F5: Matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS) in combination with proteolytic protection was used to identify the functional epitope for MAb 2F5, NEQELLELDKWASLWN, in the disulfide bond associated gp120/gp41 protein SOS-gp140 (JRFL) – this minimal epitope is much larger than the ELDKWA core epitope previously defined by peptide ELISA, and this could help explain why ELDKWA-peptides are poor immunogens in terms of eliciting a 2F5-like antibody response. Parker *et al.* [2001] (**antibody binding site definition and exposure**)
- 2F5: A peptide called 5-Helix was designed that binds to the C-peptide region of gp41 – 5-Helix is a potent inhibitor of HIV-1 entry that binds immediately COOH-terminal to the C-peptide region targeted by 5-Helix – the conformation of the bound 2F5 epitope is a hairpin turn. Root *et al.* [2001]
- 2F5: SHIV-HXBc2 is a neutralization sensitive non-pathogenic virus, and several *in vivo* passages through monkey's yielded highly pathogenic SHIV KU-1 – HXBc2 and the KU-1 clone HXBc2P3.2 differ in 12 amino acids in gp160 – substitutions in both gp120 and gp41 reduced the ability of sCD4, IgG1b12, F105 and AG1121 to Env achieve saturation and full occupancy, and neutralize KU-1 – 17b and 2F5 also bound less efficiently to HXBc2P3.2, although 2G12 was able to bind both comparably. Si *et al.* [2001]
- 2F5: A luciferase-reporter gene-expressing T-cell line was developed to facilitate neutralization and drug-sensitivity assays – luciferase and p24 antigen neutralization titer end points were found comparable using NAb from sera from HIV+ donors, and MAbs 2F5, 2G12 and IgG1b12. Spenlehauer *et al.* [2001] (**assay development**)
- 2F5: 4E10 binds proximal to 2F5 and neutralizes primary isolates of clades A, B, C, D, and E – viruses that were resistant to 2F5 were neutralized by 4E10 and vice versa. Stiegler *et al.* [2001] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)

- 2F5: A phage peptide library was screened with MAb 2F5, and from the peptides that bound the amino acids DKW were found to be most critical for binding – the mimetic peptide RDWSFDRWSLSEFWL elicited a cross-reactive Ab response to gp41 when used to immunize rabbits. Tumanova *et al.* [2001]
- 2F5: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001] (**antibody interactions**, **variant cross-recognition or cross-neutralization**)
- 2F5: Twenty HIV clade C isolates from five different countries were susceptible to neutralization by anti-clade B MAbs in a synergistic quadruple combination of mAbs IgG1b12, 2G12, 2F5, and 4E10. Xu *et al.* [2001] (**antibody interactions**)
- 2F5: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAbs alters some step after binding. York *et al.* [2001] (**variant cross-recognition or cross-neutralization**)
- 2F5: Neutralizing synergy between MAbs 1b12, 2G12 and 2F5 was studied using surface plasmon resonance to determine the binding kinetics for these three mAbs with respect to monomeric and oligomeric env protein gp160 IIIB – the 2G12 epitope is highly accessible on both monomeric and oligomeric Envs, 1b12 is highly accessible on monomers but not oligomers, and 2F5 on neither form – binding of 2G12 exposes the 2F5 epitope on gp160 oligomers. Zeder-Lutz *et al.* [2001] (**antibody interactions**)
- 2F5: This paper primarily concerns 4E10 and Z13, MAbs that both bind proximally to the 2F5 binding site to a conserved epitope, and that neutralize some primary isolates from clades B, C, and E – the minimal 2F5 epitope is determined to be EQELLELDKWASLW, based on screening a gp160 fragment expression library, longer than previous studies – broadly neutralizing MAbs 2F5, IgG1b12, and 4E10 and Z13 fail to neutralize different subsets of viruses. Zwick *et al.* [2001b] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2F5: Neutralization synergy between anti-HIV NAbs b12, 2G12, 2F5, and 4E10 was studied – a classic fixed-ratio method was used, as well as a method where one Ab was fixed at a low neutralization titer and the other was varied – using primary isolates, a two-four fold enhancement of neutralization was observed with MAb pairs, and a ten-fold enhancement with a quadruple Ab combination – no synergy was observed with any MAb pair in the neutralization of TCLA strain HXB2. Zwick *et al.* [2001c] (**antibody interactions**)
- 2F5: Paper uses IgG1 form of 2F5 – a triple combination of 2F5, F105 and 2G12 effectively neutralized perinatal infection of macaque infants when challenged with SHIV-vpu+ – the plasma half-life was 4.2 +/- 0.8 days. Baba *et al.* [2000] (**immunoprophylaxis**)
- 2F5: MAbs 98-6 and 2F5 both bind to a peptide N51-C43 complex trimer of heterodimers that approximates the core of the fusogenic form of gp41, and to C43 alone but not to N51 alone – 98-6 and 2F5 have comparable affinities for C43, but 98-6 has a higher affinity for the complex and 2F5 may bind to an epitope of C43 that is directly involved with complex formation –and IgG1 rec form of the Ab was used in this study. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
- 2F5: 2F5 is a candidate for immunotherapy, but generally IgG1 has a longer half life in humans than IgG3, so the isotype was switched – rec CHO-derived MAb 2F5 IgG1kappa and hybridoma-derived MAb 2F5 IgG3kappa displayed identical specificity, *in vitro* function, and epitope (ELDKWA) – it remains to be determined if isotype switching will prolongs beta-clearance. Kunert *et al.* [2000] (**immunotherapy**)
- 2F5: Low levels of anti-ELDKWA antibodies are observed in HIV-1 + individuals, so a C-domain P2 peptide linked to a carrier was used to immunize mice and rabbits, and stimulated a high-level anti-ELDKWA response. Liao *et al.* [2000] (**vaccine antigen design**)
- 2F5: ELDKWA peptide vaccine study. Lu *et al.* [2000c] (**vaccine antigen design**)
- 2F5: ELDKWA peptide vaccine study. Lu *et al.* [2000b] (**vaccine antigen design**)
- 2F5: Because HIV-1 is most often transmitted across mucosal surfaces, the ability of passive transfer of infused HIVIG/2F5/2G12 to protect against mucosal exposure of macaques to pathogenic SHIV 89.6PD was studied – HIVIG/2F5/2G12 protected 4/5 animals against vaginal challenge, 2F5/2G12 combined protected 2/5 animals, and 2G12 alone protected 2/4 animals – in contrast, Mascola and coworkers had previously shown single MAbs could not protect against intervenous challenge – Ab treated animals that got infected through vaginal innoculation had low viral loads and only modest declines in CD4 counts – the infused Abs were detected in the nasal, vaginal, and oral mucosa. Mascola *et al.* [2000] (**immunoprophylaxis**, **mucosal immunity**)
- 2F5: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 cluster II anti-gp41 MAbs – of these 2F5, 167-D, 126-6, and 1281 bound across clades, but usually weakly, while 98-6 and 1342 had poor cross reactivity – Clade D isolates bound most consistently to cluster II MAbs. Nyambi *et al.* [2000] (**subtype comparisons**)
- 2F5: A mini-review of observations of passive administration of IgG NAbs conferring protection against intervenous or vaginal SHIV challenge, that considers why IgG MAbs might protect against mucosal challenge. Robert-Guroff [2000] (**review**)
- 2F5: 2F5 or sCD4-IgG chimeric immunoadhesin were transferred into 3T3 cells, incorporated into a collagen structure called the neo-organ, and transplanted into SCIDhu mice that were then challenged with MN or LAI – the continuous production of the therapeutic molecules in this context resulted

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in dramatic reduction of viral load. Sanhadji *et al.* [2000] (**immunotherapy**)

- 2F5: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) – gp41 MAbs T4, D12, T3, and D50 bound less efficiently to gp140-GNC4 than did pooled sera, but T4 and D12 recognized the gp140-GNC4 timer equivalently to gp140(-), and T3 and D50 recognized the trimer at greater levels than gp140(-) – 2F5 did not bind efficiently to these constructs, presumably because of the YU2 strain has a substitution in the 2F5 epitope (ALDKWA instead of ELDKWA). Yang *et al.* [2000] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**)
- 2F5: rgp120 derived from a R5X4 subtype B virus was used to vaccinate healthy volunteers and the resulting sera were compared with sera from HIV-1 positive subjects and neutralizing MAbs. Beddows *et al.* [1999]
- 2F5: Combinations of HIVIG, 2F5, 2G12 were administered in passive-transfer experiments 24 hours prior to challenge with pathogenic SHIV 89.6PD – 3/6 animals given HIVIG/2F5/2G12 were completely protected, the others had reduced viremia and normal CD4 counts – 1/3 monkeys given 2F5/2G12 showed transient infection, the other two had reduced viral load – all monkeys that received HIVIG, 2F5, or 2G12 alone became infected and developed high-level plasma viremia, although animals that got HIVIG or 2G12 had a less profound CD4 T cell decline. Mascola *et al.* [1999] (**immunoprophylaxis**)
- 2F5: A meeting summary presented results regarding neutralization –MAbs 2G12 and 2F5 tested for their ability to neutralize primary isolate infection of genetically engineered cell lines (cMAGI and others, presented by T. Matthews, A. Trkola, J. Bradac) – an advantage of such cells lines over PBMCs is that markers (X-Gal) can be added for staining to simplify the assay – the consensus of the meeting was that these engineered cell lines did not improve the sensitivity of detection of primary isolate neutralization – D. Burton and J. Mascola presented results concerning passive immunization and protection of hu-PBL-SCID mice and macaques, respectively, and both found combinations of MAbs that were able to achieve 99% neutralization *in vitro* corresponded to efficacy *in vivo*. Montefiori & Evans [1999] (**review**)
- 2F5: In a study of 116 HIV-1 + individuals, Ab reactivity to a peptide encompassing the ELDKWA peptide decreased in CDC stage C patients compared with stage A patients, and longitudinal studies showed a decline in 6/8 patients, while overall Ab reactivity to rec soluble gp160 stayed constant. Muhlbacher *et al.* [1999]
- 2F5: Review of the neutralizing Ab response to HIV-1. Parren *et al.* [1999] (**review**)
- 2F5: Hu-PBL-SCID mice were infected with HIV-1s JRCSF and SF162 to study the effect of NAbs on an established infection – no significant differences in the initial rate of decrease in viral load or the plateau levels of viral RNA between the b12 treated and control mice were seen – in most of the Ab treated mice b12 escape mutants were observed with varying patterns of mutations – a combination of b12, 2G12 and 2F5 protected 1/3 mice, and an isolate from one of the other two was resistant to neutralization by all three MAbs. Poignard *et al.* [1999] (**immunotherapy**)
- 2F5: Post-exposure prophylaxis was effective when MAb 694/98-D was delivered 15 min post-exposure to HIV-1 LAI in hu-PBL-SCID mice, but declined to 50% if delivered 60 min post-exposure, and similar time constraints have been observed for HIVIG, 2F5 and 2G12, in contrast to MAb BAT123 that could protect delivered 4 hours post infection. Andrus *et al.* [1998] (**immunoprophylaxis**)
- 2F5: Ab from gp120 vaccinated individuals prior to infection, who subsequently became HIV infected, could not achieve 90% neutralization of the primary virus by which the individuals were ultimately infected – these viruses were not particularly refractive to neutralization, as determined by their susceptibility to neutralization by MAbs 2G12, IgG1b12, 2F5 and 447-52D. Connor *et al.* [1998] (**variant cross-recognition or cross-neutralization**)
- 2F5: The ELDKWA epitope was inserted into the antigenic site B of influenza hemagglutinin and expressed on baculovirus infected insect cells, flanked by 3 additional random amino acids, xELDKWAxx – FACS was used to isolate the clone that displayed the epitope with the most markedly increased binding capacity for 2F5, to identify particularly specific immunogenic constructs – PELDKWAPP was a high affinity form selected by FACS. Ernst *et al.* [1998] (**vaccine antigen design**)
- 2F5: Points out that 2G12 and 2F5, potent neutralizing antibodies, were identified by screening for cell surface (oligomeric Envelope) reactivity. Fouts *et al.* [1998]
- 2F5: Infection of dendritic cells cultured from CD14+ blood cells or from cadaveric human skin was blocked by neutralizing MAbs IgG1b12, or 2F5 and 2G12 delivered together, but not by control non-neutralizing anti-gp120 MAb 4.8D, indicating that NAbs could interrupt early mucosal transmission events. Frankel *et al.* [1998] (**mucosal immunity**)
- 2F5: The natural immune response to the epitope of 2F5, ELDKWA, was studied in perinatally infected children and levels of reactivity to this epitope were correlated with absolute CD4 numbers over time and health status – 3/10 children who had no antibody reactivity to ELDKWA had substitutions in the epitope (ALDKWA, ELDQWA, and KLDKWA) – 2F5 competed with the ELDKWA-reactive sera depending on the serum titer. Geffin *et al.* [1998]
- 2F5: Used as a control in the study of anti-gp41 MAb NC-1 – 2F5 does not react with HIV-2 gp41 or gp160. Jiang *et al.* [1998] (**variant cross-recognition or cross-neutralization**)
- 2F5: The complete V, J and D(H) domain was sequenced – unlike non-neutralizing anti-gp41 MAb 3D6, five neutralizing MAbs (2F5, 2G12, 1B1, 1F7, and 3D5) showed extensive somatic mutations giving evidence of persistent antigenic pressure over long periods – in contrast to Geffin98, where multiple pediatric sera were found to compete with 2F5, cross-competition was noted to be very rare in sera from HIV+ adults – Kunert *et al.* propose that because there is a binding site of human complement factor H which overlaps the 2F5 binding site, it may generally be masked from the immune system – 2F5 also has a remarkably long CDR3 loop of 22 amino acids, and this region could not be readily assigned to any described D(H) fragment, leading to the suggestion of

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recombination of two fragments from novel regions. Kunert *et al.* [1998] (**antibody sequence variable domain**)

- 2F5: Neutralization synergy was observed when the MAbs 694/98-D (V3), 2F5 (gp41), and 2G12 (gp120 discontinuous) were used in combination, and even greater neutralizing potential was seen with the addition of a fourth MAb, F105 (CD4 BS). Li *et al.* [1998] (**antibody interactions**)
- 2F5: This MAb and the results of Ugolini *et al.* [1997] are discussed – the authors propose that an Ab bound to gp41 would typically project less from the surface of the virion and so be unable to interfere with attachment Parren *et al.* [1998a]. Parren *et al.* [1998a]; Ugolini *et al.* [1997] (**review**)
- 2F5: MAbs 2G12, 2F5 and b12 are broadly neutralizing, as are some human polyconal sera, but this paper describes a set of primary isolates that are resistant to all three MAbs and 2 broadly neutralizing sera – results indicate that resistance levels of pediatric isolates might be higher than adult isolates – resistance in general did not seem to be conferred by a loss of binding affinity for gp120 or gp41, rather by a more global perturbation of oligomeric Envelope. Parren *et al.* [1998b] (**variant cross-recognition or cross-neutralization**)
- 2F5: Induces complement-mediated lysis in MN but not primary isolates – primary isolates are refractive to CML. Takefman *et al.* [1998] (**complement**)
- 2F5: A wide range of neutralizing titers was observed that was independent of co-receptor usage – 2F5 was the most potent of the MAbs tested. Trkola *et al.* [1998] (**variant cross-recognition or cross-neutralization**)
- 2F5: A neutralization assay was developed based on hemi-nested PCR amplification of the LTR (HNPCR) – LTR-HNPCR consistently revealed HIV DNA and was shown to be a rapid, specific and reliable neutralization assay based on tests with 6 MAbs and 5 isolates. Yang *et al.* [1998] (**assay development**)
- 2F5: This review summarizes results about 2F5: it binds extracellularly, near the transmembrane domain, it is the only gp41 MAb that is neutralizing, it reacts with many non-B clade viruses and has a paradoxically weak binding to virus, given the neutralizing titers. Burton & Montefiori [1997] (**review**)
- 2F5: In a multilab evaluation of monoclonal antibodies, only IgG1b12, 2G12, and 2F5 could neutralize at least half of the 9 primary test isolates at a concentration of < 25 mug per ml for 90% viral inhibition – the isolates with no 2F5 neutralizing susceptibility had the sequences ALGQWA or ELDTWA instead of EDLKWA – 7/9 primary isolates were neutralized, and ALDKWQ and ALDKWA were susceptible to neutralization. D'Souza *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- 2F5: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB Env – strong neutralizer of SHIV-vpu+ – all Ab combinations tested showed synergistic neutralization – 2F5 has synergistic response with MAbs 694/98-D (anti-V3), 2G12, b12, and F105. Li *et al.* [1997] (**antibody interactions**)
- 2F5: Using concentrations of Abs achievable *in vivo*, the triple combination of 2F5, 2G12 and HIVIG was found to be synergistic to have the greatest breadth and magnitude of response against 15 clade B primary isolates. Mascola *et al.* [1997] (**antibody interactions**, **variant cross-recognition or cross-neutralization**)
- 2F5: A JRCSF variant that was selected for IgG1b12 resistance remained sensitive to MAbs 2G12 and 2F5, for combination therapy. Mo *et al.* [1997] (**antibody interactions**)
- 2F5: Review: MAbs 2F5, 2G12 and IgG1b12 have potential for use in combination with CD4-IgG2 as an immunotherapeutic or immunoprophylactic – homologous MAbs to these are rare in humans and vaccine strategies should consider including constructs that may enhance exposure of these MAbs' epitopes. Moore & Trkola [1997] (**review**)
- 2F5: Called IAM 2F5 – antibody mediated enhancement or inhibition seemed to be determined by isolate rather than antibody specificity – in this study, only 2F5 inhibited the entry of all the viruses studied, irrespective of their phenotype, and directly proportional to its affinity to monomeric HIV-1 gp160. Schutten *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- 2F5: Of three neutralizing MAbs (257-D, IgG1b12, and 2F5), 2F5 was the only one to inhibit the entry of all viruses studied, both SI and NSI, with a potency proportional to its affinity for monomeric gp126. Schutten *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- 2F5: Binding of anti-gp120 MAbs IgG1b12 or 654-30D does not mediate significant exposure of the gp41 epitopes for MAbs 2F5 and 50-69. Stamatatos *et al.* [1997] (**antibody interactions**)
- 2F5: Used to standardize polyclonal response to CD4 BS. Turbica *et al.* [1997]
- 2F5: The only MAb out of a large panel to show no correlation between viral binding inhibition and neutralization. Ugolini *et al.* [1997]
- 2F5: IgG1b12 was more potent with greater breadth than MAb 2F5 in an infection reduction assay including 35 primary isolates. Kessler II *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- 2F5: Only 4/20 Argentinian and 3/43 Swedish HIV+ sera reacted with LLELDKWASL – sera reacting with peptides that contained ELDKWA tended to have high neutralization titers – the region carboxyl terminal to EDLKWA was found to be more important for polyclonal sera AB binding, 670-675 WNWFDI – 2F5 bound most strongly to the peptide QELLELDKWA. Calarota *et al.* [1996] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 2F5: 2F5 was infused into two chimpanzees which were then given an intravenous challenge with a primary HIV-1 isolate – both became infected, but with delayed detection and prolonged decrease in viral load relative to controls, indicating that preexisting, neutralizing antibodies (passively administered or actively elicited) affect the course of acute-phase virus replication and can be influential after the Ab can no longer be detected in the peripheral circulation. Conley *et al.* [1996] (**immunoprophylaxis**)
- 2F5: Neutralizes HXB2, primary isolates, and chimeric virus with gp120 from primary isolates in an HXB2 background. McKeating *et al.* [1996] (**variant cross-recognition or cross-neutralization**)

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- 2F5: A panel of immunotoxins were generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but killing was not directly proportional to binding. Pincus *et al.* [1996] (**immunotoxin**)
- 2F5: Review: one of three MAbs (IgG1b12, 2G12, and 2F5) generally accepted as having significant potency against primary isolates. Poignard *et al.* [1996b] (**review**)
- 2F5: Primary isolates from clade A, B, and E are neutralized by 2F5 – neutralization requires the LDKW motif – neutralization resistant isolates or 2F5 selected variants all had substitutions in the D or K. Purtscher *et al.* [1996] (**subtype comparisons**)
- 2F5: Review: only four epitopes have been described which can stimulate a useful neutralizing response to a broad spectrum of primary isolates, represented by the binding sites of MAbs: 447-52-D, 2G12, Fab b12, and 2F5. Sattentau [1996] (**review**)
- 2F5: ELDKWAS is in a gp41 binding region for the negative regulator of complement factor H (CFH) – Abs to HIV generally do not cause efficient complement-mediated lysis, but binding of 2F5 can interfere with CHF binding, facilitating HIV destruction by complement. Stoiber *et al.* [1996] (**complement**)
- 2F5: Found to neutralize MN, JRCSF, and two B subtype primary isolates, but not a D subtype primary isolate, by most labs in a multi-laboratory study involving 11 labs. D'Souza *et al.* [1995] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2F5: Broad cross-clade neutralization of primary isolates – additive neutralization in combination with anti-CD4BS MAb IgG1b12 (Called BM12). Kessler *et al.* [1995] (**subtype comparisons**)
- 2F5: Review: binds to the only generally accepted strong neutralizing epitope outside of gp120, one of only 3 MAbs with strong broad activity against primary viruses, the others are 2G12 and IgG1b12 – unique member of epitope cluster Moore & Ho [1995] and John Moore, per comm 1996. Moore & Ho [1995] (**review**)
- 2F5: MAb binding decreases the accessibility or alters the conformation of the gp41 fusion domain and of gp120 domains, including the binding site for the CD4 cell receptor. Neurath *et al.* [1995] (**antibody binding site definition and exposure**)
- 2F5: Called IAM 41-2F5 – exposed in the presence of gp120 on the cell surface, while most of gp41 is masked – binds proximal to transmembrane region. Sattentau *et al.* [1995] (**antibody binding site definition and exposure**)
- 2F5: Cross-clade primary virus neutralizing activity – LDKW defined as the core epitope. Trkola *et al.* [1995] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2F5: MAb generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994] (**antibody generation**)
- 2F5: Called IAM-41-2F5 – neutralized lab and primary isolates – t 1/2 dissociation 122 min for the peptide, and 156 min for gp41 – core D(K/R)W – Ab resistant isolate had the sequence KLDNWA. Conley *et al.* [1994b] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 2F5: Included in a multi-lab study for antibody characterization binding and neutralization assay comparison. D'Souza *et al.* [1994] (**assay development**)
- 2F5: Failed to show synergy with anti-CD4 binding site IIIB neutralizing antibodies. Laal *et al.* [1994] (**antibody interactions**)
- 2F5: 2F5 epitope ELDKWA inserted into an immunogenic loop in influenza virus hemagglutinin can elicit IIIB, MN and RF neutralizing sera in immunized mice. Muster *et al.* [1994] (**vaccine antigen design**)
- 2F5: Broadly reactive neutralizing activity, ELDKWA is relatively conserved – neutralized 2 primary isolates. Purtscher *et al.* [1994] (**variant cross-recognition or cross-neutralization**)
- 2F5: gp41 mutation (582 A/T) that reduces neutralization of anti-CD4 binding site MAbs does not alter 2F5's ability to neutralize. Thali *et al.* [1994]
- 2F5: Synergy with combinations of CD4-based molecules in inhibition of HIV-1 Env mediated cell fusion. Allaway *et al.* [1993] (**antibody interactions**)
- 2F5: Called IAM-41-2F5 – reports MAb to be IgG1 – the gp41 mutation 582(Ala to Thr) results in conformational changes in gp120 that confer neutralization resistance to conformationally sensitive neutralizing MAbs – neutralization efficiency of 2F5 is not affected. Klasse *et al.* [1993a] (**variant cross-recognition or cross-neutralization**)
- 2F5: DKWA defined as the core sequence – highly conserved epitope neutralizing MAb. Buchacher *et al.* [1992]; Muster *et al.* [1993] (**antibody binding site definition and exposure**)

No.	790
MAb ID	Z13e1
HXB2 Location	gp160 (666–677)
Author Location	
Epitope	WASLWNWFDITN
Subtype	B
Neutralizing	P
Immunogen	HIV-1 infection
Species (Isotype)	human
Ab Type	gp41 MPER (membrane proximal external region)
Research Contact	Michael Zwick, The Scripps Research Insitute, zwick@scripps.edu
References	Sun *et al.* 2008; Binley *et al.* 2008; Nelson *et al.* 2007; Kramer *et al.* 2007; Moore *et al.* 2006
Keywords	antibody binding site definition and exposure, binding affinity, neutralization, review, subtype comparisons

- Z13e1: 24 broadly neutralizing plasmas from HIV-1 subtype B an C infected individuals were investigated using a series of mapping methods to identify viral epitopes targeted by NAbs. Three different assays were used to analyze gp41-directed neutralizing activity. MAb Z13e1 was shown to neutralize fourfold more potently in the post-CD4/CCR5 assay compared to the standard assay. Weak post-CD4/CCR5 neutralization was detected in five subtype B and two subtype C

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plasmas. Z13e1 was shown to neutralize two of the MPER-engrafted mutant viruses, but the subtype B plasmas did not exactly recapitulate this activity except in two cases, where the activity of the plasmas against a mutant suggested presence of Z13e1-like Abs. Neutralization of four subtype B plasmas was substantially inhibited by a Z13e1 peptide, suggesting presence of Z13e1-like Abs. Binley *et al.* [2008] (**neutralization**, **subtype comparisons**)

- Z13e1: The MPER region was shown to have an L-shaped structure, with the conserved C-terminal residues immersed in the membrane and the variable N-terminal residues exposed to the aqueous phase. The specific binding of Z13e1 to the MPER was comparable to that of 4E10, with little or no binding to the membrane alone. It is suggested that Z13e1, like 4E10, extracts its epitope from the viral membrane, and that the key requirement for neutralization is induction of structural rearrangement of the MPER hinge by the Ab. It is also suggested that exposure of the membrane-embedded residues of the MPER region to the immune system in their native L-shaped form may elicit neutralizing Abs. Sun *et al.* [2008] (**antibody binding site definition and exposure**)
- Z13e1: This review summarizes Z13e1 Ab epitope, properties and neutralization activity. Kramer *et al.* [2007] (**review**)
- Z13e1: Z13e1, a high affinity variant of Fab Z13, was identified through targeted mutagenesis and affinity selection against gp41 and an MPER peptide. Z13e1 showed 100-fold improvement in binding affinity for MPER antigens over Z13, and improved neutralization potency against sensitive HIV-1. Alanine scanning revealed that N671 and D674 residues are crucial for peptide recognition and neutralization of HIV-1 by this Fab. Z13e1 was shown to bind with high affinity to an epitope overlapping those of 2F5 and 4E10 with the minimal epitope WASLWNWFDITN, indicating that the limited neutralization potency results from the limited access to the epitope within the envelope trimer. Nelson *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- Z13e1: In addition to gp120-gp41 trimers, HIV-1 particles were shown to bear nonfunctional gp120-gp41 monomers and gp120-depleted gp41 stumps on their surface. Z13e1 effectively neutralized wildype virus particles. Z13e1 was found to bind to both nonfunctional monomers, gp120-gp41 trimers and to gp41 stumps. Binding of Z13e1 to trimers correlated with its neutralization of wildtype virus particles. Although Z13e1 bound to monomers tightly, it was unable to capture wildtype virus particles efficiently. Moore *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)

No. 791
MAb ID 4E10
HXB2 Location gp160 (671–676)
Author Location gp160 (671–676 MN)
Epitope NWFDIT
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human (IgG3κ)
Ab Type C-term, gp41 MPER (membrane proximal external region)
Research Contact Herman Katinger, Inst. Appl. Microbiol. University of Agricultural Science, Vienna, Austria, or Polymum Scientific Inc.,
References Huarte *et al.* 2008b; Utachee *et al.* 2009; Zhang *et al.* 2008; Yamamoto & Matano 2008; Willey & Aasa-Chapman 2008; Vincent *et al.* 2008; van Montfort *et al.* 2008; Chong *et al.* 2008; Tomaras *et al.* 2008; Tasca *et al.* 2008; Sun *et al.* 2008; Srivastava *et al.* 2008; Pugach *et al.* 2008; Polonis *et al.* 2008; Peters *et al.* 2008b; Penn-Nicholson *et al.* 2008; Nelson *et al.* 2008; Matoba *et al.* 2008; Li *et al.* 2008b; Keele *et al.* 2008; Huarte *et al.* 2008a; Haynes & Shattock 2008; Gustchina *et al.* 2008; Gray *et al.* 2008; Forsman *et al.* 2008; Dey *et al.* 2008; Coutant *et al.* 2008; Blish *et al.* 2008; Bandawe *et al.* 2008; Frey *et al.* 2008; Binley *et al.* 2008; Alam *et al.* 2008; Zhang *et al.* 2006a; Yuste *et al.* 2006; Ye *et al.* 2006; Pahar *et al.* 2006; Li *et al.* 2006c; Sánchez-Martínez *et al.* 2006b; Lorizate *et al.* 2006b; Lorizate *et al.* 2006a; Gorny *et al.* 2006; Zhang & Dimitrov 2007; van Montfort *et al.* 2007; Schweighardt *et al.* 2007; Pastore *et al.* 2007; Mehandru *et al.* 2007; Gray *et al.* 2007b; Gustchina *et al.* 2007; Lin & Nara 2007; Kirchherr *et al.* 2007; Kim *et al.* 2007; Bunnik *et al.* 2007; Vcelar *et al.* 2007; Quakkelaar *et al.* 2007b; Phogat *et al.* 2007; Laakso *et al.* 2007; Huber & Trkola 2007; Gao *et al.* 2007; Blay *et al.* 2007; Beddows *et al.* 2007; Beck *et al.* 2007; Gray *et al.* 2006; Joos *et al.* 2006; Cham *et al.* 2006; Choudhry *et al.* 2006; Holl *et al.* 2006a; Hager-Braun *et al.* 2006; Brunel *et al.* 2006; Quakkelaar *et al.* 2007a; Nelson *et al.* 2007; McKnight & Aasa-Chapman 2007; Law *et al.* 2007; Kothe *et al.* 2007; Kramer *et al.* 2007; Ferrantelli *et al.* 2007; Dimitrov *et al.* 2007; Dhillon *et al.* 2007; Dey *et al.* 2007a; Derby *et al.* 2006; Choudhry *et al.* 2007; Cardoso *et al.* 2007; Brown *et al.* 2007; Blish *et al.* 2007; Alam *et al.* 2007; Luo *et al.* 2006; Liao *et al.* 2006; Holl *et al.* 2006b; Haynes & Montefiori 2006; Dong & Chen 2006; Alving *et al.* 2006; Zwick *et al.* 2005; Trkola *et al.* 2005; Stanfield & Wilson 2005; Srivastava *et al.* 2005; Rusert *et al.* 2005; Reeves *et al.* 2005; Raviv *et al.* 2005; Nakowitsch *et al.* 2005; Nabel 2005; Montefiori 2005; Mc Cann *et al.* 2005; Louder *et al.* 2005; Li *et al.* 2005a; Lenz *et al.* 2005; Jülg & Goebel 2005; Haynes *et al.* 2005b; Haynes *et al.* 2005a; Crooks *et al.* 2005; Cardoso *et al.* 2005; Burton *et al.* 2005; Safrit *et al.* 2004; Pugach *et al.* 2004; Opalka *et al.* 2004; Ferrantelli *et al.* 2004a; Ferrantelli *et al.* 2004b; Binley *et al.* 2004; Gorny & Zolla-Pazner

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2004; Kitabwalla *et al.* 2003; Wang 2003; Fiebig *et al.* 2003; Ferrantelli *et al.* 2003; Binley *et al.* 2003; Ferrantelli & Ruprecht 2002; Xu *et al.* 2002; Xu *et al.* 2001; Zwick *et al.* 2001c; Zwick *et al.* 2001b; Stiegler *et al.* 2001; D'Souza *et al.* 1994; Buchacher *et al.* 1994; Buchacher *et al.* 1992

Keywords acute/early infection, antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, assay development, assay standardization/improvement, autoantibody, binding affinity, co-receptor, dendritic cells, drug resistance, enhancing activity, escape, HAART, ART, immune evasion, immunoprophylaxis, immunotherapy, kinetics, mimics, mother-to-infant transmission, neutralization, optimal epitope, rate of progression, responses in children, review, SIV, structure, subtype comparisons, supervised treatment interruptions (STI), therapeutic vaccine, vaccine antigen design, variant cross-recognition or cross-neutralization, viral fitness and reversion

- 4E10: Neutralization susceptibility of CRF01_AE Env-recombinant viruses, derived from blood samples of Thai HIV-1 infected patients in 2006, was tested to 4E10. Most CRF01_AE viruses showed high susceptibility to 4E10, including viruses with and without conserved 4E10 epitopes, suggesting that the susceptibility of CRF01_AE to 4E10 is not determined by the conservation of the core epitope sequence. Several X4R5 viruses were less susceptible to 4E10 compared with X4 or R5 viruses. There was no correlation observed between virus neutralization susceptibility to 4E10 and viral infectivity, the length of the gp120 variable regions, or the number of PNLG sites. Utachee *et al.* [2009] (**co-receptor**, **neutralization**, **subtype comparisons**)
- 4E10: 4E10 peptide SLWNWFNITNWLWYIK was used in MAbs 5A9 and 13H11 characterization. 4E10 showed strong binding to HIV-1 infected cells Alam *et al.* [2008] (**antibody interactions**)
- 4E10: Comparing specific signals of selection among gp41 sequences from different HIV-1 M subtypes and circulating recombinant forms revealed presence of 12 sites evolving under positive selection across multiple major HIV-1 lineages. Nine sites detected to be under positive selection in the external exposed domains of gp41 had a significant tendency to be located within neutralizing and other Ab epitopes. Comparison of two matched datasets of HIV-1 subtype C, sampled from patients with acute or chronic infections, showed 6 gp41 sites evolving under different selection pressures during acute and chronic infection. One of those sites was within the epitope of 4E10, which evolved under strong positive selection in the chronically infected patients, but under neutral or mildly negative selection in the acutely infected patients. Bandawe *et al.* [2008] (**immune evasion**, **acute/early infection**, **escape**)
- 4E10: 24 broadly neutralizing plasmas from HIV-1 subtype B an C infected individuals were investigated using a series of mapping methods to identify viral epitopes targeted by NAbs. Three different assays were used to analyze gp41-directed neutralizing activity. MAb 4E10 was shown to neutralize equivalently in the standard and post-CD4/CCR5 assay. Weak post-CD4/CCR5 neutralization was detected in five subtype B and two subtype C plasmas. 4E10 was shown to neutralize several of the MPER-engrafted mutant viruses, but the subtype B plasmas did not exactly recapitulate this activity except in one case, where the activity of the plasma against two mutants suggested presence of 4E10-like Abs. Neutralization of four subtype B plasmas was substantially inhibited by a 4E10 peptide, suggesting presence of 4E10-like Abs. Binley *et al.* [2008] (**neutralization**, **subtype comparisons**)
- 4E10: This study explored features of Env that would enhance exposure of conserved HIV-1 epitopes. The changes in neutralization susceptibility, mediated by two mutations, T569A (in the HR1) and I675V (in the MPER), were unparalleled in their magnitude and breadth on diverse HIV-1 Env proteins. The variant with both TA and IV mutations was >360-fold more susceptible to 2F5, 2.8-fold more susceptible to b12, >780-fold more susceptible to sCD4 and resulted in 18-fold enhanced susceptibility to autologous plasma and >35-fold enhanced susceptibility to the plasma pool. It was also >180-fold more susceptible to 4E10. Mutants with only one IV mutation was >24-fold more susceptible to 4E10. Blish *et al.* [2008] (**antibody binding site definition and exposure**, **enhancing activity**)
- 4E10: The goal of the study was to measure NAb responses in patients infected with HIV-1 prevalent subtypes in China. g160 genes from plasma samples were used to establish a pseudovirus-based neutralization assay. 4E10 neutralized all 27 Env-pseudotyped viruses. Chong *et al.* [2008] (**neutralization**, **subtype comparisons**)
- 4E10: NMR structure of P1, a minimal MPER region that permits interaction with the mucosal galactosyl ceramide HIV-receptor, was analyzed in interaction with 4E10 at different pH. The best fit between NMR P1 and crystal structures of the Ab was at pH 6 and 5. The binding of 4E10 to P1 inserted into the liposomes of different compositions mimicking various biological membranes revealed 5- to 10-fold higher affinity of 4E10 to P1 in the lipid environment compared to aqueous environment, suggesting that specific lipid environment stabilizes the appropriate structure of the HIV-1 peptide. Coutant *et al.* [2008] (**antibody binding site definition and exposure**, **kinetics**, **binding affinity**, **structure**)
- 4E10: Five amino acids in the gp41 N-terminal region that promote gp140 trimerization (I535, Q543, S553, K567 and R588) were considered. Their influence on the function and antigenic properties of JR-FL Env expressed on the surfaces of pseudoviruses and Env-transfected cells was studied. Various non-neutralizing antibodies bind less strongly to the Env mutant, but neutralizing antibody binding is unaffected. There was no difference in 4E10 binding to wild type and mutant JR-FL, and 4E10 inhibited infection of the two pseudoviruses with comparable potencies. Dey *et al.* [2008] (**binding affinity**)
- 4E10: Variable domains of three heavy chain Abs, the VHH, were characterized. The Abs were isolated from llamas, who produce immunoglobulins devoid of light chains, immunized with HIV-1 CRF07_BC, to gp120. It was hypothesized that

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the small size of the VHH, in combination with their protruding CDR3 loops, and their preference for cleft recognition and binding into active sites, may allow for recognition of conserved motifs on gp120 that are occluded from conventional Abs. 4E10 did not inhibit binding of the three neutralizing VHH Abs to gp120. Forsman *et al.* [2008] (**antibody interactions**)

- 4E10: Molecular mechanism of neutralization by MPER antibodies, 2F5 and 4E10, was studied. Preparations of trimeric HIV-1 Env protein in the prefusion, the prehairpin intermediate and postfusion conformations were used. The epitopes for 2F5 and 4E10 were found to be exposed only on a form designed to mimic an prehairpin intermediate state during viral entry, which helps to explain the rarity of 2F5- and 2E10-like antibody responses. Frey *et al.* [2008] (**antibody binding site definition and exposure**, **binding affinity**)
- 4E10: 3 viral quasispecies from an HIV-1 C-subtype infected child had different sensitivities to neutralization by 4E10, conferred by a rare mutation, F673L in the 4E10 epitope. Moderate changes in sensitivity were modulated by secondary positions in this epitope and motifs in the cytoplasmic tail. Gray *et al.* [2008] (**neutralization**, **escape**)
- 4E10: The IC50 for 4E10 in a standard neutralization assay is 6.3 nM but is increased 10-fold in the postattachment neutralization assay to 59 nM. The neutralization half-life for 4E10 is 15.9 minutes but is increased 4-fold to 57.9 minutes in the presence of N36Mut(e,g), peptide, which is a class 3 inhibitor that prolongates temporal window of neutralization by disrupting trimerization of the N-heptad repeat (N-HR) in the prehairpin intermediate by sequestering the N-HR into N-HR/N36Mut(e,g) heterodimers. HXB2 was neutralized synergistically by 4E10 and N36Mut(e,g), where the formation of N-HR/N36Mut(e,g) heterodimers enhances the probability of 4E10 binding and the binding of 4E10 enhances the probability of N-HR/N36Mut(e,g) heterodimer formation, greatly diminishing the probability of 6-helix bundle formation. HXB2 was also synergistically neutralized by 4E10 and sCD4. Gustchina *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **kinetics**)
- 4E10: This review summarizes the obstacles that stand in the way of making a successful preventive HIV-1 vaccine, such as masked or transiently expressed Ab epitopes, polyclonal B-cell class switching, and inefficient, late, and not sufficiently robust mucosal IgA and IgG responses. Possible reasons why HIV-1 envelope constructs expressing 4E10 epitope fail to induce broadly neutralizing Abs are discussed. Haynes & Shattock [2008] (**vaccine antigen design**, **review**)
- 4E10: A MPER peptide, AISpreTM, overlapping 2F5 and 4E10 epitope sequences, was capable of breaching the permeability barrier of lipid vesicles. 4E10 blocked the peptide bilayer-destabilizing activity, however, inclusion of sphingomyelin raft-lipids into the membrane bilayer reduced significantly the affinity of 4E10 for AISpreTM. In contrast, inclusion of cholesterol induced higher 4E10 affinity for the AISpreTM peptide. AISpreTM appears to insert less deeply into the lipid bilayer in the presence of cholesterole, which might increase 4E10 epitope accessibility for Ab binding. Thus, 4E10 epitope accessibility is affected by envelope lipid composition. Huarte *et al.* [2008a] (**antibody binding site definition and exposure**)
- 4E10: The study compared the in-membrane recognition and blocking activity of the 2F5 and 4E10 MAbs, using solution-diffusing, unstressed phospholipid vesicles with sizes that approximate to that of the HIV virion, and an MPER-derived sequences that combines the full length 2F5 and 4E10 epitopes. 2F5 MAb had lower affinity for membrane-bound species than 4E10 MAb, as defined by inhibition data together with direct electron microscopy and flow cytometry determination of the vesicle-antibody association. Huarte *et al.* [2008b] (**antibody binding site definition and exposure**)
- 4E10: A mathematical model was developed and used to derive transmitted or founder Env sequences from individuals with acute HIV-1 subtype B infection. All of the transmitted or early founder Envs were sensitive to neutralization by 4E10, but there was a modest heightened resistance of acute Envs compared to chronic Envs to neutralization by 4E10. Keele *et al.* [2008] (**neutralization**, **acute/early infection**)
- 4E10: pIg-tail expression system was used to construct a panel of cell-surface expression plasmids encoding the extracellular domain of gp41 with deletion of fusion peptide (FP), and/or introduction of L568P mutation. Deletion of FP resulted in significantly increased antigenicity of 4E10 epitope, indicating that FP and MPER may interact with each other, resulting in obstruction of the 4E10 epitope in MPER. L568P mutation resulted in significant enhancement of 4E10 binding to its epitope, suggesting that the mutation may destabilize the gp41 6-HB core conformation exposing the 4E10 epitope. Mice were immunized with DNA plasmids of FP-deleted and L568P mutant gp41, and with peptide containing the 4E10 epitope. Deletion of FP did not enhance the immunogenicity of the 4E10 epitope, however, the L568P mutation resulted in increased Ab response against 4E10 epitope compared to the response by peptide alone. Li *et al.* [2008b] (**antibody binding site definition and exposure**, **vaccine antigen design**, **binding affinity**)
- 4E10: CTB-MPR649-684 (cholera toxin subunit B and residues 649-684 of gp41 MPER region) peptide was developed for vaccine studies in rabbits. 4E10 affinity to the CTB-MPR peptide was equivalent to 4E10 affinity toward an MPR peptide, indicating that the fusion peptide presented antigenically competent MPR. Sera from immunized rabbits displayed no neutralizing activity, but could inhibit epithelial transcytosis of virus, indicating elicitation of non-neutralizing Abs capable of stopping mucosal transmission and infection of target cells. Matoba *et al.* [2008] (**binding affinity**)
- 4E10: Transmission of HIV-1 by immature and mature DCs to CD4+ T lymphocytes was significantly higher for CXCR4- than for CCR5-tropic strains. In addition, 4E10 inhibited transmission of CCR5-tropic viruses while transmission of 4E10-neutralized X4 variants increased, indicating that X4 HIV-1 has an advantage over R5 in transmission when neutralized with 4E10. van Montfort *et al.* [2008] (**co-receptor**, **neutralization**, **dendritic cells**)
- 4E10: 4E10 was shown to bind to Envs used in typical epitope binding assays, unlike the neutralizing Abs 8K8, DN9, and D5 used in this study. 4E10 neutralized all HIV-1 isolates tested, and its neutralization potency was 1 to 2 orders of mag-

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nitude higher than that one of mAbs 8K8 and D5. 4E10 displayed some cardiolipin binding activity. Nelson *et al.* [2008] (**autoantibody**, **neutralization**, **binding affinity**)

- 4E10: For assessment of gp41 immunogenic properties, five soluble GST-fusion proteins encompassing C-terminal 30, 64, 100, 142, or 172 (full-length) amino acids of gp41 ectodomain were generated from M group consensus env sequence. Although all five protein fragments contained the same epitope recognized by 4E10, GST-gp41-30 and -100 fragments were about 20- and 5-fold less reactive to 4E10, respectively, compared to the other three protein fragments which had similar reactivity. Patients considered as slow progressors generally exibited larger Ab reactivity against the 30aa fragment, indicating that these Abs target MPER region and exhibit 2F5- and 4E10-like properties. Plasma from these patients also exhibited broader and more potent neutralizing activity against several HIV-1 isolates. Plasma from 4 out of 44 patients reacted with peptides that bind 4E10, indicating that these patients mounted 4E10-like Ab response. Penn-Nicholson *et al.* [2008] (**rate of progression**)
- 4E10: The sensitivity of R5 envelopes derived from several patients and sevaral tissue sites, including brain tissue, lymph nodes, blood, and semen, was tested to a range of inhibitors and Abs targeting CD4, CCR5, and various sites on the HIV envelope. All but one envelope from brain tissue were macrophage-tropic while none of the envelopes from the lymph nodes were macrophage-tropic. Macrophage-tropic envelopes were also less frequent in blood and semen. There was no clear correlation between macrophage-tropism and neutralization sensitivity to 4E10, indicating that variation in macrophage tropism is not caused by variation in the membrane proximal region of Env. Peters *et al.* [2008b] (**neutralization**)
- 4E10: This minireview summarizes data on differences in neutralizing activities of MAbs and pooled human sera using a traditional primary cell neutralization assay and the more standardized TZM-bl reporter cell line assay. Also, suggestions are made on how to improve and standardize neutralization assays for comparable use in different laboratories. 4E10 neutralization was tested against a panel of 60 HIV-1 primary isolates (10 each from clades A-D, CRF01_AE and CRF02_AG) in the two assays. 17 viruses from the PBMC assay and 1 virus from the TZM-assay were not neutralized by this Ab. Only 52% of concordance between the two assays were shown for 4E10, and, as observed in other studies, 4E10 displayed much broader neutralization in the TZM-assay. It is suggested that the process of endocytosis in the TZM-assay alters exposure of the MPER region allowing 4E10 to neutralize more efficiently. In total, however, the assay discordances were shown to be bidirectional and not attributable to assay sensitivity. Polonis *et al.* [2008] (**neutralization**, **review**, **subtype comparisons**, **assay standardization/improvement**)
- 4E10: In order to assess whether small molecule CCR5 inhibitor resistant viruses were more sensitive to neutralization by NAbs, two escape mutant viruses, CC101.19 and D1/85.16, were tested for their sensitivity to 4E10, compared to the sensitivity of CC1/85 parental isolate and the CCcon.19 control isolate. The CC101.19 escape mutant has 4 sequence changes in V3 while the D1/85.16 has no sequence changes in V3 and relies on other sequence changes for its resistance. The two escape mutant viruses were moderately more sensitive to the 4E10 neutralization than the parental isolates, which were resistant to neutralization by this Ab. There were no sequence-based explanations for the increased neutralization sensitivity of the escape viruses by 4E10. Overall, the study suggests that CCR5 inhibitor-resistant viruses are likely to be somewhat more sensitive to neutralization than their parental viruses. Pugach *et al.* [2008] (**co-receptor**, **neutralization**, **escape**)
- 4E10: Trimeric envelope glycoproteins with a partial deletion of the V2 loop derived from subtype B SF162 and subtype C TV1 were compared. 4E10 recognized both B and C trimers, indicating that the 4E10 epitope was exposed and preserved in the subtype C trimers. Subtype C trimer had many biophysical, biochemical, and immunological characteristics similar to subtype B trimer, except for a difference in the three binding sites for CD4, which showed cooperativity of CD4 binding in subtype C but not in subtype B. Srivastava *et al.* [2008] (**binding affinity**, **subtype comparisons**)
- 4E10: MPER structure and interaction with 4E10 was studied by NMR, EPR and SPR techniques. The MPER region was shown to have an L-shaped structure, with the conserved C-terminal residues immersed in the membrane and the variable N-terminal residues exposed to the aqueous phase. 4E10 was shown to extract its epitope from the viral membrane in a multistep process: i) initial interaction of the Ab with N671 residue orients the peptide with the respect to Ab binding pocket, ii) the hydrophobic residues of the Ab induce rearrangement of multiple side chains of the peptide, with the F673 residue rotated into the Ab binding pocket, iii) insertion of F673 and W672 residues into the 4E10 binding pocket bends the N-terminal segment of the peptide in the opposite direction. The key requirement for neutralization is suggested to be induction of structural rearrangement of the MPER hinge by 4E10. It is also suggested that exposure of the membrane-embedded residues of the MPER region to the immune system in their native L-shaped form may elicit neutralizing Abs. Sun *et al.* [2008] (**antibody binding site definition and exposure**, **structure**)
- 4E10: The neutralization profile of early R5, intermediate R5X4, and late X4 viruses from a rhesus macaque infected with SHIV-SF162P3N was assessed. 4E10 moderately neutralized the late X4 and the intermediate R5X4 viruses, but did not neutralize the parental R5. Tasca *et al.* [2008] (**co-receptor**, **neutralization**)
- 4E10: To investigate B-cell responses immediately following HIV-1 transmission, env-specific Ab responses to autologous and consensus Envs in plasma donors were determined. Broadly neutralizing Abs with specificity similar to 4E10 did not appear during the first 40 days after plasma virus detection. Tomaras *et al.* [2008] (**acute/early infection**)
- 4E10: 4E10 reacted with maltose-binding proteins MBP30 and MBP32, containing both HR1 and HR2 domains of gp41, and with MBP37 and MBP44, containing only the HR2 domain, but not with MBP-HR1, containing only the HR1 domain. Vincent *et al.* [2008] (**antibody binding site definition and exposure**)
- 4E10: The various effects that neutralizing and non-neutralizing anti-envelope Abs have on HIV infection are re-

viewed, such as Ab-mediated complement activation and Fc-receptor mediated activities, that both can, through various mechanisms, increase and decrease the infectivity of the virus. The importance of these mechanisms in vaccine design is discussed. The unusual features of the 4E10 MAb are described. Willey & Aasa-Chapman [2008] (**review**)

- 4E10: Current insights into CTLs and NAbs, and their possible protective mechanisms against establishment of persistent HIV/SIV infection are discussed. Pre- and post-infection sterile and non-sterile protection of NAbs against viral challenge, and potential role of NAbs in antibody-mediated antigen presentation in modification of cellular immunity, are reviewed. Use of 4E10 in immunization experiments and its in vivo antiviral activity in suppression of viral rebound in HIV-1 infected humans undergoing structured treatment interruptions are described. Yamamoto & Matano [2008] (**immunotherapy**, **supervised treatment interruptions (STI)**, **review**)
- 4E10: The newly detected mAb m44 was shown to neutralize a panel of primary HIV-1 isolates with higher potency than 4E10, and the neutralization potency of the two mAbs was comparable for a subtype C SHIV strain. 4E10 did not compete with m44 for binding. A fusion protein of gp41 constructed for alanine-scanning mutagenesis bound to 4E10, indicating that its antigenic structure was intact. 4E10 bound to self antigens in lipid binding assays. Zhang *et al.* [2008] (**neutralization**, **binding affinity**)
- 4E10: The autoantibody nature of the two membrane proximal HIV-1 neutralizing antibodies, 2F5 and 4E10, was evaluated by comparison to human anti-cardiolipin mAbs derived from a primary antiphospholipid syndrome patient. Both 2F5 and 4E10 bound specifically to cardiolipin. CDR3 sequence similarities between 2F5, 4E10 and anti-cardiolipin mAbs were observed. A difference in the binding mode of both 2F5 and 4E10 when binding to peptide in solution versus peptide conjugated to lipids was observed, in that binding to the peptide-lipid conjugate was best fit by a two step conformational change model. These results suggest that these antibdies share binding and structural similarities with human autoantibodies and their induction by vaccines or natural infection therefore might be limited by immune tolerance mechanisms. Alam *et al.* [2007] (**kinetics**, **antibody sequence variable domain**)
- 4E10: 4E10 was shown to recognize liposomes containing phosphatidylinositol-4-phosphate (PIP) to the same extent that it recognized anionic liposomes lacking PIP. Binding of 4E10 to pure PIP was inhibited by Ca2+. Once bound to PIP, 4E10 could not be stripped off by addition of Ca2+, indicating an irreversible bond of 4E10 to PIP phospholipid fatty acids. Beck *et al.* [2007] (**antibody binding site definition and exposure**)
- 4E10: Sera from rabbits immunized with either monomeric gp120, trimeric cleavage-defective gp140 or disulfide-stabilized soluble trimeric gp140 were tested for neutralization of chimeric SIVmac239 viruses expressing epitope for this Ab. Little or no neutralization was observed indicating that little or no Ab activity in these rabbit sera was directed against the gp41 region. Beddows *et al.* [2007] (**neutralization**, **vaccine antigen design**)
- 4E10: Pseudoviruses derived from gp120 Env variants that evolved in multiple macaques infected with SHIV 89.6P displayed a range of degrees of virion-associated Env cleavage. Pseudoviruses with higher amount of cleaved Env were more resistant to neutralization by 4E10. The gp41 sequence was the same in all pseudoviruses, indicating that changes in gp120 can mediate sensitivity of gp41 to neutralization. Blay *et al.* [2007] (**neutralization**)
- 4E10: 7/15 and 9/15 subtype A HIV-1 envelopes from samples taken early in infection were neutralized by MAbs 4E10 and 2F5, respectively, and the potency was generally modest. Mutational patterns in the MAb binding sites did not readily explain the observed patterns of sensitivity and resistance. Blish *et al.* [2007] (**neutralization**, **variant cross-recognition or cross-neutralization**, **acute/early infection**, **subtype comparisons**)
- 4E10: This study confirmed binding of 4E10 to cardiolipin (CL) and showed that this Ab also binds to phosphatidylinositol phosphate (PIP). Binding of 4E10 to CL and PIP was inhibited by phosphocoline and enhanced by inositol (PIP only). Anti-PIP mouse monoclonal antibodies had neutralizing antibodies against 2 HIV primary isolates. Brown *et al.* [2007] (**mimics**, **neutralization**, **binding affinity**)
- 4E10: (R5)X4 viruses from early and late timepoints after X4 emergence were found to be more sensitive to neutralization by 4E10 than their coexisting R5 variants in one patient. Only early (R5)X4 viruses were more sensitive to neutralizaion by 4E10 in another patient. Bunnik *et al.* [2007] (**co-receptor**, **neutralization**)
- 4E10: Structural effects of both increasing peptide length and introducing helix-promoting constraints in the 4E10 epitope were investigated. Helical constraints increased binding affinity of the peptide epitope for 4E10 by increasing the stability of the complex and allowing interaction with an additional helical turn including Leu679 and Trp680. Crystal structures of the 4E10 bound to peptide epitopes revealed that the gp140 residues Trp672, Phe673, Ile675, Thr676 Leu679 and Trp680 have the most significant contact with the antibody, and the core motif was redefined as: WFX(I/L)(T/S)XX(L/I)W. Cardoso *et al.* [2007] (**antibody binding site definition and exposure**, **vaccine antigen design**, **structure**)
- 4E10: 2F5, 4E10, and m46 neutralization was more potent when tested in a HeLa cell line expressing low CCR5 than in a HeLa cell line expressing high CCR5 levels. PBMC tend to have low CCR5 expression. Choudhry *et al.* [2007] (**neutralization**, **assay standardization/improvement**)
- 4E10: SOSIP Env proteins are modified by the introduction of a disulfide bond between gp120 and gp41 (SOS), and an I559P (IP) substitution in gp41, and form trimers. The KNH1144 subtype A virus formed more stable trimers than did the prototype subtype B SOSIP Env, JRFL. The stability of gp140 trimers was increased for JR-FL and Ba-L SOSIP proteins by substituting the five amino acid residues in the N-terminal region of gp41 with corresponding residues from KNH1144 virus. b12, 2G12, 2F5, 4E10 and CD4-IgG2 all bound similarly to the WT and to the stabilized JRFL SOSIP timers, suggesting that the trimer-stabilizing substitutions do not impair the overall antigenic structure of gp140 trimers. Dey *et al.* [2007a] (**vaccine antigen design**)
- 4E10: Chimeric SIV viruses containing 2F5 and 4E10 epitopes were not neutralized by the broadly neutralizing sera

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from two clade B and one clade A infected asymptomatic individuals, indicating that MPER NAb epitopes did not account for the broad neutralizing activity observed. Dhillon *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**)

- 4E10: Kinetics experiments of 4E10 binding to MPER region during viral fusion showed that the 4E10 kinetics resembled those of the six-helix bundle formation and fusion blocker C34, indicating that the function of MPER in the fusion cascade is still in effect at a late stage in the fusion reaction. Binding of 4E10 was shown to decrease upon triggering HIV-1 Env-expressing cells with appropriate target cells and addition of C34 did not counteract this loss, suggesting that changes in exposure of MPER occur independently of the six-helix bundle formation. Dimitrov *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **kinetics**, **binding affinity**)
- 4E10: Newborn macaques were challenged orally with the highly pathogenic SHIV89.6P and then treated intravenously with a combination of IgG1b12, 2G12, 2F5 and 4E10 one and 12 hours post-virus exposure. All control animals became highly viremic and developed AIDS. In the group treated with mAbs 1 hour post-virus exposure, 3/4 animals were protected from persistent systemic infection and one was protected from disease. In the group treated with mAbs 12 hour post-virus exposure, one animal was protected from persistent systemic infection and disease was prevented or delayed in two animals. IgG1b12, 2G12, and 4E10 were also given 24 hours after exposure in a separate study; 4/4 treated animals become viremic, but with delayed and lower peak viremia relative to controls. 3/4 treated animals did not get AIDS during the follow up period, and 1 showed a delayed progression to AIDS , while the 4 untreated animals died of AIDS. Thus the success of passive immunization with NAbs depends on the time window between virus exposure and the start of immunoprophylaxis. Ferrantelli *et al.* [2007] (**immunoprophylaxis**)
- 4E10: This review summarizes data on the development of HIV-1 centralized genes (consensus and ancestral) for induction of neutralizing antibody responses. Functionality and conformation of native epitopes in proteins based on the centralized genes was tested and confirmed by binding to 4E10 and other MAbs. Antibodies induced by immunization with these centralized proteins did not, however, have the breadth and potency compared to that of 4E10 and other broadly neutralizing MAbs. 4E10 physical characteristics of autoantibodies as a possible reason for lack of 4E10 broad production is also discussed. Gao *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **review**)
- 4E10: Addition of a glycosylation site at position V295N in two different subtype C envelope clones resulted in a twofold increase in neutralization sensitivity of the corresponding viruses to 4E10. Gray *et al.* [2007b] (**neutralization**)
- 4E10: The potency of 4E10 was 25-fold higher than the potency of new neutralizing Fab 3674 in neutralization of laboratory and primary strains of HIV-1 subtypes A, B and C. Gustchina *et al.* [2007] (**neutralization**, **subtype comparisons**)
- 4E10: This review summarizes current knowledge on the various functional properties of antibodies in HIV-1 infection, including 4E10 mAb, in vivo and in vitro activity of neutralizing Abs, the importance and downfalls of non-neutralizing Abs and antibodies that mediate antibody-dependent cellular cytotoxicity and the complement system, and summarizes data on areas tht need future investigation on Ab-mediated immune control. Huber & Trkola [2007] (**review**)
- 4E10: To test the immunogenicity of three molecularly engeneered gp41 variants on the cell surface their reactivity with 4E10 was assessed. The reactivity of 4cSSL24 variant was comparable to gp160 while the other two variants showed somewhat lower expression levels. When guinea pigs were immunized with the three variants, the level of the specific anti-gp41 Ab responses was low with the anti-gp41 response preferentially directed to the C-helical domain, away from the MPER region. Kim *et al.* [2007] (**vaccine antigen design**, **binding affinity**)
- 4E10: A new high throughput method was developed for neutralization analyses of HIV-1 env genes by adding cytomegalovirus (CMV) immediate enhancer/promoter to the 5' end of the HIV-1 rev/env gene PCR products. The PCR method eliminates cloning, transformation, and plasmid DNA preparation steps in the generation of HIV-1 pseudovirions and allows for sufficient amounts of pseudovirions to be obtained for a large number of neutralization assays. Pseudovirions generated with the PCR method showed similar sensitivity to 4E10 Ab, indicating that the neutralization properties are not altered by the new method. Kirchherr *et al.* [2007] (**assay development**, **neutralization**)
- 4E10: Four consensus B Env constructs: full length gp160, uncleaved gp160, truncated gp145, and N-linked glycosylation-site deleted (gp160-201N/S) were compared. All were packaged into virions, and all but the fusion defective uncleaved version mediated infection using the CCR5 co-receptor. Primary isolate Envs varied between completely resistant or somewhat sensitive to neutralization by membrane proximal Nabs 4E10 and 2F5. The most sensitive Con B construct was the truncated version of Con B Env with a stop codon immediately following the membrane spanning domain, suggesting that truncation of the gp41 cytoplasmic domain facilitates greater accessibility of the MPER region. The Con B gp160 was quite resistant, and the gp160-201N/S more sensitive, to 4E10 and 2F5. Kothe *et al.* [2007] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**)
- 4E10: This review summarizes 4E10 Ab epitope, properties and neutralization activity. 4E10 use in passive immunization studies in primates and possible mechanisms explaining protection against infection are discussed. Also, 4E10 autoreactivity and its implications for active immunizations are discussed. Kramer *et al.* [2007] (**immunotherapy**, **review**)
- 4E10: V3 loop deletions were introduced into three different primary HIV-1 strains: R3A, DH12, and TYBE. The deletions included: ΔV3(12,12) containing the first and the last 12 residues of the V3 loop, ΔV3(9,9) containing first and last 9 residues, and ΔV3(6,6) ontaining first and last 6 residues. Only HIV-1 R3A ΔV3(9,9) was able to support cell fusion. Passaging of this virus resulted in a virus strain (TA1) that replicated with wildtype kinetics, and that acquired several adaptive changes in gp120 and gp41 while retaining the V3

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loop truncation. 4E10 exhibited modestly enhanced neutralization activity against TA1 and a ΔV1/V2 virus, while it failed to neutralize R3A. Laakso *et al.* [2007] (**neutralization**)

- 4E10: High levels of gp120-specific Abs were elicited when mice and rabbits were immunized by DNA priming and protein boosting with G1 and G2 grafts, consisting of 2F5 and 4E10, and 4E10 epitopes, respectivelly, engrafted into the V1/V2 region of gp120. A consistent NAb response against the homologous JR-FL virus was detected in rabbits but not in mice. 4E10 bound to the engrafted construct, but embedding the MPER epitopes in the immunogenic V1/V2 region did not result in eliciting anti-MPER antibodies in mice or rabbits. 4E10 binding to G2 was greater than to G1, and could be enhanced by deletion of one or two amino acid residues immediately preceding the 4E10 epitope, presumably due to rotation of the epitope along the alpha-helix in the engrafted region. Law *et al.* [2007] (**vaccine antigen design**)
- 4E10: 4E10 structure, binding, neutralization, and strategies that can be used for vaccine antigen design to elicit anti-gp41 Abs, are reviewed in detail. The effect of the autoreactivity of 4E10 on vaccine antigen design is discussed. Lin & Nara [2007] (**vaccine antigen design**, **review**, **structure**)
- 4E10: This review summarizes data on possible vaccine targets for elicitation of neutralizing Abs and discusses whether it is more practical to design a clade-specific than a clade-generic HIV-1 vaccine. Development of a neutralizing Ab response in HIV-1 infected individuals is reviewed, including data that show no apparent division of different HIV-1 subtypes into clade-related neutralization groups. Also, a summary of the neutralizing activity of mAb 4E10 in different HIV-1 clades is provided. McKnight & Aasa-Chapman [2007] (**variant cross-recognition or cross-neutralization**)
- 4E10: Three MAbs, 2G12, 4E10 and 2F5, were administered to ten HIV-1 infected individuals treated with ART during acute and early infection, in order to prevent viral rebound after interruption of ART. MAb infusions were well tolerated with essentially no toxicity. Viral rebound was not prevented, but was significantly delayed in 8/10 patients. 2G12 activity was dominant among the MAbs used. Antiviral activity of 4E10 was not clearly demonstrated. Development of resistance to 4E10 was not observed despite ongoing viral replication. Plasma HIV-1 RNA levels did not increase following cessation of Ab infusion. Plasma viremia was essentially identical between patients not receiving MAb therapy and patients receiving 4E10 and 2F5 in the face of 2G12 resistance. 4E10 also failed to accumulate with repeated infusions in patient plasma. Long-term suppression of viremia was achieved in 3/10 patients. Mehandru *et al.* [2007] (**escape**, **immunotherapy**, **supervised treatment interruptions (STI)**)
- 4E10: 4E10-neutralized HIV-1 captured on Raji-DC-SIGN cells or immature monocyte-derived DCs (iMDDCs) was transfered to CD4+ T lymphocytes with 1.5 fold higher efficiency than non-neutralized virus. van Montfort *et al.* [2007] (**enhancing activity**, **neutralization**, **dendritic cells**)
- 4E10: Z13e1, a high affinity variant of Fab Z13, was identified through targeted mutagenesis and affinity selection against gp41 and an MPER peptide. Z13e1 showed 100-fold improvement in binding affinity for MPER antigens over Z13, but was still less potent than 4E10 at neutralizing several pseudotyped Envs. 4E10 was found to be less effective inhibitor of biotinylated Z13e1 than the other way around. Neutralization assays of HIV-1 JR2 MPER alanine mutants showed that mutants W666A and W672A were completely resistant to neutralization by 4E10. In contrast to a previous publication, it was also found that neutralization of HIV-1 JR-FL by 4E10 was not greatly improved in going from the Fab to IgG format. Nelson *et al.* [2007] (**antibody binding site definition and exposure**)
- 4E10: Four different co-receptor switch mutants were generated from ADA and BaL wildtype Envs (ADA-1, ADA-3, BaL-1B, and BaL2A) and the intermediate transition mutations were studied on either CCR5 or CXCR4 expressing cells for their sensitivity to 4E10 compared to wiltype. Most of the ADA-1 and ADA-3 mutants were more sensitive to 4E10 than the wildtype on both CCR5 and CXCR4 cells. BaL-1B mutants were highly sensitive to entry inhibition by 4E10 on CCR5 cells, which further increased on CXCR4 cells. BaL-2A mutants varied in their sensitivity to 4E10 inhibition, where only the final BaL-2A mutant, with all four mutations, was significantly more sensitive to 4E10 than the wildtype virus. Pastore *et al.* [2007] (**co-receptor**, **neutralization**)
- 4E10: This review provides information on the HIV-1 glycoprotein properties that make it challenging to target with neutralizing Abs. 4E10 structure and binding to HIV-1 envelope and current strategies to develop versions of the Env spike with functional trimer properties for elicitation of broadly neutralizing Abs, such as 4E10, are discussed. In addition, approaches to target cellular molecules, such as CD4, CCR5, CXCR4, and MHC molecules, with therapeutic Abs are reviewed. Phogat *et al.* [2007] (**review**)
- 4E10: This study found that, contrary to expectations, the viruses resistant to b12, 4E10, 2G12 and 2F5 neutralization did not have lower replication kinetics than viruses sensitive to neutralization. Viruses from early infection tended to have relatively low replications rates. Quakkelaar *et al.* [2007a] (**neutralization**, **viral fitness and reversion**, **escape**)
- 4E10: The ability of 4E10 to neutralize recently transmitted viruses was examined in four homosexual and two parenteral transmission couples. The vast majority of recently transmitted viruses from homosexual recipients were moderately to completely resistant to neutralization by 4E10, although viruses isolated later in the course of infection showed increased sensitivity to 4E10 in one of the patients. In the parenteral transmission, one of the recipients had early viruses resistant to 4E10 neutralization, and one had viruses sensitive to 4E10 neutralization. The neutralization sensitivity patterns of recipient viruses to 4E10 did not correlate to the neutralization sensitivity patterns of their donors in the homosexual couples, while the HIV-1 variants from the parenteral pairs were similarly resistant/sensitive to neutralization by 4E10. Resistance to 4E10 did not correlate with sequence variation within the 4E10 epitope. Quakkelaar *et al.* [2007b] (**neutralization**, **acute/early infection**, **mother-to-infant transmission**)
- 4E10: A reference panel of recently transmitted Tier 2 HIV-1 subtype B envelope viruses was developed representing a broad spectrum of genetic diversity and neutralization sensitivity. The panel includes viruses derived from male-to-male, female-to-male, and male-to-female sexual transmissions, and

CCR5 as well as CXCR4 using viruses. The envelopes displayed varying degrees of neutralization sensitivity to 4E10, with 18 of 19 enevlopes sensitive to neutralization by this Ab. Schweighardt *et al.* [2007] (**neutralization**, **assay standardization/improvement**)

- 4E10: Infusion of a MAb cocktail (4E10, 2G12 and 2F5) into HIV-1 infected subjects was shown to be associated with increased levels of serum anti-cardiolipin and anti-phosphatidylserine Ab titers, and increased coagulation times. In the absence or in the presence of adult and neonate plasma, 4E10 exhibited dose-dependent reactivity with cardiolipin and phosphatidylserine, and low binding to β2GP1 and prothrombin. 4E10 induced prolongations of clotting times in human plasma, but those were mild and did not exceed grade I toxicities. Vcelar *et al.* [2007] (**antibody interactions**, **autoantibody**, **binding affinity**, **immunotherapy**)
- 4E10: Novel approaches based on sequential (SAP) and competitive (CAP) antigen panning methodiologies, and use of antigens with increased exposure of conserved epitopes, for enhanced identification of broadly cross-reactive neutralizing Abs are reviewed. Previously known broadly neutralizing human mAbs are compared to Abs identified by these methods. Zhang & Dimitrov [2007] (**review**)
- 4E10: This review summarizes current knowledge of HIV-1 lipid-protein interactions and antibodies to liposomal phospholipids and cholesterol. A potential use of Abs to lipids to neutralize HIV-1 and a potential role of the broadly neutralizing HIV-1 Abs, mainly 2F5 and 4E10, in binding to phospholipids is discussed. Alving *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**, **review**)
- 4E10: The optimal length of the 4E10 epitope was determined to the gp41 residues 671 to 683. Several residues in the epitope were shown to be essential for 4E10 recognition (W672, F673 and T676) and five more were shown to make significant contributions to 4E10 binding (N671, D674, I675, W680 and L679). When helix-promoting residues and helix-inducing tethers were incorporated, several peptides showed imroved affinity over the starting peptide suggesting that they may be more likely to elicit 4E10-like neutralizing Abs. Brunel *et al.* [2006] (**optimal epitope**, **kinetics**, **binding affinity**, **structure**)
- 4E10: The majority of broadly cross-reactive neutralizing (BCN) Envs were neutralized at lower concentrations of 4E10 than the non-BCN Envs. Amino acid variability of the 4E10 epitope was examined. The presence of T at position 662 was associated with increased sensitivity to neutralization by this Ab. Cham *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **escape**, **subtype comparisons**)
- 4E10: Neutralization of HIV-1 primary isolates of different HIV-1 clades (A, B, C, D, E) by 4E10 was determined in cells expressing high or low surface concentrations of CD4 and CCR5 receptors. CD4 cell surface concentration had no effect on the inhibitory activity of this Ab while the CCR5 surface concentration had a significant effect decreasing the 50% inhibitory concentration of 4E10 in cell lines with low CCR5. Choudhry *et al.* [2006] (**co-receptor**, **neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 4E10: Macaques were immunized with SF162gp140, ΔV2gp140, ΔV2ΔV3gp140 and ΔV3gp140 constructs and their antibody responses were compared to the broadly reactive NAb responses in a macaque infected with SHIV SF162P4, and with pooled sera from humans infected with heterologous HIV-1 isolates (HIVIG). 4E10 was recognized less efficiently on the V2- and V3- deleted proteins than on SF162gp140. 4E10 was found to equally neutralize SF162 and Δ2F5.4E10, which is a virus with mutations in the 2F5 and 4E10 epitopes and is resistant to neutralization by 2F5 and 4E10. This indicates that 4E10-like Abs were not present in sera from the gp140-immunized animals nor in the SHIV-infected and in the HIVIG sera. Derby *et al.* [2006] (**antibody binding site definition and exposure**, **antibody generation**, **neutralization**)
- 4E10: Genetic variability and co-variation of the mAb 2F5, 4E10 and Z13 epitopes in B and non B clades was investigated. A significant shift in the predominant sequence patterns over time was observed for all three epitopes. Also, significant inter-subtype genetic variability of the three epitopes was detected. However, the 4E10 epitope displayed a more similar variability within B clade and non-B clades, concurring with the cross-clade neutralizing activity of this mAb. Epitope co-variation was also noted, as one third of the recently isolated HIV-1 strains displayed simultaneous epitope variants. Dong & Chen [2006] (**antibody binding site definition and exposure**, **subtype comparisons**)
- 4E10: This MAb was used as a positive control in the neutralization assays. It neutralized two of three subtype B and 4 of 6 non-B primary isolates. Gorny *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 4E10: Env-pseudotyped viruses were constructed from the gp160 envelope genes from seven children infected with subtype C HIV-1. 4E10 alone or in combination with IgG1b12, 2G12 and 2F5 neutralized all of the seven viruses. Gray *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **responses in children**, **mother-to-infant transmission**)
- 4E10: The antigenic determinants recognized by 4E10 were characterized using recombinant glycosylated full-length Ags, and nonglycosylated and truncated Ags. This Ab recognized three peptides located at the N-terminal region of gp120 and gp41, respectively. It is suggested that 4E10 binds to the fusogenic peptide of gp41 and the N-terminal region of gp120, inhibiting insertion of fusogenic peptide into the host cell membrane. Hager-Braun *et al.* [2006] (**antibody binding site definition and exposure**, **optimal epitope**, **variant cross-recognition or cross-neutralization**, **binding affinity**)
- 4E10: This review describes the effectiveness of the current HIV-1 immunogens in eliciting neutralizing antibody responses to different clades of HIV-1. It also summarizes different evasion and antibody escape mechanisms, as well as the most potent neutralizing MAbs and their properties. MAbs reviewed in this article are: 2G12, IgG1b12, 2F5, 4E10, A32, 447-52D and, briefly, D50. Novel immunogen design strategies are also discussed. Haynes & Montefiori [2006] (**antibody binding site definition and exposure**, **neutral-**

ization, **optimal epitope**, **escape**, **review**, **subtype comparisons**, **structure**)

- 4E10: Inhibition of R5 HIV replication by monoclonal and polyclonal IgGs and IgAs in iMDDCs was evaluated. The HIV-neutralizing activity of 4E10 was observed to be higher in iMDDCs than in PHA-stimulated PBMCs using both HIV-1 Bx08 and BaL. Holl *et al.* [2006b] (**neutralization**, **dendritic cells**)
- 4E10: The ability of this Ab to inhibit viral growth was increased when macrophages and immature dendritic cells (iDCs) were used as target cells instead of PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication by this Ab for macrophages and iDCs can occur by two distinct mechanisms, neutralization of infectivity involving only the Fab part of the IgG, and, an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**dendritic cells**)
- 4E10: Pharmacokinetic properties of this Ab were studied in HIV infected patients infused with high doses of 4E10. The Ab did not elicit an endogenous immune response and had distribution and systemic clearance values similar to other Abs. The elimination half-life was measured to 5.5 days. Joos *et al.* [2006] (**kinetics**, **immunotherapy**)
- E10: All subtype C env-pseudotyped clones derived from individuals in acute/early stage of HIV-1 infection were neutralized by this Ab. One clone had a slightly different motif (WFNM) than the reported required WFXI in the epitope, yet it was highly susceptible to neutralization by 4E10, indicating additional flexibility in the 4E10 core epitope. Li *et al.* [2006c] (**neutralization**, **variant cross-recognition or cross-neutralization**, **acute/early infection**, **subtype comparisons**)
- 4E10: The gp140δCFI protein of CON-S M group consensus protein and gp140CFI and gp140CF proteins of CON6 and WT viruses from HIV-1 subtypes A, B and C were expressed in recombinant vaccinia viruses and tested as immunogens in guinea pigs. 4E10 was shown to bind specifically to CON6, CON-S and subtype B recombinant proteins but not to subtype A and C recombinant proteins or to the two subtype B gp120 proteins. The specific binding of 4E10 to CON-S indicated that its conformational epitope was intact. Liao *et al.* [2006] (**antibody binding site definition and exposure**, **vaccine antigen design**, **subtype comparisons**)
- 4E10: This study showed that 4E10 Ab is able to specifically block the membrane-restructuring activity by recognizing preTM peptides inserted into the viral external membrane monolayer in the gp41 pre-fusion state. The recognition and blocking occurs in the presence of cholesterol and correlates with pore-formation blocking, suggesting interferance of the formation of fusion-competent complexes. Lorizate *et al.* [2006a] (**antibody binding site definition and exposure**)
- E10: Binding of this Ab to pre-TM sequence was shown not to be affected by presence of FP (fusion peptide) sequence. Lorizate *et al.* [2006b] (**antibody binding site definition and exposure**, **binding affinity**)
- 4E10: gp41 and p15E of the porcine endogenous retrovirus (PERV) share structural and functional similarities, and epitopes in the membrane proximal region of p15E are able to elicit NAbs upon immunization with soluble p15E. Rabbits immunized with a VSV recombinant expressing an HIV-1 membrane-proximal external region (MPER) fused to PERV p15E, with a fusion p15E-HIV MPER protein boost, elicited HIV specific NAbs. The MPER contains the 4E10 epitope. Luo *et al.* [2006] (**vaccine antigen design**)
- 4E10: SHIV SF162p4 virus used as challenge in ISCOM vaccinated macaques was shown to be highly sensitive to neutralization by this Ab. Pahar *et al.* [2006] (**neutralization**)
- 4E10: This Ab is shown to have the capacity to penetrate into the membrane interfaces and recognize isolated peptide-epitope sequence embeded into the membrane, where immersion into the lipid bilayer does not interfere with 4E10 recognition ability. The association of 4E10 with membranes is shown to be nonspecific. Sánchez-Martínez *et al.* [2006b] (**antibody binding site definition and exposure**)
- 4E10: Significant levels of 4E10 were shown to bind to HA/gp41 expressed on cell surfaces and this Ab did stain cells expressing HA/gp41 in a fluorescence assay. However, a much smaller percentage of the HIV 89.6 Env expressing cells were stained with this Ab than with 2G12, indicating that this Ab recognition site on gp41 is masked by the gp120 subunit in the HIV Env protein and that it is more easily accessible on the HA/gp41 chimeric protein. Ye *et al.* [2006] (**antibody binding site definition and exposure**, **binding affinity**)
- 4E10: The epitope recognition sequence for this Ab was introduced into the corresponding region of SIVmac239 and the replication of this viral variant (SIVmac239/4E10) was similar to the parental virus. SIVmac239/4E10 was specifically neutralized by MAb 4E10. SIVmac239/4E10 was neutralized by a LTNP plasma and somewhat with three other plasmas but addition of a 4E10 Ab inhibitor did not block the neutralization suggesting that 4E10 specificity represent only small fraction of neutralizing activity in plasma. Yuste *et al.* [2006] (**neutralization**, **SIV**)
- 4E10: Neutralizing activity of 4E10 against a panel of HIV-1 primary isolates from different clades was assessed in a PBMC-assay. The neutralizing activity was shown to be less potent than that of the newly characterized m48 MAb. Zhang *et al.* [2006a] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 4E10: The structure of the 4E10 MAb, particularly its CDRH3 region's binding mechanisms to the MPER region of gp41, and possibly the cellular membrane as well, are reviewed. Engineering of Abs based on revealed structures of broadly neutralizing MAbs is discussed. Burton *et al.* [2005] (**antibody binding site definition and exposure**, **review**, **structure**)
- 4E10: The crystal structure of 4E10 complexed with a 13 aa peptide (KGWNWFDITNWGK) that contains the NWFDIT binding site was resolved to 2.2 A resolution. 4E10 has a canonical beta sandwich Ig-fold, with H3/H2 loop hydrophobicity and a long CDR H3 loop that mediates C-terminal base and central amino acid interactions; it extends beyond the peptide and its orientation suggests it could potentially allow hydrophobic contacts with the viral membrane. 4E10 complex formation induces a conformational change in the peptide such that it forms an amphipathic alpha-helix with a hydrophobic face that interacts with 4E10, with Trp672 primary, and Phe673, Ile675 and Thr676 secondary, contact points. Cardoso *et al.* [2005] (**structure**)

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- 4E10: 4E10 was investigated in differnt neutralization formats, including the standard format that measures activity over the entire infection period and several formats that emphasize various stages of infection. Neutralization by 4E10 in the standard format was undetectable, which changed to modest with the gp41 tail truncation and/or addition of a disulfide bridge linking gp120 and gp41. 4E10 was also able to neutralize in post-CD4 and post-CD4/CCR5 formats, suggesting that it binds Env trimers at various stages of infection. None of the analyzed HIV-1 + human plasmas neutralized in the post-CD4/CCR5 format indicating absence of 2F5 and 4E10 - like Abs. Crooks *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **assay standardization/improvement**)
- 4E10: 2F5 and 4E10 both bind to membrane proximal regions of gp41, and have long hydrophobic CDR3 regions characteristic of polyspecific autoreactive antibodies. Of 35 Env-specific MAbs tested, only 2F5 and 4E10 were found to be reactive with phospholipid cardiolipin. Vaccine induction of antibodies that react with these gp41 membrane proximal regions may be rare because of elimination due to autoantigen mimicry. 4E10 also reacted with systemic lupus erythematosis (SLE) autoantigen SS-A/Ro, and both 4E10 and 2F5 reacted with HEp-2 cells with diffuse cytoplasmic and nuclear patterns indicating polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)
- 4E10: This review summarizes data on the polyspecific reactivities to host antigens by the broadly neutralizing MAbs IgG1b12, 2G12, 2F5 and 4E10. It also hypothesizes that some broadly reactive Abs might not be routinely made because they are derived from B cell populations that frequently make polyspecific Abs and are thus subjected to B cell negative selection. Haynes *et al.* [2005b] (**antibody generation**, **antibody interactions**, **review**)
- 4E10: Why broadly neutralizing Abs, such as 2G12, 2F5 and 4E10, are extremely rare, and their protective abilities and potential role in immunotherapy are discussed. Jülg & Goebel [2005] (**neutralization**, **immunotherapy**, **review**)
- 4E10: A trimeric gp41 construct comprising the env transmembrane domain and the extracellular C-terminal region (gp41ctm) was incorporated into liposomes. 4E10 bound to the liposome-incorporated gp41ctm, indicating that its extracellular region is accessible to this Ab. Sera from mice immunized with either gp41ctm alone or with gp41ctm-liposome did not show any significant neutralization activity, indicating that the construct might not properly expose its 4E10 epitope. Lenz *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**)
- 4E10: Full-length gp160 clones were derived from acute and early human HIV-1 infections and used as env-pseudotyped viruses in neutralization assays for their characterization as neutralization reference agents. All 19 pseudotyped viruses were highly sensitive to neutralization by 4E10 as were the MN, SF162.LS and IIIB strains. All 12 Env-pseudotyped viruses were more sensitive to neutralization by 4E10 than their uncloned parental PBMC-grown viruses. Li *et al.* [2005a] (**neutralization**, **assay standardization/improvement**)
- 4E10: Pseudoviruses expressing HIV-1 envelope glycoproteins from BL01, BR07 and 89.6 strains were compared in neutralization assays to replication competent clone derived from transfection of 293T cells (IMC-293T) and to the IMC-293T derived from a single passage through PBMC (IMC-PBMC). The neutralization responses of pseudoviruses and corresponding IMC-293T to 4E10 were similar, while a significant decrease in viral neutralization sensitivity to 4E10 was observed for all three IMC-PBMC viruses. The decrease was associated with an increase in average virion envelope glycoprotein content on the PBMC-derived virus. Louder *et al.* [2005] (**neutralization**, **assay standardization/improvement**)
- 4E10: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**, **immunotherapy**)
- 4E10: This short review summarizes recent findings of the role of neutralizing Abs in controlling HIV-1 infection. Certain neutralizing MAbs and their potential role in immunotherapy and vaccination, as well as the reasons for their poor immunogenicity, are discussed. Montefiori [2005] (**antibody binding site definition and exposure**, **therapeutic vaccine**, **escape**, **immunotherapy**)
- 4E10: A short review of studies on 4E10 interaction with autoantigens, epitope accessibility, structure, and neutralizing capability. The reasons why 4E10 appears infrequently in nature are discussed. Nabel [2005] (**antibody binding site definition and exposure**, **antibody generation**, **neutralization**, **immunotherapy**, **review**)
- 4E10: Passive immunization of 8 HIV-1 infected patients with 4E10, 2F5 and 2G12 (day 0, 4E10; days 7, 14 and 21 4E10+2G12+2F5; virus isolated on days 0 and 77) resulted in 0/8 patients with virus that escaped all three NAbs. No viruses escaped 4E10, but only one virus in one patient had the NWFDIT epitope sequence; the W, F and I were conserved in all patients but the other amino acids varied both before and after treatment. A patient carrying the epitope sequence nwfSit had the least 4E10 sensitive virus. In a companion in vitro study, resistance to a single MAb emerged in 3-22 weeks, but triple combination resistance was slower and characterized by decreased viral fitness. In the core of the 4E10 epitope, NWFDIT, 5/11 cases had a T->I escape; 2/11 had a F->L change; and 2/11 had substantial deletions, of WNWF overlapping, or NWLWYI adjacent to the epitope. The lack of resistance to the combination of MAbs in vivo and the reduced fitness of the escape mutants selected in vitro suggests passive immunotherapy may be of value in HIV infection. Nakowitsch *et al.* [2005] (**escape**, **immunotherapy**)
- 4E10: Retrovirus inactivation for vaccine antigen delivery was

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explored through lipid modification by hydrophobic photoinduced alkylating probe 1.5 iodonaphthylazide (INA). The viral proteins were shown to be structurally intact in the treated non-infectious virus, through the preservation of antibody binding sites for polyclonal anti-gp120 serum, and for broadly neutralizing MAbs 2G12, b12 and 4E10, although the modifications of the lipid disabled viral infection. Raviv *et al.* [2005] (**vaccine antigen design**)

- 4E10: Escape mutations in HR1 of gp41 that confer resistance to Enfuvirtide reduced infection and fusion efficiency and also delayed fusion kinetics of HIV-1. The mutations also conferred increased neutralization sensitivity of virus to 4E10. Enhanced neutralization correlated with reduced fusion kinetics, indicating that the mutations result in Env proteins remaining in the CD4-triggered state for a longer period of time. Reeves *et al.* [2005] (**antibody binding site definition and exposure**, **drug resistance**, **neutralization**, **escape**, **HAART, ART**)
- 4E10: More that 90% of viruses from both acutely and chronically infected HIV-1 patients were inhibited by this Ab, however, viruses from acute patients were significantly more sensitive to 4E10 than viruses from chronic patients. The epitope of this Ab was highly conserved among all isolates tested suggesting that the higher susceptibility of acute viruses may be due to better epitope accessibility. The sensitivity of viruses to 4E10 was also highly correlated to their sensitivities to 2F5. Rusert *et al.* [2005] (**antibody binding site definition and exposure**, **antibody interactions**, **neutralization**, **acute/early infection**)
- 4E10: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **immunotherapy**, **review**, **structure**)
- 4E10: This review summarizes data on 447-52D and 2219 crystallographic structures when bound to V3 peptides and their corresponding neutralization capabilities. 4E10, like 447-52D and like other HIV-1 neutralizing Abs, was shown to have long CDR H3 loop, which is suggested to help Abs access recessed binding sites on the virus. Stanfield & Wilson [2005] (**antibody binding site definition and exposure**, **review**, **structure**)
- 4E10: Six acutely and eight chronically infected patients were passively immunized with a mix of 2G12, 2F5 and 4E10 neutralizing Abs during treatment interruption. Two chronically and four acutely infected individuals showed evidence of a delay in viral rebound during Ab treatment suggesting that NAbs can contain viremia in HIV-1 infected individuals. All subjects with virus sensitive to 2G12 developed Ab escape mutants resulting in loss of viremia and failure to treatment while no escape was observed for 4E10 and 2F5. Plasma levels of 2G12 were substantially higher than those of 2F5 and 4E10, and the 2G12 levels exceeded the in vitro required 90% inhibitory doses by two orders of magnitude in subjects that responded to Ab treatment. No such differences were observed for 2F5 or 4E10, suggesting that high levels of NAbs are required for inhibition in vivo, and that the in vivo concentrations of 4E10 and 2F5 might have been to low to control viremia and exert a selective pressure. Trkola *et al.* [2005] (**acute/early infection**, **escape**, **immunotherapy**, **HAART, ART**, **supervised treatment interruptions (STI)**)
- 4E10: Alanine scanning mutations of the 21 amino acid region between positions 660-680 showed only 3 substitutions that reduced 4E10 binding, positions lleldkwanlwnWFdisnwlW. No single Ala mutation was resistant to both 2F4 and 4E10. Ala substitutions in 11/20 positions enhanced neutralization sensitivity, LLeLdkWanLWNwfdIsNWLw. For peptides T20 and 4E10 neutralization was synergistic. Zwick *et al.* [2005] (**antibody binding site definition and exposure**, **escape**)
- 4E10: 93 viruses from different clades were tested for their neutralization cross-reactivity using a panel of HIV antibodies. 4E10 was the most cross-reactive, moderately reactive in all 93 viruses tested from each subtype. WFXI was defined as the core motif, and this core is highly conserved in all M group gp41 sequences. How potent the neutralizing activity is is somewhat context dependent. Binley *et al.* [2004] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 4E10; Neonatal rhesus macaques were exposed orally to a pathogenic SHIV, 89.6P. 4/8 were given an intramuscular, passive immunization consisting of NAbs 2G12, 2F5 and 4E10, each given at a different body sites at 40 mg/kg per Ab, at one hour and again at 8 days after exposure to 89.6P. The four animals that were untreated all died with a mean survival time of 5.5 weeks, the four animals that got the NAb combination were protected from infection. This model suggests antibodies may be protective against mother-to-infant transmission of HIV. Ferrantelli *et al.* [2004b] (**mother-to-infant transmission**)
- 4E10: Nabs against HIV-1 M group isolates were tested for their ability to neutralize 6 randomly selected HIV-1 O group strains. IgG1b12 could neutralize some O group strains when used on its own, and quadruple combination of b12, 2F5, 2G12, and 4E10, could neutralize the six Group O viruses tested between 62-97%. The linear epitope, NWFDIT, of 4E10 is conserved in 3/6 group O strains. Ferrantelli *et al.* [2004a] (**variant cross-recognition or cross-neutralization**)
- 4E10: This paper reviews MAbs that bind to HIV-1 Env. 4E10 binds to a region of gp41 proximal to cluster II (aa 662-676), neighboring the binding site of the broadly neutralizing MAb 2F5 and overlapping the epitope of neutralizing Fab Z13. 4E10 is the most broadly neutralizing MAb, neutralizing primary isolates from clades A, B, C, D, and CRF01 (E), although not the most potent. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 4E10: An antigen panel representing different regions of gp41 was generated, and sera from 23 individuals were screened. Anti-gp41 titers were very high, and sera bound to many regions of gp41, there were no immunologically silent regions. Many individuals had broad responses to diverse regions. High titer responses tended to focus on the N-heptad,

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C-heptad and 2F5-4E10 regions, but there was no correlation between neutralization capacity of sera and the particular peptides recognized. 4E10 responded to the three antigens that carried the minimal NWFNIT epitope, but was conformation and context sensitive. Opalka *et al.* [2004] (**assay development**, **assay standardization/improvement**)

- 4E10: A primary isolate, CC1/85, was passaged 19 times in PBMC and gradually acquired increased sensitivity to FAb b12 and sCD4 that was attributed to changes in the V1V2 loop region, in particular the loss of a potential glycosylation site. The affinity for sCD4 was unchanged in the monomer, suggesting that the structural impact of the change was manifested at the level of the trimer. The passaged virus, CCcon19, retained an R5 phenotype and its neutralization susceptibility to other Abs was essentially the same as CC1/85. The IC50 for 4E10 was greater than 50 for CCcon19, and was 44 for CC1/85, so the primary virus was weakly neutralized by 4E10. Pugach *et al.* [2004] (**variant cross-recognition or cross-neutralization**, **viral fitness and reversion**)
- 4E10: This review discusses research presented at the Ghent Workshop of prevention of breast milk transmission and immunoprophylaxis for HIV-1 in pediatrics (Seattle, Oct. 2002), and makes the case for developing passive or active immunoprophylaxis in neonates to prevent mother-to-infant transmission. Macaque studies have shown that passive transfer of NAb combinations (for example, IgG1b12, 2G12, 2F5, and 4E10) can confer partial or complete protection to infant macaques from subsequent oral SHIV challenge. Safrit *et al.* [2004] (**immunoprophylaxis**, **mother-to-infant transmission**)
- 4E10: The SOS mutant envelope protein introduces a covalent disulfide bond between gp120 surface and gp41 transmembrane proteins into the R5 isolate JR-FL by adding cysteines at residues 501 and 605. Pseudovirions bearing this protein bind to CD4 and co-receptor bearing cells, but do not fuse until treatment with a reducing agent, and are arrested prior to fusion after CD4 and co-receptor engagement. gp41 NAbs 2F5 and 4E10 are able to potently neutralize the SOS pseudovirion post-attachment. Binley *et al.* [2003] (**vaccine antigen design**)
- 4E10: Four newborn macaques were challenged with pathogenic SHIV 89.6 and given post exposure prophylaxis using a combination of NAbs 2F5, 2G12, 4E10 and IgG1b12. 2/4 treated animals did not show signs of infection, and 2/4 macaques maintained normal CD4+ T cell counts and had a lower delayed peak viremia compared to the controls. Ferrantelli *et al.* [2003] (**antibody interactions**, **immunoprophylaxis**, **mother-to-infant transmission**)
- 4E10: Porcine endogenous retroviruses (PERVS) are a concern in the context of porcine xenotransplantation into humans; possible strategies for protection include PERV knockout animals or vaccines. Goats immunized with the PERV transmembrane protein revealed two NAb epitope, E1 and E2. E2's epitope (FEGWFN) binds to a sequence that is perfectly preserved in all PERVS and highly conserved in all gammaretroviruses: MuLV carries FEGLFN, FeLV FEGWFN, and it shares three amino acids with the core epitope for the anti-HIV human neutralizing MAb 4E10, (LWNWFN). Fiebig *et al.* [2003]
- 4E10: MAbs IgG1b12, 2G12, 2F5 and 4E10 were tested for their ability to neutralize two primary HIV-1 clade A isolates (UG/92/031 and UG/92/037) and two primary HIV-1 clade D isolates (UG/92/001 and UG/92/005). 4E10 demonstrated the most potent cross-neutralization activity. Quadruple administration of MAbs IgG1b12, 2G12, 2F5, and 4E10 induced strong synergistic neutralization of 4 clade A isolates (UG/92/031, UG/92/037, RW/92/020 and RW/92/025) as well as 5 clade D isolates (UG/92/001,UG/9/005, /93/086/RUG/94/108, UG/94/114). The authors note this combination of 4 MAbs neutralizes primary HIV A, B, C, and D isolates. Kitabwalla *et al.* [2003] (**antibody interactions**, **immunoprophylaxis**, **variant cross-recognition or cross-neutralization**, **mother-to-infant transmission**, **subtype comparisons**)
- 4E10: Review of current neutralizing antibody-based HIV vaccine candidates and strategies of vaccine design. Strategies for targeting of the epitopes for NAbs 2F5, 2G12, 4E10, b12, and Z13 are described. Wang [2003] (**vaccine antigen design**, **review**)
- 4E10: Review of NAbs illustrating gp41's conformational change and exposure of the 4E10/Z13 epitope in the transient pre-hairpin form. Ferrantelli & Ruprecht [2002] (**antibody binding site definition and exposure**)
- 4E10: Passive immunization of neonate macaques with a combination of F105+2G12+2F5 conferred complete protection against oral challenge with SHIV-vpu+ —the combination b12+2G12+2F5 conferred partial protection against SHIV89.6—such combinations may be useful for prophylaxis at birth and against milk born transmission—the synergistic combination of IgG1b12, 2G12, 2F5, and 4E10 neutralized a collection of HIV clade C primary isolates. Xu *et al.* [2002] (**antibody interactions**, **immunoprophylaxis**, **subtype comparisons**)
- 4E10: 4E10 binds proximal to 2F5 and neutralizes primary isolates of clades A, B, C, D, and E. Viruses that were resistant to 2F5 were neutralized by 4E10 and vice versa. Stiegler *et al.* [2001] (**antibody binding site definition and exposure**)
- 4E10: Twenty HIV clade C isolates from five different countries were susceptible to neutralization by anti-clade B MAbs in a synergistic quadruple combination of mAbs IgG1b12, 2G12, 2F5, and 4E10. Xu *et al.* [2001] (**antibody interactions**, **subtype comparisons**)
- 4E10: MAbs 4E10 and Z13 both bind proximally to 2F5 to a conserved linear epitope that has some conformational aspects – both bind to MN virions, bind weakly to infected cells in a manner that is not disrupted by sCD4 and neutralize some primary isolates from clades B, C, and E – maps minimal 4E10 epitope to NWFDIT, contrary to an earlier report – different strains were refractive to neutralization by broadly neutralizing Abs IgG1b12, 2F5, Z13 and 4E10. Zwick *et al.* [2001b] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 4E10: Neutralization synergy between anti-HIV NAbs b12, 2G12, 2F5, and 4E10 was studied – a classic fixed-ratio method was used, as well as a method where one Ab was fixed at a low neutralization titer and the other was varied – using primary isolates, a two-four fold enhancement of neutralization was observed with MAb pairs, and a ten-fold enhance-

ment with a quadruple Ab combination – no synergy was observed with any MAb pair in the neutralization of TCLA strain HXB2. Zwick *et al.* [2001c] (**antibody interactions**)

- 4E10: MAbs generated by hybridoma, electrofusion of PBL from HIV-1 + volunteers with CB-F7 heteromyeloma cells – also binds to MHC class II proteins – anti-class II Abs are only found in HIV-1 positive people – this paper maps 4E10's binding site to AEGTDRV, gp160(823-829), but the later Zwick *et al.* study in 2001 revised the epitope location. Buchacher *et al.* [1994] (**antibody binding site definition and exposure**, **antibody generation**)
- 4E10: Included in a multi-lab study for antibody characterization, binding and neutralization assay comparison. D'Souza *et al.* [1994] (**variant cross-recognition or cross-neutralization**)

No. 792
MAb ID Z13
HXB2 Location gp160 (671–676)
Author Location gp41 (671–676 MN)
Epitope `NWFDIT`
Subtype B
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type C-term, gp41 MPER (membrane proximal external region)
References Zhang *et al.* 2008; Penn-Nicholson *et al.* 2008; Kanduc *et al.* 2008; Crooks *et al.* 2008; Phogat *et al.* 2007; Lin & Nara 2007; Kramer *et al.* 2007; Huber & Trkola 2007; Zhang *et al.* 2006a; Yuste *et al.* 2006; Zhang & Dimitrov 2007; Cham *et al.* 2006; Nelson *et al.* 2007; Moore *et al.* 2006; Luo *et al.* 2006; Dong & Chen 2006; Srivastava *et al.* 2005; Mc Cann *et al.* 2005; Gorny & Zolla-Pazner 2004; Wang 2003; Ferrantelli & Ruprecht 2002; Zwick *et al.* 2001b
Keywords antibody binding site definition and exposure, antibody generation, binding affinity, neutralization, review, SIV, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- Z13: The study compared Ab neutralization against the JR-FL primary isolate and trimer binding affinities judged by native PAGE. There was direct quantitative relationship between monovalent Fab-trimer binding and neutralization, implying that neutralization begins as each trimer is occupied by one Ab. In BN-PAGE, neutralizing Fabs, Z13 in particular, and sCD4 were able to shift JR-FL trimers. In contrast, most non-neutralizing Fabs bound to monomer, but their epitopes were conformationally occluded on trimers, confirming the exclusive relationship of trimer binding and neutralization. Crooks *et al.* [2008] (**neutralization**, **binding affinity**)
- Z13: Similarity level of the Z13 binding site pentapeptide NWFDI to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 1 time, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- Z13: For assessment of gp41 immunogenic properties, five soluble GST-fusion proteins encompassing C-terminal 30, 64, 100, 142, or 172 (full-length) amino acids of gp41 ectodomain were generated from M group consensus env sequence. Plasma from 5 of 44 HIV-1 infected individuals reacted with a peptide that binds Z13, indicating that these patients mounted Z13-like Ab response. Penn-Nicholson *et al.* [2008]
- Z13: The newly detected mAb m44 was shown to neutralize a panel of primary HIV-1 isolates with higher potency than Fab Z13. In binding assays, Z13 did not bind to 5Hb region, but did bind the 6HB with the same potency as m44. Z13 did not compete with m44 for binding. A fusion protein of gp41 constructed for alanine-scanning mutagenesis bound to Z13, indicating that its antigenic structure was intact. Zhang *et al.* [2008] (**neutralization**)
- Z13: This review summarizes current knowledge on the various functional properties of antibodies in HIV-1 infection, including Z13 mAb, in vivo and in vitro activity of neutralizing Abs, the importance and downfalls of non-neutralizing Abs and antibodies that mediate antibody-dependent cellular cytotoxicity and the complement system, and summarizes data on areas tht need future investigation on Ab-mediated immune control. Huber & Trkola [2007] (**review**)
- Z13: This review summarizes Z13 Ab epitope, properties and neutralization activity. Kramer *et al.* [2007] (**review**)
- Z13: Z13 structure, binding, neutralization, and strategies that can be used for vaccine antigen design to elicit anti-gp41 Abs, are reviewed in detail. Lin & Nara [2007] (**review**)
- Z13: Z13e1, a high affinity variant of Fab Z13, was identified through targeted mutagenesis and affinity selection against gp41 and an MPER peptide. Z13e1 showed 100-fold improvement in binding affinity for MPER antigens over Z13, and improved neutralization potency against sensitive HIV-1. Alanine scanning revealed that N671 and D674 residues are crucial for peptide recognition and neutralization of HIV-1 by this Fab. Z13e1 was shown to bind with high affinity to an epitope overlapping those of 2F5 and 4E10 with the minimal epitope WASLWNWFDITN, indicating that the limited neutralization potency results from the limited access to the epitope within the envelope trimer. Nelson *et al.* [2007] (**variant cross-recognition or cross-neutralization**)
- Z13: This review provides information on the HIV-1 glycoprotein properties that make it challenging to target with neutralizing Abs. Z13 neutralization properties and binding to HIV-1 envelope, and current strategies to develop versions of the Env spike with functional trimer properties for elicitation of broadly neutralizing Abs, are discussed. In addition, approaches to target cellular molecules, such as CD4, CCR5, CXCR4, and MHC molecules, with therapeutic Abs are reviewed. Phogat *et al.* [2007] (**review**)
- Z13: Novel approaches based on sequential (SAP) and competitive (CAP) antigen panning methodologies, and use of antigens with increased exposure of conserved epitopes, for enhanced identification of broadly cross-reactive neutralizing Abs are reviewed. Previously known broadly neutralizing human mAbs are compared to Abs identified by these methods. Zhang & Dimitrov [2007] (**review**)

- Z13: This Ab was shown to infrequently neutralize cloned Envs (clades A, B, C, D, F1, CRF01_AE, CRF02_AG, CRF06_cpx and CRF11_cpx) derived from donors with and without broadly cross-reactive neutralizing antibodies. Cham *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- Z13: Genetic variability and co-variation of the mAb 2F5, 4E10 and Z13 epitopes in B and non B clades was investigated. A significant shift in the predominant sequence patterns over time was observed for all three epitopes. Also, significant inter-subtype genetic variability of the three epitopes was detected. However, the 4E10 epitope displayed a more similar variability within B clade and non-B clades, concurring with the cross-clade neutralizing activity of this mAb. Epitope co-variation was also noted, as one third of the recently isolated HIV-1 strains displayed simultaneous epitope variants. Dong & Chen [2006] (**antibody binding site definition and exposure**, **subtype comparisons**)
- Z13:gp41 and p15E of the porcine endogenous retrovirus (PERV) share structural and functional similarities, and epitopes in the membrane proximal region of p15E are able to elicit NAbs upon immunization with soluble p15E. Rabbits immunized with a VSV recombinant expressing an HIV-1 membrane-proximal external region (MPER) fused to PERV p15E, with a fusion p15E-HIV MPER protein boost, elicited HIV specific NAbs. The MPER contains the Z13 epitope. Luo *et al.* [2006] (**vaccine antigen design**)
- Z13: In addition to gp120-gp41 trimers, HIV-1 particles were shown to bear nonfunctional gp120-gp41 monomers and gp120-depleted gp41 stumps on their surface. Z13 is able to recognize both gp120-gp41 trimers and monomers, as well as trimeric and monomeric gp41 stumps. Z13 failed to bind to VLPs before treatment with detergent but did after the treatment, suggesting that Z13 epitope becomes fully available only after the Env trimers are liberated by detergent. Moore *et al.* [2006] (**antibody binding site definition and exposure**)
- Z13: Epitope recognition sequences for Abs 2F5 and 4E10 were introduced into the corresponding region of SIVmac239. SIVmac239/4E10 and SIVmac239/2F5 were not neutralized by Z13 in spite of the overlap of Z13 and 4E10 sequences. Yuste *et al.* [2006] (**neutralization**, **SIV**)
- Z13: Competition of free gp120 89.6 with immobilized gp140 89.6 for binding to Z13 was assesed. The binding of this Ab to coated gp140 was decreased at the highest concentration of gp120. Neutralizing activity of Z13 against a panel of HIV-1 primary isolates from different clades was assessed in a PBMC-assay. The neutralizing activity was shown to be less potent than that of the newly characterized m48 MAb. Zhang *et al.* [2006a] (**neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)
- Z13: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **review**)
- Z13: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **review**)
- Z13: This paper reviews MAbs and Fabs that bind to HIV-1 Env. Z13 binds to a region of gp41 proximal to cluster II (aa 662-676), neighboring the binding site of the broadly neutralizing MAb 2F5 and overlapping the epitope of neutralizing MAb 4E10. Z13 is broadly neutralizing, neutralizing primary isolates from clades A, B, C, D and CRF01 (E). Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure**, **review**)
- Z13: Review of current neutralizing antibody-based HIV vaccine candidates and strategies of vaccine design. Strategies for targeting of the epitopes for NAbs 2F5, 2G12, 4E10, b12, and Z13 are described. Wang [2003] (**vaccine antigen design**, **review**)
- Z13: Review of NAbs that notes Z13 is a phage display generated FAb fragment from a B clade infected individual and that illustrates gp41's conformational change and exposure of the 4E10/Z13 epitope in the transient pre-hairpin form. Ferrantelli & Ruprecht [2002] (**antibody binding site definition and exposure**, **antibody generation**)
- Z13: MAb 4E10 and FAb Z13 both bind proximally to 2F5 to a relatively conserved linear epitope that has some conformational aspects – both bind to MN virions, bind weakly to infected cells in a manner that is not disrupted by sCD4 and can neutralize some primary isolates from clades B, C, and E – Z13 was selected using a phage display library with the MN gp41 peptide LLELDKWASLWNWFDITNWSW from an HIV infected donor who had an exceptionally broad NAb response – different strains were refractive to neutralization by broadly neutralizing Abs IgG1b12, 2F5, Z13 and 4E10 – epitope location noted here is by analogy to MAb 4E10. Zwick *et al.* [2001b] (**antibody binding site definition and exposure**, **antibody generation**, **variant cross-recognition or cross-neutralization**)

No.	793
MAb ID	B30
HXB2 Location	gp160 (720–734)
Author Location	gp41 (720–734 BH10)
Epitope	`HLPIPRGPDRPEGIE`
Neutralizing	
Immunogen	vaccine *Vector/Type:* protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype)	mouse (IgG1)
Research Contact	George Lewis
References	Abacioglu *et al.* 1994

B Cell

- B30: Epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

No. 794
MAb ID polyclonal
HXB2 Location gp160 (724–745)
Author Location gp41 (731–752)
Epitope PRGPDRPEGIEEEGGERDRDRS
Neutralizing
Immunogen vaccine
Vector/Type: Cowpea mosaic virus *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse (IgA, IgG2a)
References Durrani *et al.* 1998

- Comparison of intranasal and oral immunization of HIV-1 peptide expressed in a plant viral vector – intranasal gave the better response. Durrani *et al.* [1998]

No. 795
MAb ID 41S-2
HXB2 Location gp160 (725–745)
Author Location gp160 (732–750)
Epitope RGPDRPEGIEEEGGERDRDRS
Neutralizing yes
Immunogen vaccine
Vector/Type: peptide keyhole limpet hemocyanin (KLH) conjugate *HIV component:* gp41
Species (Isotype) mouse (IgG2bκ)
References Hifumi *et al.* 2003; Hifumi *et al.* 2002; Hifumi *et al.* 2000b; Hifumi *et al.* 2000a
Keywords anti-idiotype, antibody sequence variable domain

- 41S-2: A murine Ab called i41SL1-2 was raised against the complementary determining region of the 41S-2 light chain, CRDL-1 (RSSKSLLYSNGNTYLY). As with 41S-2-L, the light chain of i41SL1-2 also had catalytic activity and degraded the immunizing peptide, initially cleaving between the Arg1 and Ser2. i41SL1-2 did not cross-react with gp41 peptide, gp120 V3 loop peptide and bound weakly to 41S-2-L.i41SL1-2 shows homology to the anti-VIP Ab (VIP, vasoactive intestinal peptide) that also has peptidase character. Both light chains contain a catalytic triad composed of Asp, Ser, and His (for i41SL1-2: Asp73, Ser 76 or Ser70 and His 79). Intact i41SL1-2 was unable to degrade CDRL-1, possibly due to an immobile inactive conformation of the catalytic triad. Hifumi *et al.* [2003] (**anti-idiotype**, **antibody sequence variable domain**)
- 41S-2: 41S-2-L refers to the light chain of 41S-2, which can enzymatically decompose the gp41 protein of HIV-1, but doesn't degrade unrealted proteins. The peptide RGPDRPEGIEEEGGERDRDRS, against which the MAb was raised, can also be cleaved, initially between Glu12-Gly13, followed by successive cleavage reactions. Hifumi *et al.* [2002]
- 41S-2: BALBc mice were immunized with gp41 peptide and a MAb specific for the peptide was generated – isolated MAb light chains displayed proteolytic activity toward the peptide epitope which may be due to a catalytic triad on light chain (Asp73, Ser76, and His79) – no catalytic activity was observed for the whole antibody. Hifumi *et al.* [2000a]
- 41S-2: The complementary determining region of 41S-2-L, the light chain of 41S-2, is strongly involved in gp41 recognition. This light chain can serve as a molecular catalyst for gp41 degredation. Hifumi *et al.* [2000b]

No. 796
MAb ID C8
HXB2 Location gp160 (727–732)
Author Location gp41 (727–732 BH10)
Epitope PDRPEG
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG1)
Ab Type C-term
References Heap *et al.* 2005a; Dimmock 2005; McLain *et al.* 2001; Abacioglu *et al.* 1994; Pincus *et al.* 1993; Pincus & McClure 1993
Keywords review

- C8: This review summarizes the complex antigenic properties of an external loop in the gp41 tail (spanning the Kennedy sequence), highlighting specific MAbs. C8 binds to the epitope PDRPEG and does not neutralize virus. Dimmock [2005] (**review**)
- C8: Unlike SAR1, a MAb that binds near the C8 epitope within the Kennedy peptide, C8 cannot inhibit fusion between HIV-1 infected and target cells. C8 recognizes PDRPEG on the surface of HIV-1 infected cells, but not on virions and is non-neutralizing. Heap *et al.* [2005a]
- C8: The substitution 725 RG (P[R–>G]GPDRPEGIEEEGGERDRDRS) alters the antigenic exposure of this region on the virion resulting in the loss of the downstream neutralizing epitope ERDRD, increased exposure of the epitope GPDRPEG in the virion, while the epitope IEEE remains unchanged. McLain *et al.* [2001]
- C8: Epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]
- C8: Immunotoxin of C8 coupled to ricin-A does not mediate cells killing, and is not affected by sCD4. Pincus & McClure [1993]
- C8: Ab response in IIIB lab workers was compared to gp160 LAI vaccine recipients – C8 was used as a control – the dominant response among vaccinees was to this mid-gp41 region, but not among the infected lab workers – Abs binding this region do not neutralize, bind to infected cells, nor serve as immunotoxins. Pincus *et al.* [1993]

No. 797
MAb ID B31
HXB2 Location gp160 (727–734)
Author Location gp41 (727–734 BH10)
Epitope PDRPEGIE
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG1)
References Abacioglu *et al.* 1994

B Cell

- B31: Epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

No. 798
MAb ID B33
HXB2 Location gp160 (727–734)
Author Location gp41 (727–734 BH10)
Epitope PDRPEGIE
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43 *HIV component:* gp160
Species (Isotype) mouse (IgG1)
References Bristow *et al.* 1994; Abacioglu *et al.* 1994

- B33: Epitope boundaries mapped by peptide scanning IgG1. Abacioglu *et al.* [1994]
- B33: There are two MAbs in the literature named B33, see also gp120, positions 123-142 – MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp160 IIIB:NL43, MicroGenSys. Bristow *et al.* [1994]

No. 799
MAb ID 1576
HXB2 Location gp160 (728–745)
Author Location gp41 (735–752 IIIB)
Epitope DRPEGIEEEGGERDRDRS
Neutralizing no
Immunogen vaccine
Vector/Type: poliovirus *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse
References Vella *et al.* 1993

- 1576: Not neutralizing. Vella *et al.* [1993]

No. 800
MAb ID 1578
HXB2 Location gp160 (728–745)
Author Location gp41 (735–752 IIIB)
Epitope DRPEGIEEEGGERDRDRS
Neutralizing no
Immunogen vaccine
Vector/Type: poliovirus *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse
References Vella *et al.* 1993; Evans *et al.* 1989

- 1578: Core epitope: IEEE – in this study, neutralized IIIB, but not RF or MN. Vella *et al.* [1993]
- 1578: No neutralizing activity – epitope may be formed by regions from both poliovirus and HIV. Evans *et al.* [1989]

No. 801
MAb ID 1579
HXB2 Location gp160 (728–745)
Author Location gp41 (735–752 IIIB)
Epitope DRPEGIEEEGGERDRDRS
Neutralizing no
Immunogen vaccine
Vector/Type: poliovirus *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse
References Vella *et al.* 1993

- 1579: Core epitope: IEEE – neutralized IIIB, but not RF or MN. Vella *et al.* [1993]

No. 802
MAb ID 1583
HXB2 Location gp160 (728–745)
Author Location gp41 (735–752 IIIB)
Epitope DRPEGIEEEGGERDRDRS
Neutralizing no
Immunogen vaccine
Vector/Type: poliovirus *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse
References Heap *et al.* 2005a; Dimmock 2005; Sattentau *et al.* 1995; Vella *et al.* 1993; Evans *et al.* 1989
Keywords review

- 1583: This review summarizes the complex antigenic properties of an external loop in the gp41 tail (Kennedy sequence), highlighting specific MAbs. 1577 and 1583 bind to the epitope ERDRD and do not neutralize virus. Dimmock [2005] (**review**)
- 1583: Unlike SAR1, a MAb that binds near the 1583 epitope within the Kennedy peptide, 1583 cannot inhibit fusion between HIV-1 infected and target cells. 1583 and 1577 neturalize only in the presence of complement. Heap *et al.* [2005a]
- 1583: Suggested to bind to a cytoplasmic domain, epitope not exposed at the surface of HIV-1 infected cells. Sattentau *et al.* [1995]
- 1583: Core epitope: ERDRD – Could neutralize HIV IIIB but not HIV RF. Vella *et al.* [1993]
- 1583: Neutralizing activity, less broad than 1577. Evans *et al.* [1989]

No. 803
MAb ID 1899
HXB2 Location gp160 (728–745)
Author Location gp41 (735–752 IIIB)
Epitope DRPEGIEEEGGERDRDRS
Neutralizing no
Immunogen vaccine
Vector/Type: poliovirus *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse
References Vella *et al.* 1993

- 1899: Could neutralize HIV IIIB and HIV RF. Vella *et al.* [1993]

No. 804
MAb ID 1907
HXB2 Location gp160 (728–745)
Author Location gp41 (735–752 IIIB)
Epitope DRPEGIEEEGGERDRDRS
Neutralizing no
Immunogen vaccine
Vector/Type: poliovirus *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse

B Cell

References Vella *et al.* 1993

- 1907: Could not neutralize HIV IIIB, RF or MN. Vella *et al.* [1993]

No. 805
MAb ID 1908
HXB2 Location gp160 (728–745)
Author Location gp41 (735–752 IIIB)
Epitope DRPEGIEEEGGERDRDRS
Neutralizing no
Immunogen vaccine
Vector/Type: poliovirus *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse
References Sattentau *et al.* 1995; Vella *et al.* 1993; Evans *et al.* 1989

- 1908: Cytoplasmic domain, epitope not exposed at the surface of HIV-1 infected cells. Sattentau *et al.* [1995]
- 1908: Neutralized IIIB, but not RF or MN. Vella *et al.* [1993]

No. 806
MAb ID 1909
HXB2 Location gp160 (728–745)
Author Location gp41 (735–752 IIIB)
Epitope DRPEGIEEEGGERDRDRS
Neutralizing no
Immunogen vaccine
Vector/Type: poliovirus *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse
References Vella *et al.* 1993

- 1909: Neutralized HIV IIIB but not HIV RF. Vella *et al.* [1993]

No. 807
MAb ID 41-1
HXB2 Location gp160 (728–745)
Author Location gp41 (735–752 IIIB)
Epitope DRPEGIEEEGGERDRDRS
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse (IgMκ)
References Dalgleish *et al.* 1988; Mani *et al.* 1994

- 41-1: This antibody gp41(735-752 IIIB) Dalgleish *et al.* [1988] seems to have been named the same as a different MAb to gp41(584-609) Mani *et al.* [1994]. Dalgleish *et al.* [1988]; Mani *et al.* [1994]
- 41-1: Neutralizes HIV-1 but not HIV-2 strains. Dalgleish *et al.* [1988]

No. 808
MAb ID 41-2
HXB2 Location gp160 (728–745)
Author Location gp41 (735–752 IIIB)
Epitope DRPEGIEEEGGERDRDRS
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse (IgMκ)
References Dalgleish *et al.* 1988

- 41-2: Neutralizes HIV-1 but not HIV-2 strains. Dalgleish *et al.* [1988]

No. 809
MAb ID 41-3
HXB2 Location gp160 (728–745)
Author Location gp41 (735–752 IIIB)
Epitope DRPEGIEEEGGERDRDRS
Neutralizing no
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse (IgMκ)
References Dalgleish *et al.* 1988

- 41-3: Neutralizes HIV-1 but not HIV-2 strains. Dalgleish *et al.* [1988]

No. 810
MAb ID ED6
HXB2 Location gp160 (728–745)
Author Location gp41 (735–752 IIIB)
Epitope DRPEGIEEEGGERDRDRS
Neutralizing no
Immunogen
Species (Isotype) mouse (IgM)
References Evans *et al.* 1989

No. 811
MAb ID LA9 (121-134)
HXB2 Location gp160 (728–745)
Author Location gp41 (735–752 IIIB)
Epitope DRPEGIEEEGGERDRDRS
Neutralizing no
Immunogen
Species (Isotype) mouse (IgM)
References Evans *et al.* 1989

No. 812
MAb ID 1575
HXB2 Location gp160 (728–745)
Author Location gp41 (735–752 IIIB)
Epitope DRPEGIEEEGGERDRDRS
Neutralizing no
Immunogen vaccine
Vector/Type: poliovirus *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse
Ab Type C-term
Research Contact C. Vella, NIBSC, Potters Bar UK
References Heap *et al.* 2005a; Dimmock 2005; Cleveland *et al.* 2000a; Buratti *et al.* 1997; Vella *et al.* 1993; Evans *et al.* 1989
Keywords review

B Cell

- 1575: This review summarizes the complex antigenic properties of an external loop in the gp41 tail (Kennedy sequence), highlighting specific MAbs. 1575 is noted to bind to the epitope IEEE and does not neutralize virus. Dimmock [2005] (**review**)
- 1575: Unlike SAR1, a MAb that binds near the 1575 epitope within the Kennedy peptide, 1575 cannot inhibit fusion between HIV-1 infected and target cells. Heap *et al.* [2005a]
- 1575: Ab binding to IEEE suppresses neutralizing Ab binding to adjacent epitope ERDRD. Cleveland *et al.* [2000a]
- 1575: Study shows that MAb 1575 can recognize the IEEE sequence in both gp41, and in the HPG30 region of the p17 protein – motif is conserved in both regions in different HIV-1 clades. Buratti *et al.* [1997]
- 1575: Core epitope: IEEE – neutralized IIIB, but not RF or MN. Vella *et al.* [1993]
- 1575: Neutralizing activity, less broad than 1577. Evans *et al.* [1989]

No. 813
MAb ID 88-158/02
HXB2 Location gp160 (732–747)
Author Location gp41 (732–752 IIIB)
Epitope `GIEEEGGERDRDRSIR`
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse (IgG2b)
References Niedrig *et al.* 1992a

- 88-158/02: Mild inhibition of *in vitro* activity at high MAb concentrations – profound enhancing activity at low concentrations – significant reactivity to virion – domain non-immunogenic in humans. Niedrig *et al.* [1992a]

No. 814
MAb ID 88-158/022
HXB2 Location gp160 (732–747)
Author Location gp41 (732–752 IIIB)
Epitope `GIEEEGGERDRDRSIR`
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse (IgG2b)
References Niedrig *et al.* 1992a

- 88-158/022: Mild inhibition of *in vitro* activity at high MAb concentrations – profound enhancing activity at low concentrations – significant reactivity to virion – domain non-immunogenic in humans. Niedrig *et al.* [1992a]

No. 815
MAb ID 88-158/079
HXB2 Location gp160 (732–747)
Author Location gp41 (732–752 IIIB)
Epitope `GIEEEGGERDRDRSIR`
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse (IgG1)
References Niedrig *et al.* 1992a

- 88-158/079: Mild inhibition of HIV *in vitro* at high MAb concentrations – profound enhancing activity at low concentrations – weak binding to virion – domain non-immunogenic in humans. Niedrig *et al.* [1992a]

No. 816
MAb ID polyclonal
HXB2 Location gp160 (733–736)
Author Location gp41 (735–752 IIIB)
Epitope `IEEE`
Neutralizing L
Immunogen vaccine
Vector/Type: Cowpea mosaic virus *HIV component:* gp41
Species (Isotype) mouse (IgG)
Ab Type C-term
References McLain *et al.* 2001; Cleveland *et al.* 2000b

- The substitution 725 RG (P[R–>G]GPDRPEGIEEEGGERDRDRS) alters the antigenic exposure of this region on the virion resulting in the loss of the downstream neutralizing epitope ERDRD, increased exposure of the epitope GPDRPEG in the virion, while the epitope IEEE remains unchanged. McLain *et al.* [2001]
- When PRGPDRPEGIEEEGGERDRDRS was used as antigen an immunodominant, non-neutralizing response to IEEE was observed, but immunization GERDRDR shifts the response to ERDRD. Cleveland *et al.* [2000b]

No. 817
MAb ID polyclonal
HXB2 Location gp160 (733–736)
Author Location gp41 (735–752 NL43)
Epitope `IEEE`
Neutralizing L
Immunogen vaccine
Vector/Type: Cowpea mosaic virus *HIV component:* gp41
Species (Isotype) mouse (IgG)
Ab Type C-term
References McLain *et al.* 2001

- The substitution 725 RG (P[R–>G]GPDRPEGIEEEGGERDRDRS) alters the antigenic exposure of this region on the virion resulting in the loss of the downstream neutralizing epitope ERDRD, increased exposure of the epitope GPDRPEG in the virion, while the epitope IEEE remains unchanged. McLain *et al.* [2001]

No. 818
MAb ID B8
HXB2 Location gp160 (733–741)
Author Location gp41 (733–741 BH10)
Epitope `IEEEGGERD`
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI *HIV component:* gp160
Species (Isotype) mouse (IgG1)
References Abacioglu *et al.* 1994; Pincus *et al.* 1993

B Cell

- B8: Epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]
- B8: Ab response in IIIB lab workers was compared to gp160 LAI vaccine recipients – B8 was used as a control – the dominant response among vaccinees was to this mid-gp41 region, but not among the infected lab workers – Abs binding this region do not neutralize, bind to infected cells, nor serve as immunotoxins. Pincus *et al.* [1993]

No. 819
MAb ID SAR1
HXB2 Location gp160 (738–744)
Author Location gp41 (735–752 IIIB)
Epitope GERDRDR
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: Cowpea mosaic virus *HIV component:* gp41
Species (Isotype) mouse (IgG2aκ)
Ab Type C-term
References Heap *et al.* 2005a; Dimmock 2005
Keywords antibody binding site definition and exposure, review

- SAR1: This ERDRD-specific MAb recognizes an externalized loop of the gp41 C-terminal domain, and can reduce the yield of infectious progeny and inhibit fusion post-attachment, but not neutralize free virus. Dimmock [2005] (**review**)
- SAR1: This paper confirms the post-attachment neutralization (PAN) activity of this gp41 C-terminal tail-specific Ab – cell fusion between infected and uninfected cells is inhibited and is temperature dependent. This MAb does not neutralize free virus, and due to PAN activity, is considered to bind an epitope on the external surface of the membrane. The SAR1 epitope is exposed optimally after infected and non-infected cells have attached, prior to fusion. sCD4 binding does not enhance binding of SAR1. MAbs to adjacent epitopes do not have PAN activity. Heap *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 820
MAb ID 1577 (735-752)
HXB2 Location gp160 (739–743)
Author Location gp41 (735–752 IIIB)
Epitope ERDRD
Neutralizing no
Immunogen vaccine
Vector/Type: poliovirus *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse
Ab Type C-term
Research Contact C. Vella or Morag Ferguson (NIBSC, Potters Bar UK)
References Teeraputon *et al.* 2005; Holl *et al.* 2006a; Heap *et al.* 2005a; Dimmock 2005; Cleveland *et al.* 2000a; Vella *et al.* 1993; D'Souza *et al.* 1991; Evans *et al.* 1989
Keywords dendritic cells, neutralization, review

- 1577: UK Medical Research Council AIDS reagent: ARP317.
- 1577: NIH AIDS Research and Reference Reagent Program: 1172.
- 1577: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication occurs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 1577: This review summarizes the complex antigenic properties of an external loop in the gp41 tail (Kennedy sequence), highlighting specific MAbs. 1577 and 1583 bind to the epitope ERDRD and do not neutralize virus. Dimmock [2005] (**review**)
- 1577: Unlike SAR1, a MAb that binds near the 1577 epitope within the Kennedy peptide, 1577 cannot inhibit fusion between HIV-1 infected and target cells. Heap *et al.* [2005a]
- 735-752: A T-cell line adapted strain (TCLA) of CRF01_AE primary isolate DA5 (PI) was equally neutralization sensitive to 735-752 as the primary isolate. Mutant virus derived from the CRF01_AE PI strain, that lacked N-linked glycosylation at position 197 in the C2 region of gp120, was significantly more sensitive then the PI strain to neutralization by V3, CD4bs and CD4i MAbs but not to neutralization by 735-752. Teeraputon *et al.* [2005] (**neutralization**)
- 1577: Ab binding to IEEE suppresses neutralizing Ab binding to adjacent epitope ERDRD. Cleveland *et al.* [2000a]
- 1577: Core epitope: ERDRD – could neutralize HIV IIIB and HIV RF. Vella *et al.* [1993]
- 1577: Non-neutralizing in this multi-lab study. D'Souza *et al.* [1991]
- 1577: Raised against IIIB peptide chimera – neutralized African and American HIV-1 lab strains. Evans *et al.* [1989]

No. 821
MAb ID polyclonal (EPES)
HXB2 Location gp160 (739–743)
Author Location gp41 (735–752 IIIB)
Epitope ERDRD
Subtype B
Neutralizing L
Immunogen vaccine
Vector/Type: Cowpea mosaic virus *HIV component:* gp41
Species (Isotype) mouse (IgG1, IgG2a, IgG2b)
Ab Type C-term
References Dimmock 2005; McLain *et al.* 2001; Cleveland *et al.* 2000b
Keywords review

- ERDRD-specific IgG recognizes an externalized loop of the gp41 C-terminal domain, and these polyclonal antibodies are the only ones known to bind to this domain that can neutralize cell-free virus. This paper calls these antibodies EPES for Epitope Purified and ERDRD specific. Dimmock [2005] (**review**)
- The substitution 725 RG (P[R–>G]GPDRPEGIEEEGGERDRDRS) alters the antigenic exposure of this region on the virion resulting in the loss of the downstream neutralizing epitope ERDRD, increased exposure of the epitope GPDRPEG in the virion, while the epitope IEEE remains unchanged. McLain *et al.* [2001]

B Cell

- ERDRD-specific IgG recognizes an externalized loop of the gp41 C-terminal tail with high affinity – neutralized HIV-1 B clade strains IIIB, NL-4.3, RF, MN and D clade virus CBL-4, but HXB-2D (clade B) was not recognized – when PRGP-DRPEGIEEEGGERDRDRS was used as antigen an immunodominant, non-neutralizing response to IEEE was observed, but immunization GERDRDR shifts the response to ERDRD – NAb does not inhibit attachment of free virus, but does inhibit by an event that precedes fusion-entry. Cleveland *et al.* [2000b]

No. 822
MAb ID DZ
HXB2 Location gp160 (822–855)
Author Location gp41 (827–860 BRU)
Epitope VAEGTDRVIEVVQGACRAIRHIPRRIRQGLER-IL
Neutralizing L
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* Env
Species (Isotype) human (IgG1λ)
References Boyer *et al.* 1991

- DZ: Weakly neutralizing IIIB – binds to peptides 827-843 and 846-860 of BRU – reacted specifically with IIIB and RF. Boyer *et al.* [1991]

No. 823
MAb ID 3019
HXB2 Location gp160
Author Location gp120
Epitope
Subtype CRF02_AG
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
References Krachmarov *et al.* 2006; Gorny *et al.* 2006
Keywords binding affinity, neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- 3019: This MAb was derived from plasma from a patient with env clade A virus with the GPGQ V3 motif. When cross-reactivity was tested, this Ab bound to both the V3subtypeB-fusion protein containing GPGR motif and V3subtypeA-fusion protein containing GPGQ motif. This Ab was also shown to be able to neutralize both clade B psSF162 (GPGR) and clade C psMW965 (GPGQ) virus and the majority of subtype B and non-B primary isolates. Gorny *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)
- 3019: This Ab was shown to neutralize SF162 and the neutralization sensitivity increased in the SF162 variant with a JR-FL V3 loop, SF162(JR-FL V3). In contrast, a great reduction in sensitivity to neutralization was observed in the SF162(JR-FL V1/V2) variant and was somewhat restored in the SF162(JR-FL V1/V2/V3) variant, indicating that the masking of the V1/V2 loop plays a much greater role in restricting neutralization sensitivity than the variations in V3. This Ab was shown to neutralize viruses with V3 sequences from several different subtypes (B, F, A1, H, C, CRF02_AG and CRF01_AE). This Ab failed to neutralize SF162(JR-FL V1/V2) with V3 derived from different HIV-1 clades except A1, indicating effective V1/V2-mediated masking of several HIV-1 clades. The effect on the neutralization sensitivity of the residue at the crown of the V3 loop (position 18) was shown to be low for this Ab. Krachmarov *et al.* [2006]

No. 824
MAb ID 5A9
HXB2 Location gp160
Author Location
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: Other *Strain:* M group Consensus *HIV component:* gp140 *Adjuvant:* CpG immunostimulatory sequence (ISS), Ribi adjuvant (MPL+TDM) (RIBI), monophosphoryl lipid A
Species (Isotype) mouse (IgG2aκ)
Ab Type gp41 cluster II, gp41 MPER (membrane proximal external region)
References Alam *et al.* 2008
Keywords antibody generation, antibody interactions, binding affinity, kinetics

- 5A9: THis is a novel murine MAb that partially blocked 2F5 MAb binding to ENV but did not neutralize primary isolates or bind host lipids. Two murine MPER MAbs 13H11 and 5A9 completely blocked each other's binding. While length of peptide had no effect on 2F5 binding, dissociation rate constants For 5A9 and 13H11 were several fold greater when bound to shorter (15-mer) peptide EQELLELDKWASLWN compared to 20-mer and 35-mer peptides, indicating conformational nature of 5A9 and 13H11 epitopes. Alam *et al.* [2008] (**antibody generation**, **antibody interactions**, **kinetics**, **binding affinity**)

No. 825
MAb ID P3G9
HXB2 Location gp160
Author Location gp41
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp140
Species (Isotype) mouse (IgG2aκ)
Research Contact Nina Derby or Leo Stamatatos, Seattle Biomedical Research Institute, Seattle, WA, USA, leo.stamatotos@sbri.org
References Derby *et al.* 2007
Keywords antibody binding site definition and exposure, binding affinity, kinetics, neutralization, optimal epitope

B Cell

- P3G9: This Ab recognized trimeric ΔV2gp140 but not monomeric ΔV2gp140, suggesting that the epitope is affected by the state of Env oligomerization. P3G9 did not neutralize homologous SF162, nor viruses lacking V1 loop. The neutralizing potential of P3G9 was marginally affected by the V2 loop. Lack of neutralizing activity of this Ab could not be attributed to its binding kinetics. P3G9 did not neutralize any of the viruses with Envs lacking specific glycosylation sites. Derby *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **optimal epitope**, **kinetics**, **binding affinity**)

No. 826
MAb ID P4A3
HXB2 Location gp160
Author Location gp41
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with protein boost *Strain:* B clade SF162 *HIV component:* gp140
Species (Isotype) mouse (IgG2aκ)
Research Contact Nina Derby or Leo Stamatatos, Seattle Biomedical Research Institute, Seattle, WA, USA, leo.stamatotos@sbri.org
References Derby *et al.* 2007
Keywords antibody binding site definition and exposure, binding affinity, kinetics, neutralization, optimal epitope

- P4A3: This Ab recognized trimeric ΔV2gp140 but not monomeric ΔV2gp140, suggesting that the epitope is affected by the state of Env oligomerization. P4A3 did not neutralize homologous SF162, nor viruses lacking V1 or V2 loops. Lack of neutralizing activity of this Ab could not be attributed to its binding kinetics. P4A3 did not neutralize any of the viruses with Envs lacking specific glycosylation sites. Derby *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **optimal epitope**, **kinetics**, **binding affinity**)

No. 827
MAb ID P4C2
HXB2 Location gp160
Author Location gp41
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with protein boost *Strain:* B clade SF162 *HIV component:* gp140
Species (Isotype) mouse (IgG1κ)
Research Contact Nina Derby or Leo Stamatatos, Seattle Biomedical Research Institute, Seattle, WA, USA, leo.stamatotos@sbri.org
References Derby *et al.* 2007
Keywords antibody binding site definition and exposure, binding affinity, kinetics, neutralization, optimal epitope

- P4C2: This Ab recognized trimeric ΔV2gp140 but not monomeric ΔV2gp140, suggesting that the epitope is affected by the state of Env oligomerization. P4C2 did not neutralize homologous SF162, nor viruses lacking V1 or V2 loops. Lack of neutralizing activity of this Ab could not be attributed to its binding kinetics. P4C2 did not neutralize any of the viruses with Envs lacking specific glycosylation sites. Derby *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **optimal epitope**, **kinetics**, **binding affinity**)

No. 828
MAb ID polyclonal
HXB2 Location gp160
Author Location gp120
Epitope
Neutralizing
Immunogen HIV-1 infection, vaccine
Strain: B clade MN, B clade GNE8 *HIV component:* gp120
Species (Isotype) human
References Forthal *et al.* 2007
Keywords ADCC

- AB-dependent, cell-mediated virus inhibition (ADCVI) following rgp120 vaccinations from the Vax 004 trial was examined. It was found that the level of ADCVI activity correlated inversely with the rate of HIV infection following vaccination. For every 10% increase in ADCVI activity there was a 6.3% decrease in infection rate. The degree to which the ADCVI Ab response predicted the rate of infection was shown to be influenced by polymorphisms at the FcγRIIa and RIIIa gene loci. Forthal *et al.* [2007] (**ADCC**)

IV-C-17 Env Antibodies

No. 829
MAb ID
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp120 *Adjuvant:* GM-CSF
Species (Isotype) mouse (IgG1)
References Rodríguez *et al.* 1999

- The murine Ab response to a chimeric of granulocyte-macrophage colony stimulating factor GM-CSF/gp120 in vaccinia was not higher titer that the response to a gp120-vaccinia construct, but the breadth of the Ab response was greater, in particular to the C-term region of gp120 – a cellular response of greater intensity was trigged to the GM-CSF/gp120 vaccinia construct, as measured by Elispot assay. Rodríguez *et al.* [1999]

No. 830
MAb ID
HXB2 Location Env

B Cell

Author Location Env (384–467)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: hepatitis B surface antigen lipoprotein particles (HsBAg) *HIV component:* V3
Species (Isotype) macaque, rabbit
References Michel *et al.* 1993

- Immunization with recombinant HIV1 V3/HBsAg hybrid particles into rabbits or macaques elicited and maintained for several months anti-V3 or HIV-1 Env proliferative, CTL and Ab responses. Michel *et al.* [1993]

No. 831
MAb ID
HXB2 Location Env
Author Location
Epitope
Neutralizing yes
Immunogen HIV-1 infection, vaccine
Species (Isotype) human
References Burton & Parren 2000

- This review article touches on why natural immune responses do not tend to favor potent neutralizing Ab production, and discusses possible vaccine strategies to counter this problem. Burton & Parren [2000]

No. 832
MAb ID
HXB2 Location Env
Author Location
Epitope
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
References Pellegrin *et al.* 1996

- Detection of an autologous NAb response in 12 patients with primary infections was delayed – for patients with a viral isolate obtained at month 1, autologous NAbs to viral isolates were generally not observed before month 6, and there was no apparent relationship between the emergence of neutralizing activity and the decrease of plasma viral load. Pellegrin *et al.* [1996]

No. 833
MAb ID 1.4C
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 adjacent to CD4BS
References Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure

- 1.4C: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 1.4C has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 834
MAb ID 1.4G
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 adjacent to CD4BS
References Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure

- 1.4G: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 835
MAb ID 1.9E
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 CCR5BS
References Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure

- 1.9E: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 1.9E has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 836
MAb ID 1.9F
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 CCR5BS
References Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure

- 1.9F: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 1.9F has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 837
MAb ID 10/540.w
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) (IgG1)
Ab Type gp120 V3
References Holl *et al.* 2006a
Keywords dendritic cells, neutralization

- 10/540.w: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)

No. 838
MAb ID 1010
HXB2 Location Env
Author Location gp41
Epitope
Subtype B
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human
Ab Type gp41 six-helix bundle and the internal trimeric coiled-coil of N-helices
Research Contact G. Marius Clore or Carole Bewley, NIH, Bethesda, Maryland. marius@intra.niddk.nih.gov or caroleb@mail.nih.gov
References Louis *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation

- 1010: This is one of nine anti-gp41 bivalent Fabs selected from a non-immune human phage display library. This Fab was classified as class B, and inhibits LAV mediated Env-mediated cell fusion with an IC50 of 6 +/-2 ug/ml (the range for the 9 new Fabs was 6-61 ug/ml – for context, 2F5 and 2G12 (IC50s of 0.5-1.5 ug/ml) were about an order of magnitude more potent in this assay than the best Fabs generated here). 1010 and 1018, both class B, were the most potent Fabs. The class B Fabs interact with the six-helix bundle and the internal coiled-coil of N-helices of gp41. Louis *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**)

No. 839
MAb ID 1014
HXB2 Location Env
Author Location gp41
Epitope
Subtype B
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human
Ab Type gp41six-helix bundle
Research Contact G. Marius Clore or Carole Bewley, NIH, Bethesda, Maryland. marius@intra.niddk.nih.gov or caroleb@mail.nih.gov
References Louis *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation

- 1014: This is one of nine anti-gp41 bivalent Fabs selected from a non-immune human phage display library. This Fab was classified as class A, and inhibits LAV mediated Env-mediated cell fusion with an IC50 of 36 +/-1 ug/ml (the range for the 9 new Fabs was 6-61 ug/ml – for context, 2F5 and 2G12 were about an order of magnitude more potent in this assay than the best Fabs generated here). Class A Fabs interact with the six-helix bundle of gp41. Louis *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**)

No. 840
MAb ID 1018
HXB2 Location Env
Author Location gp41
Epitope
Subtype B
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human
Ab Type gp41 six-helix bundle and the internal trimeric coiled-coil of N-helices
Research Contact G. Marius Clore or Carole Bewley, NIH, Bethesda, Maryland. marius@intra.niddk.nih.gov or caroleb@mail.nih.gov
References Gustchina *et al.* 2008; Louis *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation, kinetics, neutralization

- Fab 1018: Bivalent Fab 1018 (bF-1018) does not neutralize HXB2 on its own, but it reduces the neutralization IC50 of N36Mut(e,g) peptide, which is a class 3 inhibitor that disrupts trimerization of the N-heptad repeat (N-HR) in the prehairpin intermediate by sequestering the N-HR into N-HR/N36Mut(e,g) heterodimers. bF-1018 also fails to neutralize SF162, but in the presence of N36Mut(e,g) neutralization activity is observed. Gustchina *et al.* [2008] (**neutralization**, **kinetics**)
- 1018: This is one of nine anti-gp41 bivalent Fabs selected from a non-immune human phage display library. This Fab was classified as class B, and inhibits LAV mediated Env-mediated cell fusion with an IC50 of 7 +/- 1 ug/ml (the range for the 9 new Fabs was 6-61 ug/ml – for context, 2F5 and 2G12 (IC50s of 0.5-1.5 ug/ml) were about an order of magnitude more potent in this assay than the best Fabs generated here). 1010 and 1018, both class B, were the most potent Fabs. The class B Fabs interact with the six-helix bundle and the internal coiled-coil of N-helices of gp41. Louis *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**)

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No. 841
MAb ID 1019
HXB2 Location Env
Author Location gp41
Epitope
Subtype B
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human
Ab Type gp41six-helix bundle
Research Contact G. Marius Clore or Carole Bewley, NIH, Bethesda, Maryland. marius@intra.niddk.nih.gov or caroleb@mail.nih.gov
References Louis *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation

- 1019: This is one of nine anti-gp41 bivalent Fabs selected from a non-immune human phage display library. This Fab was classified as class A, and inhibits LAV mediated Env-mediated cell fusion with an IC50 of 61 +/- 20 ug/ml (the range for the 9 new Fabs was 6-61 ug/ml – for context, 2F5 and 2G12 were about an order of magnitude more potent in this assay than the best Fabs generated here). Class A Fabs interact with the six-helix bundle of gp41. Louis *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**)

No. 842
MAb ID 102
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4BS
Research Contact Ning Yi Jin, Genetic Engineering Laboratory, Academy of Military Medical Sciences, Changchun, China. ningyj@yahoo.com
References Wang *et al.* 2005a
Keywords binding affinity, neutralization

- 102: A genetically engineered single chain antibody (scFv102) was produced from neutralizing mAb 102 cDNA, covering coding variable regions of its heavy and light chains. scFv102 had 5-fold lower affinity than the parental mAb, but inhibited viral replication and infection by 90% in neutralization assays of a range of primary subtype B isolates. Wang *et al.* [2005a] (**neutralization**, **binding affinity**)

No. 843
MAb ID 102-135
HXB2 Location Env
Author Location gp41 (HAM112, O group)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* O group HAM112 *HIV component:* gp160
Species (Isotype) mouse (IgG1κ)
References Scheffel *et al.* 1999

- 102-135: Overlapping peptides based on group O HAM112 Env were tested for MAb reactivity – 102-135 bound to two non-contiguous peptides in combination, assumed to form some type of helical structure, and not to either individually. Scheffel *et al.* [1999]

No. 844
MAb ID 1020
HXB2 Location Env
Author Location gp41
Epitope
Subtype B
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human
Ab Type gp41 six-helix bundle and the internal trimeric coiled-coil of N-helices
Research Contact G. Marius Clore or Carole Bewley, NIH, Bethesda, Maryland. marius@intra.niddk.nih.gov or caroleb@mail.nih.gov
References Louis *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation

- 1020: This is one of nine anti-gp41 bivalent Fabs selected from a non-immune human phage display library. This Fab was classified as class B, and inhibits LAV mediated Env-mediated cell fusion with an IC50 of 20 +/- 3 ug/ml (the range for the 9 new Fabs was 6-61 ug/ml – for context, 2F5 and 2G12 (IC50s of 0.5-1.5 ug/ml) were about an order of magnitude more potent in this assay than the best Fabs generated here). The class B Fabs interact with the six-helix bundle and the internal coiled-coil of N-helices of gp41. Louis *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**)

No. 845
MAb ID 1022
HXB2 Location Env
Author Location gp41
Epitope
Subtype B
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human
Ab Type gp41 six-helix bundle and the internal trimeric coiled-coil of N-helices
Research Contact G. Marius Clore or Carole Bewley, NIH, Bethesda, Maryland. marius@intra.niddk.nih.gov or caroleb@mail.nih.gov
References Louis *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation

- 1022: This is one of nine anti-gp41 bivalent Fabs selected from a non-immune human phage display library. This Fab was classified as class B, and inhibits LAV mediated Env-mediated cell fusion with an IC50 of 40 +/- 10 ug/ml (the range for the 9 new Fabs was 6-61 ug/ml – for context, 2F5

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and 2G12 (IC50s of 0.5-1.5 ug/ml) were about an order of magnitude more potent in this assay than the best Fabs generated here). The class B Fabs interact with the six-helix bundle and the internal coiled-coil of N-helices of gp41. Louis *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**)

No. 846
MAb ID 1025
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Berman *et al.* 1997

- 1025: Binds to 1/7 isolates from breakthrough cases from a MN gp120 vaccine trial. Berman *et al.* [1997]

No. 847
MAb ID 103-14E9
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Julia L. Hurwitz, St. Jude Children's research Hospital, julia.hurwitz@stjude.org
References Slobod *et al.* 2005
Keywords variant cross-recognition or cross-neutralization

- 103-14E9: A binding analysis of this Ab to four different Env proteins showed that 103-14E9 bound to one out of four Envs. Slobod *et al.* [2005] (**variant cross-recognition or cross-neutralization**)

No. 848
MAb ID 103-14F5
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Julia L. Hurwitz, St. Jude Children's research Hospital, julia.hurwitz@stjude.org
References Slobod *et al.* 2005
Keywords variant cross-recognition or cross-neutralization

- 103-14F5: A binding analysis of this Ab to four different Env proteins showed that 103-14F5 bound to one out of four Envs. Slobod *et al.* [2005] (**variant cross-recognition or cross-neutralization**)

No. 849
MAb ID 103-16B9
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Julia L. Hurwitz, St. Jude Children's research Hospital, julia.hurwitz@stjude.org
References Slobod *et al.* 2005
Keywords variant cross-recognition or cross-neutralization

- 103-16B9: A binding analysis of this Ab to four different Env proteins showed that 103-16B9 bound to one out of four Envs. Slobod *et al.* [2005] (**variant cross-recognition or cross-neutralization**)

No. 850
MAb ID 103-4E11
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Julia L. Hurwitz, St. Jude Children's research Hospital, julia.hurwitz@stjude.org
References Slobod *et al.* 2005
Keywords variant cross-recognition or cross-neutralization

- 103-4E11: A binding analysis of this Ab to four different Env proteins showed that 103-4E11 bound to one out of four Envs. Slobod *et al.* [2005] (**variant cross-recognition or cross-neutralization**)

No. 851
MAb ID 103-6H7
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Julia L. Hurwitz, St. Jude Children's research Hospital, julia.hurwitz@stjude.org
References Slobod *et al.* 2005
Keywords variant cross-recognition or cross-neutralization

- 103-6H7: A binding analysis of this Ab to four different Env proteins showed that 103-6H7 bound to one out of four Envs. Slobod *et al.* [2005] (**variant cross-recognition or cross-neutralization**)

No. 852
MAb ID 1034
HXB2 Location Env
Author Location gp41
Epitope
Subtype B
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human
Ab Type gp41 internal trimeric coiled-coil of N-helices

Research Contact G. Marius Clore or Carole Bewley, NIH, Bethesda, Maryland. marius@intra.niddk.nih.gov or caroleb@mail.nih.gov
References Louis *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation

- 1034: This is one of nine anti-gp41 bivalent Fabs selected from a non-immune human phage display library. This Fab was classified as class C, and inhibits LAV mediated Env-mediated cell fusion with an IC50 of 17 +/- 2 ug/ml (the range for the 9 new Fabs was 6-61 ug/ml – for context, 2F5 and 2G12 (IC50s of 0.5-1.5 ug/ml) were about an order of magnitude more potent in this assay than the best Fabs generated here). The class C Fabs interact with the internal coiled-coil of N-helices of gp41. Louis *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**)

No. 853
MAb ID 104-14A2
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Julia L. Hurwitz, St. Jude Children's research Hospital, julia.hurwitz@stjude.org
References Slobod *et al.* 2005
Keywords variant cross-recognition or cross-neutralization

- 104-14A2: A binding analysis of this Ab to four different Env proteins showed that 104-14A2 bound to two out of four Envs. Slobod *et al.* [2005] (**variant cross-recognition or cross-neutralization**)

No. 854
MAb ID 105-134
HXB2 Location Env
Author Location gp41 (652–681 HAM112, O group)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* O group HAM112 *HIV component:* gp160
Species (Isotype) mouse (IgG1κ)
References Scheffel *et al.* 1999

- 105-134: Overlapping peptides based on group O HAM112 Env were tested for MAb reactivity. Scheffel *et al.* [1999]

No. 855
MAb ID 106-11F10
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Julia L. Hurwitz, St. Jude Children's research Hospital, julia.hurwitz@stjude.org
References Slobod *et al.* 2005
Keywords variant cross-recognition or cross-neutralization

- 106-11F10: A binding analysis of this Ab to four different Env proteins showed that 106-11F10 bound to three out of four Envs. Slobod *et al.* [2005] (**variant cross-recognition or cross-neutralization**)

No. 856
MAb ID 106-9H11
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Julia L. Hurwitz, St. Jude Children's research Hospital, julia.hurwitz@stjude.org
References Slobod *et al.* 2005
Keywords variant cross-recognition or cross-neutralization

- 106-9H11: A binding analysis of this Ab to four different Env proteins showed that 106-9H11 bound to one out of four Envs. Slobod *et al.* [2005] (**variant cross-recognition or cross-neutralization**)

No. 857
MAb ID 10E9
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) mouse (IgG1)
References Papsidero *et al.* 1988

- 10E9: 100/100 HIV+ human sera could inhibit 10E9 binding. Papsidero *et al.* [1988]

No. 858
MAb ID 1101
HXB2 Location Env
Author Location gp120 (V3)
Epitope
Subtype B
Neutralizing
Immunogen
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
Research Contact Immuno Diagnostics Inc.
References Hu *et al.* 2007
Keywords antibody binding site definition and exposure, escape, neutralization

- 1101: HIV-1 env clones resistant to cyanovirin (CV-N), a carbohydrate binding agent, showed amino acid changes that resulted in deglycosylation of high-mannose type residues in the C2-C4 region of gp120. Compared to their parental virus HIV-1 IIIB, these resistant viruses were 8-10 times more sensitive to 1101, indicating that deglycosylation in CV-N resistant viruses is likely o make the V3 loop more accessible to

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Abs. Hu *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **escape**)

No. 859
MAb ID 113-1B4
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Julia L. Hurwitz, St. Jude Children's research Hospital, julia.hurwitz@stjude.org
References Slobod *et al.* 2005
Keywords variant cross-recognition or cross-neutralization

- 113-1B4: A binding analysis of this Ab to four different Env proteins showed that 113-1B4 bound to one out of four Envs. Slobod *et al.* [2005] (**variant cross-recognition or cross-neutralization**)

No. 860
MAb ID 113-20E11
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Julia L. Hurwitz, St. Jude Children's research Hospital, julia.hurwitz@stjude.org
References Slobod *et al.* 2005
Keywords variant cross-recognition or cross-neutralization

- 113-20E11: A binding analysis of this Ab to four different Env proteins showed that 113-20E11 bound to one out of four Envs. Slobod *et al.* [2005] (**variant cross-recognition or cross-neutralization**)

No. 861
MAb ID 113-2G1
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Julia L. Hurwitz, St. Jude Children's research Hospital, julia.hurwitz@stjude.org
References Slobod *et al.* 2005
Keywords variant cross-recognition or cross-neutralization

- 113-2G1: A binding analysis of this Ab to four different Env proteins showed that 113-2G1 bound to one out of four Envs. Slobod *et al.* [2005] (**variant cross-recognition or cross-neutralization**)

No. 862
MAb ID 114-12F2
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Julia L. Hurwitz, St. Jude Children's research Hospital, julia.hurwitz@stjude.org
References Slobod *et al.* 2005
Keywords variant cross-recognition or cross-neutralization

- 114-12F2: A binding analysis of this Ab to four different Env proteins showed that 114-12F2 bound to one out of four Envs. Slobod *et al.* [2005] (**variant cross-recognition or cross-neutralization**)

No. 863
MAb ID 114-13A6
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Julia L. Hurwitz, St. Jude Children's research Hospital, julia.hurwitz@stjude.org
References Slobod *et al.* 2005
Keywords variant cross-recognition or cross-neutralization

- 114-13A6: A binding analysis of this Ab to four different Env proteins showed that 114-13A6 bound to one out of four Envs. Slobod *et al.* [2005] (**variant cross-recognition or cross-neutralization**)

No. 864
MAb ID 114-13F6
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Julia L. Hurwitz, St. Jude Children's research Hospital, julia.hurwitz@stjude.org
References Slobod *et al.* 2005
Keywords variant cross-recognition or cross-neutralization

- 114-13F6: A binding analysis of this Ab to four different Env proteins showed that 114-13F6 bound to three out of four Envs. Slobod *et al.* [2005] (**variant cross-recognition or cross-neutralization**)

No. 865
MAb ID 114-4G5
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)

B Cell

Research Contact Julia L. Hurwitz, St. Jude Children's research Hospital, julia.hurwitz@stjude.org
References Slobod *et al.* 2005
Keywords variant cross-recognition or cross-neutralization

- 114-4G5: A binding analysis of this Ab to four different Env proteins showed that 114-4G5 bound to one out of four Envs. Slobod *et al.* [2005] (**variant cross-recognition or cross-neutralization**)

No. 866
MAb ID 12.19
HXB2 Location Env
Author Location
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) (IgG)
Ab Type gp120 V3
References Koefoed *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 12.19: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. This antibody bound to a V3-fusion protein. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**, **kinetics**, **antibody sequence variable domain**)

No. 867
MAb ID 12.9
HXB2 Location Env
Author Location
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) (IgG)
Ab Type gp120 V3
References Koefoed *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 12.9: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. This antibody bound to a V3-fusion protein. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**, **kinetics**, **antibody sequence variable domain**)

No. 868
MAb ID 126-50
HXB2 Location Env
Author Location gp41 (HXB2)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG2κ)
References Xu *et al.* 1991; Robinson *et al.* 1991; Tyler *et al.* 1990; Robinson *et al.* 1990b

- 126-50: No enhancing or neutralizing activity. Robinson *et al.* [1991]
- 126-50: Specific for a conformational epitope. Xu *et al.* [1991]
- 126-50: No enhancing activity for HIV-1 IIIB. Robinson *et al.* [1990b]
- 126-50: Serves as target for antibody-dependent cellular cytotoxicity ADCC. Tyler *et al.* [1990]

No. 869
MAb ID 126-7
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type C-HR
Research Contact Xu1991
References Vincent *et al.* 2008
Keywords antibody binding site definition and exposure

- 126-7: 126-7 reacted with maltose-binding proteins MBP30 and MBP32, containing both HR1 and HR2 domains of gp41, but did not react with MBP37 and MBP44, containing only the HR2 domain, nor with MBP-HR1, containing only the HR1 domain. In ELISA, 126-7 reacted with the complex formed between MBP-HR1 and H44 (His-targeted protein) and C34, but failed to recognize the mixture of MBP-HR1 and T20, MBP3 and C34, and MBP3 and H44. In addition, 126-7 recognized the peptide complex N36/C34 but not the peptides individually. Vincent *et al.* [2008] (**antibody binding site definition and exposure**)

No. 870
MAb ID 12H2
HXB2 Location Env
Author Location gp41 (530–677 HXB2)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: Semliki-Forest Virus *HIV component:* Env
Species (Isotype) mouse (IgMκ)
References Giraud *et al.* 1999

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- 12H2: Env in a Semliki-Forest Virus (SFV) vector was used to vaccinate mice intramuscularly as naked RNA, and an Ab response was induced to Env from which 12H2 was derived – and advantage of this method is that the protein is properly expressed. Giraud *et al.* [1999]

No. 871
MAb ID 13.10 (No. 13)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Research Contact Evan Hersh and Yoh-Ichi Matsumoto
References Wisnewski *et al.* 1996; Moran *et al.* 1993; Lake *et al.* 1989

- 13.10: NIH AIDS Research and Reference Reagent Program: 377.
- 13.10: 13.10 is V H1 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996]
- 13.10: Heavy (V HI) and light (V lambdaII) chain sequenced – no enhancing or neutralizing activity – called No. 13. Moran *et al.* [1993]
- 13.10: First HIV-1 specific human-mouse hybridoma that produces a MAb that binds to gp120 and gp160. Lake *et al.* [1989]

No. 872
MAb ID 1331-D
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Eda *et al.* 2006b
Keywords variant cross-recognition or cross-neutralization

- 1331-D: The neutralization potency of this Ab against 7 HIV-1 primary isolates was compared to the neutralization potency of the Ab KD-247. Higher concentrations of 1331-D were needed for the neutralization of all of the HIV-1 isolates suggesting a lower neutralization potency of this Ab. Eda *et al.* [2006b] (**variant cross-recognition or cross-neutralization**)

No. 873
MAb ID 13H11
HXB2 Location Env
Author Location gp41
Epitope
Subtype M
Neutralizing No
Immunogen vaccine
Strain: M group Consensus *HIV component:* gp140
Species (Isotype) mouse
Ab Type gp41 adjacent to cluster II, gp41 MPER (membrane proximal external region)
Research Contact Barton Haynes, Duke University, Durham, NC, USA, haynes002@mc.duke.edu
References Alam *et al.* 2008; Alam *et al.* 2007; Haynes *et al.* 2005b
Keywords antibody binding site definition and exposure, antibody generation, antibody interactions, binding affinity, kinetics, review

- 13H11: This MAb partially blocked 2F5 MAb binding to Env but did not neutralize primary isolates or bind host lipids. MAb 13H11 and the 3 cluster II human MAbs 98-6, 126-6 and 167-D blocked 2F5 binding to gp41 epitopes to variable degrees; the combination of 98-6 and 13H11 completely blocked 2F5 binding.Two murine MPER MAbs 13H11 and 5A9 completely blocked each other's binding. While length of peptide had no effect on 2F5 binding, dissociation rate constants For 5A9 and 13H11 were several fold greater when bound to shorter (15-mer) peptide EQELLELDKWASLWN compared to 20-mer and 35-mer peptides, indicating conformational nature of 5A9 and 13H11 epitopes. Alam *et al.* [2008] (**antibody generation**, **antibody interactions**, **kinetics**, **binding affinity**)
- 13H11: This was a non-neutralizing anti-gp41 membrane proximal antibody raised in mice immunized with an M group consensus (Con-S) HIV-1 gp140 oligomer that expressed the 2F5 epitope. Like 2F5, 13H11 bound to the gp140 heptad repeat-2 peptide (DP178) and could cross-block binding of 2F5 to DP178. Unlike 2F5, 13H11 could not bind to phospholipids, including cardiolipin, and cannot neutralize primary isolates. Alam *et al.* [2007] (**antibody binding site definition and exposure**, **antibody generation**, **antibody interactions**)
- 13H11: This review summarizes data on the polyspecific reactivities to host antigens by the broadly neutralizing MAbs IgG1b12, 2G12, 2F5 and 4E10. It also hypothesizes that some broadly reactive Abs might not be routinely made because they are derived from B cell populations that frequently make polyspecific Abs and are thus subjected to B cell negative selection. Different types of anti-MPER Abs are discussed, including 13H11. Haynes *et al.* [2005b] (**antibody generation**, **antibody interactions**, **review**)

No. 874
MAb ID 13K3
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing No
Immunogen vaccine
Vector/Type: peptide *HIV component:* mimotopes *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (Isotype) rabbit
Ab Type gp41 NHR (N-heptad repeat), gp41 six-helix bundle and the internal trimeric coiled-coil of N-helices, gp41 five-helix bundle (one CHR peptide of six helix bundle is missing)
Research Contact Michael B. Zwick, The Acripps Research Institute, La Jolla, CA, USA, zwick@scripps.edu

B Cell

References Nelson *et al.* 2008
Keywords antibody generation, antibody sequence variable domain, neutralization

- 13K3: 13K3 was derived from a rabbit Fab phage display library prepared using the bone marrow RNA extracted from N35ccg-N13 immunized rabbits. The library was screened with N35ccg-N13 peptide, which is a soluble homotrimer corresponding to the HIV-1 gp41 N-heptad repeat (NHR) region. The CDR H3 region of 13K3 was 12 residues in length. 13K3 did not neutralize HIV-1 HXB2. Unlike neutralizing Abs in this study, whose heavy chain variable regions were encoded by a rarely expressed VH gene, the non-neutralizing Ab 13K3 was encoded by the usually expressed VH1a1 gene. Nelson *et al.* [2008] (**antibody generation**, **neutralization**, **antibody sequence variable domain**)

No. 875
MAb ID 13a15
HXB2 Location Env
Author Location (JRFL)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4BS
References Koefoed *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 13a15: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. Most of the Fabs bound to the CD4BS, including this one, as they could be blocked with sCD4 and murine anti-CD4BS Abs. Fab 13a15 was not neutralizing. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**, **kinetics**, **antibody sequence variable domain**)

No. 876
MAb ID 13a23
HXB2 Location Env
Author Location (JRFL)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4BS
References Koefoed *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 13a23: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. Most of the Fabs bound to the CD4BS, including this one, as they could be blocked with sCD4 and murine anti-CD4BS Abs; 13a23 was somewhat different from the other CD4BS Fabs isolated in this study, in that its binding was enhanced by anti-C1 MAbs. Fab 13a23 was not neutralizing. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**, **kinetics**, **antibody sequence variable domain**)

No. 877
MAb ID 13a3
HXB2 Location Env
Author Location
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4BS
References Koefoed *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 13a3: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. Most of the Fabs bound to the CD4BS, including this one, as they could be blocked with sCD4 and murine anti-CD4BS Abs. Fab 13a3 weakly neutralized MN, but not HXB2 Ba-L or JRFL. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**, **kinetics**, **antibody sequence variable domain**)

No. 878
MAb ID 13a6
HXB2 Location Env
Author Location
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4BS
References Koefoed *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 13a6: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to using bone marrow for generating libraries, which is often difficult to obtain. Most of the Fabs bound to the CD4BS, including this one, as they could be blocked with sCD4 and murine anti-CD4BS Abs. Fab 13a6 was not neutralizing. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**, **kinetics**, **antibody sequence variable domain**)

No. 879
MAb ID 13a7
HXB2 Location Env
Author Location
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4BS
References Koefoed *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 13a7: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. Most of the Fabs bound to the CD4BS, including this one, as they could be blocked with sCD4 and murine anti-CD4BS Abs. Fab 13a7 was not neutralizing. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**, **kinetics**, **antibody sequence variable domain**)

No. 880
MAb ID 13b18
HXB2 Location Env
Author Location gp120 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4BS
References Koefoed *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 13b18: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. Most of the Fabs bound to the CD4BS, including this one, as they could be blocked with sCD4 and murine anti-CD4BS Abs. Fab 13b18 was not neutralizing. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**, **kinetics**, **antibody sequence variable domain**)

No. 881
MAb ID 13b23
HXB2 Location Env
Author Location gp120 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 C1
References Koefoed *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 13b120: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. Most of the Fabs bound to the CD4BS, but not 13b120; this Fab was partially inhibited by anti-C1 mAb MAG45, and enhanced by CD4i MAb b17 and anti-C1 MAb 1331290. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**, **kinetics**, **antibody sequence variable domain**)

No. 882
MAb ID 13b53
HXB2 Location Env
Author Location (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4BS
References Koefoed *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 13b53: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. Most of the Fabs bound to the CD4BS, including this one, as they could be blocked with sCD4 and murine anti-CD4BS Abs. Fab 13b53 was not neutralizing. Koefoed *et al.* [2005]

B Cell

(**antibody binding site definition and exposure**, **antibody generation**, **kinetics**, **antibody sequence variable domain**)

No. 883
MAb ID 13b61
HXB2 Location Env
Author Location (LAI)
Epitope
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4BS
References Koefoed *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 13b61: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. Most of the Fabs bound to the CD4BS, including this one, as they could be blocked with sCD4 and murine anti-CD4BS Abs. Fab 13b61 could neutralize HXB2 at 25 ug/ml, but not MN, Ba-L or JRFL. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**, **kinetics**, **antibody sequence variable domain**)

No. 884
MAb ID 1492
HXB2 Location Env
Author Location gp41
Epitope
Subtype B
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human
Ab Type gp41 internal trimeric coiled-coil of N-helices
Research Contact G. Marius Clore or Carole Bewley, NIH, Bethesda, Maryland. marius@intra.niddk.nih.gov or caroleb@mail.nih.gov
References Louis *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation

- 1492: This is one of nine anti-gp41 bivalent Fabs selected from a non-immune human phage display library. This Fab was classified as class C, and inhibits LAV mediated Env-mediated cell fusion with an IC50 of 25 +/- 2 ug/ml (the range for the 9 new Fabs was 6-61 ug/ml – for context, 2F5 and 2G12 (IC50s of 0.5-1.5 ug/ml) were about an order of magnitude more potent in this assay than the best Fabs generated here). The class C Fabs interact with the internal coiled-coil of N-helices of gp41. Louis *et al.* [2005] (**antibody binding site definition and exposure**, **antibody generation**)

No. 885
MAb ID 19e
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 CD4i
References DeVico *et al.* 2007
Keywords neutralization

- 19e: Macaques were immunized with either CD4, gp120, cross-linked gp120-human CD4 complex (gp120-CD4 XL), and with single chain complex containing gp120 rhesus macaque CD4 domains 1 and 2 (rhFLSC). Sera from the rhFLSC immunized animals showed highest competition titers, being able to block gp120-CD4 complex interactions with 19e more efficiently than sera from animals immunized with the three other proteins. Competition titers of 19e correlated with the absence of detectable tissue viremia. DeVico *et al.* [2007] (**neutralization**)

No. 886
MAb ID 1A3
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 V3
References Kim *et al.* 2005
Keywords antibody binding site definition and exposure

- 1A3: A trimeric recombinant gp140 construct was developed for immunization studies. Its structural integrity was assessed by a panel of MAbs. The trimeric gp140 was recognized by 1A3 with similar efficiency as monomeric gp120, indicating that the V3 loop is well exposed on the construct. Kim *et al.* [2005] (**antibody binding site definition and exposure**)

No. 887
MAb ID 1B1
HXB2 Location Env
Author Location Env
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human
Research Contact Herman Katinger, Inst. Appl. Microbiol. University of Agricultural Science, Vienna, Austria
References Kunert *et al.* 1998; Purtscher *et al.* 1994; Buchacher *et al.* 1994

- 1B1: The complete V, J and D(H) domain was sequenced – unlike non-neutralizing anti-gp41 MAb 3D6, five neutralizing MAbs (2F5, 2G12, 1B1, 1F7, and 3D5) showed extensive somatic mutations giving evidence of persistent antigenic pressure over long periods. Kunert *et al.* [1998]

B Cell

- 1B1: Generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994]

No. 888
MAb ID 1D10
HXB2 Location Env
Author Location gp120 (34–55)
Epitope
Neutralizing
Immunogen vaccine
Species (Isotype)
Research Contact Phil Berman
References Callahan *et al.* 1991

- 1D10: Polyanionic polysaccharides were proposed to inhibit viral functions such as binding and syncytia formation through interations mediated through the local high positive charge density in the V3 loop. The binding of this N-term binding antibody is increased by dextransulfate, in contrast to anti-V3 antibodies that are inhibited. Callahan *et al.* [1991]

No. 889
MAb ID 1F7
HXB2 Location Env
Author Location Env
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human
Research Contact Herman Katinger, Inst. Appl. Microbiol. University of Agricultural Science, Vienna, Austria
References Grant *et al.* 2000; Kunert *et al.* 1998; Purtscher *et al.* 1994; Buchacher *et al.* 1994

- 1F7: There is an anti-idiotype MAb named 1F7 that was raised against pooled IgG from HIV-1 + subjects that recognizes a set of antibodies against HIV Gag, Pol, and Env, and this MAb is reported to inhibit anti-HIV CTL activity—this is not the same as the 1F7 described by Buchacher *et al.*. Grant *et al.* [2000]
- 1F7: The complete V, J and D(H) domain was sequenced – unlike non-neutralizing anti-gp41 MAb 3D6, five neutralizing MAbs (2F5, 2G12, 1B1, 1F7, and 3D5) showed extensive somatic mutations giving evidence of persistent antigenic pressure over long periods. Kunert *et al.* [1998]
- 1F7: Generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994]

No. 890
MAb ID 2.10H
HXB2 Location Env
Author Location gp120 (V3)
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 V3
Research Contact James Robinson
References Patel *et al.* 2008
Keywords antibody binding site definition and exposure, binding affinity, neutralization, subtype comparisons

- 2.10H: To examine sequence and conformational differences between subtypes B and C, several experiments were preformed with 11 MAbs regarding binding and neutralization. Both binding and neutralization studies revealed that the 11 MAbs could be divided in three different groups, and that the most differences between the subtypes were located in the stem and turn regions of V3. 2.10H belonged to the group 2 MAbs, which are able to bind subtype B but not subtype C gp120, and are able to bind both V3 peptides. For subtype B, 2.10H required an R18 residue in order to bind, but the binding was not significantly affected by the H13R change. For subtype C, Q18R mutation did not restore binding to gp120, but the R13H-Q18R double mutation did. Peptide binding was affected only by the R13H mutation, indicating that the poor binding of Q18R gp120 mutant has a structural basis. 2.10H was not able to neutralize JR-FL nor SF162 isolates. However, a chimeric SF162 variant with a JR-FL-like V3 sequence was hypersensitive to neutralization by this Ab. Patel *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**, **subtype comparisons**)

No. 891
MAb ID 2.1E
HXB2 Location Env
Author Location gp120 (V3)
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 V3
Research Contact James Robinson
References Patel *et al.* 2008
Keywords antibody binding site definition and exposure, binding affinity, neutralization, subtype comparisons

- 2.1E: To examine sequence and conformational differences between subtypes B and C, several experiments were preformed with 11 MAbs regarding binding and neutralization. Both binding and neutralization studies revealed that the 11 MAbs could be divided in three different groups, and that the most differences between the subtypes were located in the stem and turn regions of V3. 2.1E belonged to the group 2 MAbs, which are able to bind subtype B but not subtype C gp120, and are able to bind both V3 peptides. 2.1E was able to bind subtype B V3 in the subtype C Env backbone chimera, but not the reverse, indicating that 2.1E binds to a structure created by the subtype B V3 sequence that is not impacted by the gp120 backbone. For subtype B, 2.1E required an R18 residue in order to bind, but the binding was not significantly affected by the H13R change. For subtype C, Q18R mutation did not restore binding to gp120, but the R13H-Q18R double mutation did. Peptide binding was affected only by the R13H mutation, indicating that the poor binding of Q18R gp120 mutant has a structural basis. 2.1E was not able to neutralize JR-FL isolate, and somewhat neutralized SF162. A chimeric SF162 variant with a JR-FL-like V3 sequence was hypersensitive to neutralization by this Ab. Patel *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**, **subtype comparisons**)

B Cell

No. 892
MAb ID 2.5E
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 CCR5BS
References Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure

- 2.5E: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 2.5E has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 893
MAb ID 20-2-C8.5F3
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 C4
References Srivastava *et al.* 2008
Keywords subtype comparisons

- 20-2-C8.5F3: Trimeric envelope glycoproteins with a partial deletion of the V2 loop derived from subtype B SF162 and subtype C TV1 were compared. Purified subtype C ΔV2 trimer was recognized by the 20-2-C8.5F3 MAb. Srivastava *et al.* [2008] (**subtype comparisons**)

No. 894
MAb ID 25G
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 CD4BS
References Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure

- 25G: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 25G has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 895
MAb ID 2601
HXB2 Location Env
Author Location
Epitope
Subtype A, CRF02_AG
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V3
References Krachmarov *et al.* 2006; Gorny *et al.* 2006; Krachmarov *et al.* 2005
Keywords antibody binding site definition and exposure, binding affinity, neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- 2601: This MAb was derived from plasma from a patient with env clade A virus with the GPGQ V3 motif. When cross-reactivity was tested, this Ab bound to the V3subtypeA-fusion protein containing GPGQ motif and not to V3subtypeB-fusion protein containing GPGR motif. This Ab was also shown to be able to neutralize clade C psMW965 (GPGQ) but not clade B psSF162 (GPGR) virus and only one subtype B and three non-B primary isolates. Gorny *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)
- 2601: This Ab did not neutralize SF162 but the neutralization sensitivity increased in the SF162 variant with a JR-FL V3 loop, SF162(JR-FL V3). In contrast, no neutralization was observed of the SF162(JR-FL V1/V2) and the SF162(JR-FL V1/V2/V3) variants. This Ab was shown to neutralize viruses with V3 sequences from several different subtypes (B, F, A1, H, C and CRF02_AG) except CRF01_AE. This Ab failed to neutralize SF162(JR-FL V1/V2) with V3 derived from different clades except A1, indicating effective V1/V2-mediated masking of somel HIV-1 clades. The effect on the neutralization sensitivity of the residue at the crown of the V3 loop (position 18) was shown to be low for this Ab. Krachmarov *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2601: Sera from subtype A infected individuals from Cameroon have antibodies that react strongly with subtype A and subtype B V3 loops in fusion proteins, and neutralize SF162 pseudotypes, while sera from 47 subtype B infected individuals reacted only with subtype B V3s. Sera from Cameroon did not neutralize primary A or B isolates, due to indirect masking by the V1/V2 domain rather than due to loss of the target epitope. 2601 was derived from a person infected with a clade A or CRF02 virus, and binds to A but not to B V3 loops.Neutralization of JR-FL and SF162(UG V3) by anti-V3 MAbs 2557, 2558, 2601, but not subtype A primary isolates despite binding to the subtype A V3 loops, suggested masking by V1V2 blocking of neutralization by these antibodies. Krachmarov *et al.* [2005] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 896
MAb ID 2909
HXB2 Location Env
Author Location
Epitope

B Cell

Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type quaternary structure
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU, NY
References Pantophlet & Burton 2006; Honnen *et al.* 2007; Gorny *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- 2909: Replacing V3 domain of SF162, which is neutralized by 2909, with V3 from different HIV-1 clades resulted in significant reductions in sensitivity to neutralization by this antibody. However, the only variant totally resistant was CRF01_AE. The main requirement for reactivity of 2909 in V2 was a rare polymorphism at position 160 or 161, and to a lesser extent at positions 167 and 169. It was also found that the neutralization sensitive SF162 variant actually expressed a suboptimal form of 2909 epitope where a mutation N167D resulted in more robust neutralization. Position 167 in V2 dictates the specificities of three type-specific neutralizing MAbs that bind to an otherwise realtively conserved epitope in involving V2: 2909, C108g, and 10/76b. Honnen *et al.* [2007] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 2909: The neutralizing activity of V1 and V2 Abs, such as mAb 2909, is reviewed. Pantophlet & Burton [2006] (**antibody binding site definition and exposure**, **neutralization**)
- 2909: 2909 is a NAb that was produced by fusion of heteromyeloma SHM-D33 with Epstein-Barr virus transformed PBMC and selection by a neutralization assay. The PBMC were derived from an HIV-1 infected individual who maintained a low viral load after 15 years of infection with no therapy. The MAb very potently neutralizes SF162, but has a narrow range of activity, and did not neutralize autologous virus, nor primary isolates from clade A (VI191, CA1, and 92RW021),clades B (BX08, CA5, and BaL), clade C (95ZW2036) and clade F (CA20 and 93BR029). Sequence analysis of the variable domain of the heavy chain of 2909 shows that it is comprised of IgHV3-43, IgHJ6, and IgHD5-12. 2909 recongizes a quartenary structure present on intact SF162 virions and does not bind to soluble or recombinant Envelope proteins. ELISA-based competition assays and subsequent mutational analysis determined that the CD4BS and V2 and V3 loops contribute to the 2909 epitope: 2909 binding was inhibited by MAbs 447-52d (anti-V3), 830A (anti-V2), and IgG1b12 (anti-CD4BS) and sCD4. 2909 was not inhibited by MAbs 670 (anti-C5), 1418 (irrelevant control MAb), nor 2G12 (anti-carbohydrate); in fact, 2G12 enhanced 2909 binding. Gorny *et al.* [2005] (**antibody generation**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**, **antibody sequence variable domain**)

No. 897
MAb ID 2B7
HXB2 Location Env
Author Location gp120
Epitope
Subtype C
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* C clade 97CN54 *HIV component:* Other
Species (Isotype) mouse (IgG1)
Ab Type gp120 V3
References Chen *et al.* 2008a
Keywords antibody binding site definition and exposure, neutralization, variant cross-recognition or cross-neutralization

- 2B7: Mice were immunized with a construct of the outer domain (OD) of gp120 of subtype C fused with Fc, and MAbs specific for the CN54 OD were derived by exhaustive screening of the mice sera. 2B7 was shown to be V3-specific, its specificity mapped to the centre of the loop, including the GPG crown, and strong interaction with a peptide derived upstream of the crown. 2B7 effectively neutralized 93MW965.26 isolate, more effectively than b12, but neutralized the MN isolate only marginally. 2B7 neutralized CN54 isolate in a dose-dependent manner. Chen *et al.* [2008a] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**)

No. 898
MAb ID 2G12 (c2G12)
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing L P
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 carbohydrates at glycosylation residues in C2, C3, C4, and V4
Research Contact Herman Katinger, Inst. Appl. Microbiol. or Polymun Scientific Inc., Vienna, Austria,
References Rademacher *et al.* 2008; Utachee *et al.* 2009; Zhang *et al.* 2008; Yamamoto & Matano 2008; Wang *et al.* 2008; Willey & Aasa-Chapman 2008; Chong *et al.* 2008; van Montfort *et al.* 2008; Vaine *et al.* 2008; Tomaras *et al.* 2008; Taylor *et al.* 2008; Tasca *et al.* 2008; Pugach *et al.* 2008; Peters *et al.* 2008b; Perdomo *et al.* 2008; Patel *et al.* 2008; Nora *et al.* 2008; Menendez *et al.* 2008; Martin *et al.* 2008; Luallen *et al.* 2008; Keele *et al.* 2008; Joyce *et al.* 2008; Hrin *et al.* 2008; Haynes & Shattock 2008; Gustchina *et al.* 2008; Gopi *et al.* 2008; Forsman *et al.* 2008; Crooks *et al.* 2008; Dey *et al.* 2008; Ching *et al.* 2008; Chen *et al.* 2008a; Frey *et al.* 2008; Binley *et al.* 2008; Astronomo *et al.* 2008; Yuan *et al.* 2006; Ye *et al.* 2006; Yang *et al.* 2006; Pahar *et al.* 2006; Pantophlet & Burton 2006; Li *et al.* 2006c; Krachmarov *et al.*

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2006; Rits-Volloch *et al.* 2006; Wang *et al.* 2006a; Zhang & Dimitrov 2007; van Montfort *et al.* 2007; Sirois *et al.* 2007; Sheppard *et al.* 2007b; Shan *et al.* 2007; Schweighardt *et al.* 2007; Scanlan *et al.* 2007; Phogat *et al.* 2007; Li *et al.* 2007b; Hu *et al.* 2007; Gray *et al.* 2007b; Gao *et al.* 2007; Dunfee *et al.* 2007; Bunnik *et al.* 2007; Rainwater *et al.* 2007; Wang *et al.* 2007b; Vcelar *et al.* 2007; Quakkelaar *et al.* 2007b; Naarding *et al.* 2007; Mehandru *et al.* 2007; McKnight & Aasa-Chapman 2007; McFadden *et al.* 2007; Marzi *et al.* 2007; Kramer *et al.* 2007; Hong *et al.* 2007; DeVico *et al.* 2007; Crooks *et al.* 2007; Chen *et al.* 2007a; Blay *et al.* 2007; Balzarini 2007; Gray *et al.* 2006; Joos *et al.* 2006; Braibant *et al.* 2006; Davis *et al.* 2006; Cham *et al.* 2006; Holl *et al.* 2006a; Herrera *et al.* 2006; Lin & Nara 2007; Law *et al.* 2007; Kirchherr *et al.* 2007; Huskens *et al.* 2007; Huber & Trkola 2007; Huang *et al.* 2007b; Honnen *et al.* 2007; Haim *et al.* 2007; Dey *et al.* 2007a; Kothe *et al.* 2007; Ferrantelli *et al.* 2007; Dhillon *et al.* 2007; Dey *et al.* 2007b; Bowley *et al.* 2007; Blish *et al.* 2007; Billington *et al.* 2007; Vu *et al.* 2006; Pashov *et al.* 2006; Moore *et al.* 2006; Liao *et al.* 2006; Holl *et al.* 2006b; Haynes & Montefiori 2006; Derby *et al.* 2006; Blay *et al.* 2006; Binley *et al.* 2006; Zolla-Pazner 2005; Yuan *et al.* 2005; Yang *et al.* 2005c; Trkola *et al.* 2005; Srivastava *et al.* 2005; Selvarajah *et al.* 2005; Rusert *et al.* 2005; Reeves *et al.* 2005; Raviv *et al.* 2005; Poon *et al.* 2005; Pinter *et al.* 2005; Pashov *et al.* 2005a; Pashov *et al.* 2005b; Pancera & Wyatt 2005; Nakowitsch *et al.* 2005; Nabel 2005; Montefiori 2005; Miller *et al.* 2005; Mc Cann *et al.* 2005; Martín-García *et al.* 2005; Lusso *et al.* 2005; Louis *et al.* 2005; Louder *et al.* 2005; Li *et al.* 2005a; Krachmarov *et al.* 2005; Kang *et al.* 2005; Kalia *et al.* 2005; Jülg & Goebel 2005; Herrera *et al.* 2005; Haynes *et al.* 2005b; Haynes *et al.* 2005a; Grundner *et al.* 2005; Gorny *et al.* 2005; Gao *et al.* 2005a; Forsell *et al.* 2005; Crooks *et al.* 2005; Chen *et al.* 2005; Calarese *et al.* 2005; Burton *et al.* 2005; Burrer *et al.* 2005; Brown *et al.* 2005; Beddows *et al.* 2005b; Wang *et al.* 2004; Safrit *et al.* 2004; Pugach *et al.* 2004; Pinter *et al.* 2004; Pantophlet *et al.* 2004; Opalka *et al.* 2004; Nabatov *et al.* 2004; Lorin *et al.* 2004; Liao *et al.* 2004; Jeffs *et al.* 2004; Ferrantelli *et al.* 2004a; Ferrantelli *et al.* 2004b; Dacheux *et al.* 2004; Biorn *et al.* 2004; Binley *et al.* 2004; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Wolbank *et al.* 2003; Ohagen *et al.* 2003; Montefiori *et al.* 2003; Louis *et al.* 2003; Kitabwalla *et al.* 2003; Raja *et al.* 2003; Singh *et al.* 2003; Wang 2003; Richman *et al.* 2003; Mascola 2003; Mascola *et al.* 2003; Hart *et al.* 2003; Ferrantelli *et al.* 2003; Dey *et al.* 2003; Cavacini *et al.* 2003; Binley *et al.* 2003; Abrahamyan *et al.* 2003; Albu *et al.* 2003; Herrera *et al.* 2003; Pantophlet *et al.* 2003a; Choe *et al.* 2003; Calarese *et al.* 2003; Stiegler *et al.* 2002; Kwong *et al.* 2002; Gorry *et al.* 2002; Cavacini *et al.* 2002; Bures *et al.* 2002; Liu *et al.* 2002; Ferrantelli & Ruprecht 2002; Zhang *et al.* 2002; Mascola 2002; Grundner *et al.* 2002; Edwards *et al.* 2002; Armbruster *et al.* 2002; Chakrabarti *et al.* 2002; Xu *et al.* 2002; Yang *et al.* 2002; Schulke *et al.* 2002; Scanlan *et al.* 2002; Sanders *et al.* 2002; Golding *et al.* 2002b; Savarino *et al.* 2001; Xu *et al.* 2001; Hofmann-Lehmann *et al.* 2001; Spenlehauer *et al.* 2001; Stiegler *et al.* 2001; Verrier *et al.* 2001; Zeder-Lutz *et al.* 2001; Poignard *et al.* 2001; Moore *et al.* 2001; Barnett *et al.* 2001; Zwick *et al.* 2001c; Mascola & Nabel 2001; Si *et al.* 2001; Park *et al.* 2000; Grovit-Ferbas *et al.* 2000; Baba *et al.* 2000; Robert-Guroff 2000; Binley *et al.* 1999; Mascola *et al.* 2000; Mascola *et al.* 1999; Parren *et al.* 1999; Poignard *et al.* 1999; Crawford *et al.* 1999; Altmeyer *et al.* 1999; Beddows *et al.* 1999; Montefiori & Evans 1999; Schonning *et al.* 1998; Kunert *et al.* 1998; Frankel *et al.* 1998; Wyatt & Sodroski 1998; Li *et al.* 1998; Parren *et al.* 1998b; Takefman *et al.* 1998; Fouts *et al.* 1998; Trkola *et al.* 1998; Binley *et al.* 1998; Connor *et al.* 1998; Sullivan *et al.* 1998b; Parren *et al.* 1998a; Mondor *et al.* 1998; Wyatt *et al.* 1998; Andrus *et al.* 1998; Parren *et al.* 1997b; Burton & Montefiori 1997; Ugolini *et al.* 1997; Mascola *et al.* 1997; Moore & Trkola 1997; Li *et al.* 1997; Fouts *et al.* 1997; Binley *et al.* 1997a; Mo *et al.* 1997; D'Souza *et al.* 1997; Sattentau 1996; Trkola *et al.* 1996a; Poignard *et al.* 1996b; Moore & Sodroski 1996; Trkola *et al.* 1996b; McKeating 1996; McKeating *et al.* 1996; Moore & Ho 1995; Trkola *et al.* 1995; Buchacher *et al.* 1994

Keywords acute/early infection, antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, assay development, assay standardization/improvement, autoantibody, autologous responses, binding affinity, brain/CSF, co-receptor, complement, dendritic cells, drug resistance, early treatment, enhancing activity, escape, HAART, ART, immunoprophylaxis, immunotherapy, isotype switch, kinetics, mimics, mimotopes,

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mother-to-infant transmission, mucosal immunity, neutralization, rate of progression, responses in children, review, structure, subtype comparisons, supervised treatment interruptions (STI), therapeutic vaccine, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization, viral fitness and reversion

- 2G12: UK Medical Research council AIDS reagent: ARP3030.
- 2G12: NIH AIDS Research and Reference Reagent Program: 1476.
- 2G12: Neutralization susceptibility of CRF01_AE Env-recombinant viruses, derived from blood samples of Thai HIV-1 infected patients in 2006, was tested to 2G12. Most of the 35 viruses tested replicated efficiently in the presence of 2G12, in spite of highly conserved PNLG sites recognized by this Ab, indicating that CRF01_AE is not susceptible to neutralization by 2G12. These results suggest that the protein structure , including conformation of the CD4 binding domain, may somehow be different between CRF01_AE and subtype B Env gp120. Utachee *et al.* [2009] (**neutralization**)
- 2G12: The study explores the development of a carbohydrate immunogen that could elicit 2G12-like neutralizing ABs to contribute to an AIDS vaccine. Specifically, the study describes the development of neoglycoconjugates displaying variable copy numbers of synthetic tetramannoside (Man(4) on bovine serum albumin (BSA) molecules by conjugation to Lys residues. Immunization of rabbits with BSA-(Man(4))(14) elicits significant serum Ab titers to Man(4). However, these Abs are unable to bind gp120. Astronomo *et al.* [2008] (**vaccine antigen design**)
- 2G12: 24 broadly neutralizing plasmas from HIV-1 subtype B an C infected individuals were investigated using a series of mapping methods to identify viral epitopes targeted by NAbs. In competitive virus capture assays on 2G12 coated plates, some of the subtype B plasmas, and two of the subtype C plasmas, inhibited virus capture. Mutant versions of JR-FL trimers were designed to selectively eliminate neutralization epitopes, but the plasma titers against the 2G12-eliminated mutant were similar to those against the wildtype. This indicated that very few, if any, 2G12-like Abs were present in the plasmas, and that a fraction of patients developed Abs that overlap the 2G12 epitope but do not neutralize the virus. Binley *et al.* [2008] (**neutralization**, **binding affinity**)
- 2G12: Three constructs of the outer domain (OD) of gp120 of subtype C, fused with Fc, were generated for immunization of mice: OD(DL3)-Fc (has 29 residues from the centre of the V3 loop removed), OD(2F5)-Fc (has the same deletion reconstructed to contain the sequence of 2F5 epitope), and the parental OD-Fc molecule. All OD variants contained substitutions at residues 295 and 394 that reintroduced the 2G12 epitope into the used sequence. All three OD-variants reacted with 2G12, indicating that the isolated outer domain is conformationally immobile. Despite the presence of the 2G12 epitope, none of the sera from mice immunized with the three OD-constructs showed 2G12-like reactivity. Chen *et al.* [2008a] (**vaccine antigen design**)
- 2G12: The study explores how the V1 loop of Env influences the neutralization susceptibilities of heterologous viruses to antibodies elicited by the SF162gp140 immunogen. All viruses expressing the WT Envs were susceptible to neutralization by 2G12. Replacement of the V1 loops by that of SF162 did not alter the neutralization susceptibilities of the viruses. Ching *et al.* [2008] (**neutralization**)
- 2G12: The goal of the study was to measure nAb responses in patients infected with HIV-1 prevalent subtypes in China. g160 genes from plasma samples were used to establish a pseudovirus-based neutralization assay. 2G12 neutralized 33% of subtype B clones but not subtype BC and AE clones. Chong *et al.* [2008] (**neutralization**, **subtype comparisons**)
- 2G12: The study compared Ab neutralization against the JR-FL primary isolate and trimer binding affinities judged by native PAGE. There was direct quantitative relationship between monovalent Fab-trimer binding and neutralization, implying that neutralization begins as each trimer is occupied by one Ab. In BN-PAGE, neutralizing Fabs, 2G12 in particular, and sCD4 were able to shift JR-FL trimers. In contrast, most non-neutralizing Fabs bound to monomer, but their epitopes were conformationally occluded on trimers, confirming the exclusive relationship of trimer binding and neutralization. For 2G12, there was a ladder of partially and fully liganded trimers Crooks *et al.* [2008] (**neutralization**, **binding affinity**)
- 2G12: Five amino acids in the gp41 N-terminal region that promote gp140 trimerization (I535, Q543, S553, K567 and R588) were considered. Their influence on the function and antigenic properties of JR-FL Env expressed on the surfaces of pseudoviruses and Env-transfected cells was studied. Various non-neutralizing antibodies bind less strongly to the Env mutant, but neutralizing antibody binding is unaffected. There was no difference in 2G12 binding to wild type and mutant JR-FL, and 2G12 inhibited infection of the two pseudoviruses with comparable potencies. Dey *et al.* [2008] (**binding affinity**)
- 2G12: Variable domains of three heavy chain Abs, the VHH, were characterized. The Abs were isolated from llamas, who produce immunoglobulins devoid of light chains, immunized with HIV-1 CRF07_BC, to gp120. It was hypothesized that the small size of the VHH, in combination with their protruding CDR3 loops, and their preference for cleft recognition and binding into active sites, may allow for recognition of conserved motifs on gp120 that are occluded from conventional Abs. 2G12 provided some inhibition of binding of the three neutralizing VHH Abs to gp120, suggesting that 2G12 imposes steric hinderance to binding of the VHH Abs to gp120. Forsman *et al.* [2008] (**binding affinity**)
- 2G12: Molecular mechanism of neutralization by MPER antibodies, 2F5 and 4E10, was studied using preparations of trimeric HIV-1 Env protein in the prefusion, the prehairpin intermediate and postfusion conformations. MAb 2G12 was used to analyze antigenic properties of construct 92UG-gp140-Fd, derived from isolate 92UG037.8 and stabilized by a C-terminal foldon tag. 92UG-gp140-Fd binds 2G12 with high affinity. Frey *et al.* [2008] (**binding affinity**)
- 2G12: A series of peptide conjugates were constructed via click reaction of both aryl and alkyl acetylenes with an internally incorporated azidoproline 6 derived from parent pep-

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tide RINNIPWSEAMM. Many of these conjugates exhibited increase in both affinity for gp120 and inhibition potencies at both the CD4 and coreceptor binding sites. None of the high affinity peptides inhibited the interactions of YU2 gp120 with 2G12 Ab. The aromatic, hydrophobic, and steric features in the residue 6 side-chain were found important for the increased affinity and inhibition of the high-affinity peptides. Gopi *et al.* [2008]

- 2G12: Mab 2G12 binds to gp120 and is essentially inactive after CD4 engagement, with a neutralization half-life of less than 1 minute. Thus, the binding site for 2G12 on gp120 is unavailable once the CD4-induced conformational changes in gp120 have occurred. Gustchina *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **kinetics**)
- 2G12: This review summarizes the obstacles that stand in the way of making a successful preventive HIV-1 vaccine, such as masked or transiently expressed Ab epitopes, polyclonal B-cell class switching, and inefficient, late, and not sufficiently robust mucosal IgA and IgG responses. Possible reasons why HIV-1 envelope constructs expressing 2G12 epitope fail to induce broadly neutralizing Abs are discussed. Haynes & Shattock [2008] (**vaccine antigen design**, **review**)
- 2G12: Synergy of 2F5 with MAbs 2G12, D5, and peptide C34 was examined. 2G12 exhibited synergy in inhibition of HIV-1 89.6 with MAb 2F5. 2G12 was not as synergistic when combined with D5 as 2F5 was. Hrin *et al.* [2008] (**antibody interactions**)
- 2G12: A divalent Man9ClcNAc2 glycopeptide, that binds to 2G12, was covalently coupled to the OMPC carrier and used as immunogen to test its efficacy to induce 2G12-like neutralizing Ab response. High levels of carbohydrate-specific Ab were induced in both guinea pigs and rhesus macaques, but these Ab showed poor recognition of recombinant gp160 and failed to neutralize a panel of subtype B isolates. Sera from HIV-1 positive individuals was tested for binding to the synthetic antigen but failed to recognize the mimetics, although two of the patients showed presence of 2G12-like Abs. These results suggest that presentation of Man9ClcNAc2 on the constrained cyclic scaffold is insufficient to induce a polyclonal response that recognizes native 2G12 epitope. Joyce *et al.* [2008] (**mimotopes**, **neutralization**, **vaccine antigen design**)
- 2G12: A mathematical model was developed and used to derive transmitted or founder Env sequences from individuals with acute HIV-1 subtype B infection. All of the transmitted or early founder Envs were sensitive to neutralization by 2G12. Keele *et al.* [2008] (**neutralization**, **acute/early infection**)
- 2G12: A yeast strain was produced (TM) with a deletion of genes encoding two key carbohydrate processing enzymes, Och1 and Mnn1, that resulted in efficient recognition of the TM yeast by 2G12 mAb. Four heavily glycosylated yeast proteins were isolated that supported 2G12 binding.Removal of high-mannose-type N-linked carbohydrates from the proteins resulted in loss of 2G12 recognition. Sera from rabbits immunized with TM yeast cells contained Abs that could cross-react with HIV-1 gp120 and that recognized a variety of clade B, C and SIV gp120 proteins. Like 2G12, binding of these Abs to Env proteins was abrogated by removal of N-linked high mannose glycans. The elicited Abs had 50-100-fold lower gp120 binding activity than 2G12, and the antiserum recognized a larger variety of mannose-dependent epitopes. There was no observed neutralizing activity of the sera. The results indicate that immunizations with TM yeast can elicit 2G12-like Abs. Luallen *et al.* [2008] (**vaccine antigen design**)
- 2G12: A new purification method was developed using a high affinity peptide mimicking CD4 as a ligand in affinity chromatography. This allowed the separation in one step of HIV envelope monomer from cell supernatant and capture of pre-purified trimer. Binding of 2G12 to gp120SF162 purified by the miniCD4 affinity chromatography and a multi-step method was comparable, suggesting that the miniCD4 allows the separation of HIV-1 envelope with intact 2G12 epitope. gp140DF162ΔV2 was purified by the miniCD4 method to asses its ability to capture gp140 trimers. Binding of 2G12 to gp140DF162ΔV2 purified by the miniCD4 affinity chromatography and a multi-step method was comparable, suggesting that the SF162 trimer antigenicity was preserved. Martin *et al.* [2008] (**assay development**, **binding affinity**)
- 2G12: A peptide 2G12.1, that binds to 2G12, was derived by screening of phage-displayed peptide libraries with 2G12. Comparison of the crystal structure of the Fab 2G12 bound to 2G12.1 peptide, and 2G12 bound to carbohydrate, revealed that 2G12 binding to peptide and carbohydrate occurs through different Ab interactions. The 2G12.1 peptide occupied a site different from, but adjacent to, the primary carbohydrate binding site on 2G12. Thus, this does not support structural mimicry of the peptide to the native carbohydrate epitope on gp120. In addition, the 2G12.1 peptide was not an immunogenic mimic of the 2G12 epitope either, since the sera from mice immunized with the peptide did not bind gp120. Menendez *et al.* [2008] (**mimics**, **structure**)
- 2G12: Transmission of HIV-1 by immature and mature DCs to CD4+ T lymphocytes was significantly higher for CXCR4- than for CCR5-tropic strains. In addition, preneutralization of X4 virus with 2G12 prior to capture efficiently blocked transmission to 36%, while transmission of R5 was blocked to 63%, indicating that 2G12 treatment results in more efficient transfer of X4 than of R5 HIV-1. van Montfort *et al.* [2008] (**co-receptor**, **neutralization**, **dendritic cells**)
- 2G12: Contemporaneous biological clones of HIV-1 were isolated from plasma of chronically infected patients and tested for their functional properties. The clones showed striking functional diversity both within and among patients, including differences in infectivity and sensitivity to inhibition by 2G12. There was no correlation between clonal virus infectivity and sensitivity to 2G12 inhibition, indicating that these properties are dissociable. The sensitivity to 2G12 inhibition was, however, a property shared by viruses from a given patient, suggesting that the genetic determinants that define this sensitivity may lie in regions that are not necessarily subject to extensive diversity. Nora *et al.* [2008] (**neutralization**)
- 2G12: To examine sequence and conformational differences between subtypes B and C, several experiments were preformed with 11 MAbs regarding binding and neutralization. Both binding and neutralization studies revealed that the 11 MAbs could be divided in three different groups, and that the most differences between the subtypes were located in the stem and turn regions of V3. 2G12 was used as control in neu-

tralization assays, and was able to neutralize JR-FL and SF162 isolates, as well as a chimeric SF162 variant with a JR-FL-like V3 sequence. Patel *et al.* [2008] (**neutralization**)

- C2G12: Neutralization of HIV-1 IIIB LAV isolate by 2G12 was within the same range as the neutralization of the virus by natural antibodies from human sera against the gal(α1,3)gal disaccaride linked to CD4 gp120-binding peptides, indicating that the activity of natural antibodies can be re-directed to neutralize HIV-1. Perdomo *et al.* [2008] (**neutralization**)
- 2G12: The sensitivity of R5 envelopes derived from several patients and several tissue sites, including brain tissue, lymph nodes, blood, and semen, was tested against a range of inhibitors and Abs targeting CD4, CCR5, and various sites on the HIV envelope. All but one envelopes from brain tissue were macrophage-tropic while none of the envelopes from the lymph nodes were macrophage-tropic. Macrophage-tropic envelopes were also less frequent in blood and semen. There was a clear variation in sensitivity to 2G12, where most envelopes were sensitive, while some were resistant to neutralization by this Ab. There was a significant correlation between increased envelope macrophage-tropism and decreased 2G12 sensitivity. It is suggested that the macrophage-tropic brain variants are less protected by glycosylation due to absence of Abs in the brain, thus lacking N-glycosylation sites critical for 2G12 neutralization. Three of nine brain envelopes were resistant to 2G12, while only one of nine lymph node envelopes were resistant to 2G12. Peters *et al.* [2008b] (**antibody binding site definition and exposure**, **neutralization**)
- 2G12: In order to assess whether small molecule CCR5 inhibitor resistant viruses were more sensitive to neutralization by NAbs, two escape mutant viruses, CC101.19 and D1/85.16, were tested for their sensitivity to neutralization by 2G12, compared to the sensitivity of CC1/85 parental isolate and the CCcon.19 control isolate. The CC101.19 escape mutant has 4 sequence changes in V3 while the D1/85.16 has no sequence changes in V3 and relies on other sequence changes for its resistance. D1/85.16, but not CC101.19 escape variant, was markedly more sensitive to neutralization by 2G12 (∼50-fold). As 2G12 had no significantly higher affinity for gp120 from D1/85.16, the increased sensitivity of this virus is most likely due to alternation in the conformation or accessibility of the 2G12 epitope on its Env trimer. Overall, the study suggests that CCR5 inhibitor-resistant viruses are likely to be somewhat more sensitive to neutralization than their parental viruses. Pugach *et al.* [2008] (**co-receptor**, **neutralization**, **escape**, **binding affinity**)
- 2G12: Maize was evaluated as a potential inexpensive large-scale production system for therapeutic antibodies against HIV. 2G12 was expressed in maize endosperm. In vitro cell assays demostrated that the HIV-neutralizing properties of the maize-produced 2G12 MAb were equivalent to those of Chinize hamster ovary cell-derived MAb 2G12. Rademacher *et al.* [2008]
- 2G12: The neutralization profile of early R5, intermediate R5X4, and late X4 viruses from a rhesus macaque infected with SHIV-SF162P3N was assessed. 2G12 neutralized all three viruses with similar low potency. Tasca *et al.* [2008] (**co-receptor**, **neutralization**)
- 2G12: An R5 HIV variant, in contrast to its parental virus, was shown to infect T-cell lines expressing low levels of cell surface CCR5 and to infect cells in the absence of CD4. The variant was neutralized less efficiently by 2G12 than the parental virus, indicating conformational changes in gp120. These properties of the mutant virus were determined by alternations in gp41. Taylor *et al.* [2008] (**co-receptor**, **neutralization**)
- 2G12: To investigate B-cell responses immediately following HIV-1 transmission, Env-specific Ab responses to autologous and consensus Envs in plasma donors were determined. Broadly neutralizing Abs with specificity similar to 2G12 did not appear during the first 40 days after plasma virus detection. Tomaras *et al.* [2008] (**antibody generation**, **acute/early infection**)
- 2G12: Sera from both gp120 DNA prime-protein boost immunized rabbits and from protein-only immunized rabbits did not compete for binding to 2G12, indicating no elicitation of 2G12-like Abs by either of the immunization regimens. Vaine *et al.* [2008] (**vaccine antigen design**)
- 2G12: Concentrations of neutralizing Abs in long-term nonprogressors (LNTPs) were significantly higher than the concentrations in asymptomatic subjects and subjects with AIDS, with no statistically significant difference between the two latter groups. Amino acid substitutions in the 2G12 epitope were found in both asymptomatic subjects and subjects with AIDS, while no such mutations were found among LNTPs. Eight different mutations were found at five N-glycosylation linked sites: 295V/T/D/K, 297I, 332E. 334N, and 386D. The mutation rates of the conserved 2G12 neutralization epitopes were significantly different among LNTPs, asymptomatic patients, and patients with AIDS. Wang *et al.* [2008] (**escape**, **rate of progression**)
- 2G12: The various effects that neutralizing and non-neutralizing anti-envelope Abs have on HIV infection are reviewed, such as Ab-mediated complement activation and Fc-receptor mediated activities, that both can, through various mechanisms, increase and decrease the infectivity of the virus. The importance of these mechanisms in vaccine design is discussed. The unusual features of the 2G12 MAb, and its neutralization capacities, are described. Willey & Aasa-Chapman [2008] (**neutralization**, **review**)
- 2G12: Current insights into CTLs and NAbs, and their possible protective mechanisms against establishment of persistent HIV/SIV infection are discussed. Pre- and post-infection sterile and non-sterile protection of NAbs against viral challenge, and potential role of NAbs in antibody-mediated antigen presentation in modification of cellular immunity, are reviewed. Use of 2G12 in immunization experiments and its in vivo antiviral activity in suppression of viral rebound in HIV-1 infected humans undergoing structured treatment interruptions are described. Yamamoto & Matano [2008] (**immunotherapy**, **supervised treatment interruptions (STI)**, **review**)
- 2G12: 2G12 did not neutralize a clade C SHIV strain in the TZM-bl based assay. Zhang *et al.* [2008] (**neutralization**)
- 2G12: Crabohydrate-binding agents, including 2G12, are reviewed regarding to their antiviral activity, resistance development, and their potential use as therapeutic agents. Balzarini [2007] (**review**)

- 2G12: This Ab was found to be able to bind to a highly stable trimeric rgp140 derived from a HIV-1 subtype D isolate containing intermonomer V3-derived disulfide bonds and lacking gp120/gp41 cleavage. Billington *et al.* [2007]
- 2G12: Pseudoviruses derived from gp120 Env variants that evolved in multiple macaques infected with SHIV 89.6P displayed a range of degrees of virion-associated Env cleavage. Pseudoviruses with higher amount of cleaved Env were more sensitive to neutralization by 2G12, as they contained peripheral glycan N386, not present in the wildtype 89.6P. Blay *et al.* [2007] (**neutralization**)
- 2G12: 15 subtype A HIV-1 envelopes from early in infection were not neutralized by 2G12, likely because of a deletion or shift in one or more of the 5 glycosylation sites associated with 2G12 recognition. SF162 was neutralized as expected. Blish *et al.* [2007] (**neutralization**, **acute/early infection**, **subtype comparisons**)
- 2G12: Yeast display was compared to phage display and shown to select all the scFv identified by phage display and additional novel antibodies. Biotinylated C11 and 2G12 were used to minimize selection of non-gp120 specific clones from the yeast displayed antibody library; these MAbs were used as they have unique epitopes with limited overlap with with most known epitopes. Bowley *et al.* [2007] (**assay standardization/improvement**)
- 2G12: Increased neutralization sensitivity was observed for (R5)X4 viruses from timepoints both early and late after emergence of X4 compared to their coexisting R5 variants in one patient, and only for the early (R5)X4 viruses in another patient. In a third patient, in contrast, late (R5)X4 viruses were found to be significantly more resistant to 2G12 neutralization than their coexisting R5 variants. Bunnik *et al.* [2007] (**co-receptor**, **neutralization**)
- 2G12: 2 glycosylation site additions to asparagines 295 and 392 on the clade C gp120 backbone (gp120CN54+) were used to reconstruct the 2G12 epitope, as the gp120CN54+ construct showed excellent reactivity with 2G12. gp120CN54+ and an Fc tagged outer domain of gp120 (ODCN54+-Fc) bound equally well to 2G12, while Fc fusion to gp120CN54+ reduced 2G12 binding, indicating partial occlusion of the 2G12 epitope. Chen *et al.* [2007a] (**antibody binding site definition and exposure**, **binding affinity**)
- 2G12: 2G12-blocking activity was very low in all of the sera from guinea pigs immunized with gp120 protein, or with three types of VLPs: disulfide-shackled functional trimers (SOS-VLP), uncleaved nonfunctional Env (UNC-VLP), naked VLP bearing no Env. Crooks *et al.* [2007] (**neutralization**, **vaccine antigen design**)
- 2G12: Macaques were immunized with either CD4, gp120, cross-linked gp120-human CD4 complex (gp120-CD4 XL), and with single chain complex containing gp120 rhesus macaque CD4 domains 1 and 2 (rhFLSC). Sera from the rhFLSC immunized animals showed slightly higher competition titers, being able to block gp120-CD4 complex interactions with 2G12 slightly more efficiently than sera from animals immunized with the three other proteins. DeVico *et al.* [2007] (**neutralization**)
- 2G12: gp120 proteins were developed with double mutation T257S+S375W, which alters the cavity at the epicenter of the CD4 binding region, and used to immunize rabbits. The ability of rabbit sera to affect binding of CD4 to unmodified gp120 proteins was tested. CD4 binding to gp120 was unaffected by 2G12. Dey *et al.* [2007b] (**antibody binding site definition and exposure**)
- 2G12: SOSIP Env proteins are modified by the introduction of a disulfide bond between gp120 and gp41 (SOS), and an I559P (IP) substitution in gp41, and form trimers. The KNH1144 subtype A virus formed more stable trimers than did the prototype subtype B SOSIP Env, JRFL. The stability of gp140 trimers was increased for JR-FL and Ba-L SOSIP proteins by substituting the five amino acid residues in the N-terminal region of gp41 with corresponding residues from KNH1144 virus. b12, 2G12, 2F5, 4E10 and CD4-IgG2 all bound similarly to the WT and to the stabilized JRFL SOSIP timers, suggesting that the trimer-stabilizing substitutions do not impair the overall antigenic structure of gp140 trimers. Dey *et al.* [2007a]
- 2G12: This Ab was used to help define the antigenic profile of envelopes used in serum depletion experiments to attempt to define the neutralizing specificities of broadly cross-reactive neutralizing serum. It bound to JR-FL and JR-CSF gp120 monomers and to a lesser extent to core JR-CSF gp120 monomer. Dhillon *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**)
- 2G12: A D386N change in the V4 region, which results in restoration of N-glycosylation at this site, did not have any impact on the neutralization of a mutant virus by 2G12 compared to wildtype. Also, there was no association between increased sensitivity to 2G12 neutralization and enhanced macrophage tropism. Dunfee *et al.* [2007] (**antibody binding site definition and exposure**)
- 2G12: Newborn macaques were challenged orally with the highly pathogenic SHIV89.6P and then treated intravenously with a combination of IgG1b12, 2G12, 2F5 and 4E10 one and 12 hours post-virus exposure. All control animals became highly viremic and developed AIDS. In the group treated with mAbs 1 hour post-virus exposure, 3/4 animals were protected from persistent systemic infection and one was protected from disease. In the group treated with mAbs 12 hour post-virus exposure, one animal was protected from persistent systemic infection and disease was prevented or delayed in two animals. IgG1b12, 2G12, and 4E10 were also given 24 hours after exposure in a separate study; 4/4 treated animals become viremic, but with delayed and lower peak viremia relative to controls. 3/4 treated animals did not get AIDS during the follow up period, and 1 showed a delayed progression to AIDS , while the 4 untreated animals died of AIDS. Thus the success of passive immunization with NAbs depends on the time window between virus exposure and the start of immunoprophylaxis. Ferrantelli *et al.* [2007] (**immunoprophylaxis**)
- 2G12: This review summarizes data on the development of HIV-1 centralized genes (consensus and ancestral) for induction of neutralizing antibody responses. Functionality and conformation of native epitopes in proteins based on the centralized genes was tested and confirmed by binding to 2G12 and other MAbs. Antibodies induced by immunization with these centralized proteins did not, however, have the breadth and potency compared to that of 2G12 and other broadly neu-

tralizing MAbs. Gao *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **review**)

- 2G12: Addition of a glycosylation site at position V295N in three different subtype C envelope clones (COT9.6, COT6.15 and Du151.2) resulted in increase in binding of 2G12. However, only one of the viral clones (COT9.6) became sensitive to neutralization by 2G12 at high Ab concentrations. Introduction of glycosylation site at position 448 in COT6.15 further increased its binding to 2G12 and resulted in viruses more sensitive to neutralization. Furthermore, addition of glycosylation at position 442 increased binding and neutralization sensitivity of the corresponding viruses to 2G12, and deletion of glycosylation at position 386 resulted in reduction in binding and resistance to neutralization by 2G12. Gray *et al.* [2007b] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**, **subtype comparisons**)
- 2G12: Controlled attachment of Ab-bound HIV to cells was not affected by the presence of this Ab. However, the virus was still efficiently neutralized indicating that binding of 2G12 to the cell-free virus interferes with a step of infection subsequent to cell attachment. Haim *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **kinetics**)
- 2G12: A recombinant gp120-Fc bound to 2G12, indicating it was conformationally intact. 2G12 binding to gp120 was inhibited by the soluble recombinant extracellular domain (ECD) of DC-SIGN in a dose-dependent fashion, but 2G12 did not inhibit binding of gp120 to DC-SIGN. Many single, double, and triple N-glycan mutations in the 2G12 epitope did not affect binding of gp120 to DC-SIGN, however, some of the N-glycan sites within the 2G12 epitope were shown to be optimally positioned to significantly contribute to DC-SIGN binding. Thus, it is suggested that DC-SIGN can bind to a flexible combination of N-glycans on gp120, both within and outside of the 2G12 epitope, but that its optimal binding site overlaps with specific N-glycans within the 2G12 epitope. Hong *et al.* [2007] (**binding affinity**)
- 2G12: The neutralizing activity of this antibody for the JR-FL Env variant with the N160K/E160K mutations was measured in comparison with the neutralizing activity of 2909, which was found to be higher. Honnen *et al.* [2007] (**neutralization**, **variant cross-recognition or cross-neutralization**)
- 2G12: HIV-1 env clones resistant to cyanovirin (CV-N), a carbohydrate binding agent, showed amino acid changes that resulted in deglycosylation of high-mannose type residues in the C2-C4 region of gp120. Compared to their parental virus HIV-1 IIIB, these CV-N resistant viruses were also completely resistant to 2G12, as they lost one or more 2G12 binding glycans on gp120. Hu *et al.* [2007] (**neutralization**, **escape**)
- 2G12: Binding of 2G12 to gp120 was not significantly affected by the small molecule HIV-1 entry inhibitor IC9564. IC9564 induces conformational change of gp120 to allow CD4i antibody 17b to bind, but inhibits CD4-induced gp41 conformational changes. Huang *et al.* [2007b] (**antibody binding site definition and exposure**)
- 2G12: This review summarizes current knowledge on the various functional properties of antibodies in HIV-1 infection, including 2G12 mAb, in vivo and in vitro activity of neutralizing Abs, the importance and downfalls of non-neutralizing Abs and antibodies that mediate antibody-dependent cellular cytotoxicity and the complement system, and summarizes data on areas tht need future investigation on Ab-mediated immune control. Huber & Trkola [2007] (**review**)
- 2G12: Cross-neutralization was limited in this study. 2G12 neutralized subtype A strain UG273 and subtype B strains US2, NL4-3, and IIIB. It did not neutralize subtype C strain ETH2220, subtype D UG270, CRF01 A/E ID12; subtype F BZ163; nor subtype G BCF06. 3 HIV-2 strains and SIVmac 251 were also not neutralized. 2G12 bound to MN and NDK, but did not neutralize them. Neutralization resistance was selected in culture using strains NL43 and IIIB. NL43 escaped via loss of the glycosylation sequon at positions 295-297, IIIB escaped via sequon losses at positions 392-394 and 295-297, or 406-408, as expected from earlier studies defining critical mannose residues for 2G12 binding. The loss of the mannose actually enhanced mannose-specific lectin inhibition of the virus. Huskens *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**, **escape**, **subtype comparisons**)
- 2G12: A new high throughput method was developed for neutralization analyses of HIV-1 env genes by adding cytomegalovirus (CMV) immediate enhancer/promoter to the 5' end of the HIV-1 rev/env gene PCR products. The PCR method eliminates cloning, transformation, and plasmid DNA preparation steps in the generation of HIV-1 pseudovirions and allows for sufficient amounts of pseudovirions to be obtained for a large number of neutralization assays. Pseudovirions generated with the PCR method showed similar sensitivity to 2G12 Ab, indicating that the neutralization properties are not altered by the new method. Kirchherr *et al.* [2007] (**assay development**, **neutralization**)
- 2G12: Four consensus B Env constructs: full length gp160, uncleaved gp160, truncated gp145, and N-linked glycosylation-site deleted (gp160-201N/S) were compared. All were packaged into virions, and all but the fusion defective uncleaved version mediated infection using the CCR5 coreceptor. Primary isolate Envs were completely resistant or just somewhat sensitive to neutralization by 2G12 while the consensus B constructs were sensitive. Thus the 2G12 epitope is present on the consensus B Env glycoprotein and was not influenced by the Env modifications in this study. Kothe *et al.* [2007] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**)
- 2G12: This review summarizes 2G12Ab epitope, properties and neutralization activity. 2G12 use in passive immunization studies in primates and possible mechanisms explaining protection against infection are discussed. Kramer *et al.* [2007] (**immunotherapy**, **review**)
- 2G12: G1 and G2 recombinant gp120 proteins, consisting of 2F5 and 4E10, and 4E10 epitopes, respectively, engrafted into the V1/V2 region of gp120, were tested as an immunogen to see if they could elicit MPER antibody responses. Deletion of V1/V2 from gp120 or its replacement with G1 and G2 grafts, did not greatly affect binding of 2G12 to gp120. Shortening of the N and C termini of the V3 loop nearly abolished binding of 2G12. Law *et al.* [2007] (**vaccine antigen design**)
- 2G12: 32 human HIV-1 positive sera neutralized most viruses from clades A, B, and C. Two of the sera stood out as par-

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ticularly potent and broadly reactive. Two CD4-binding site defective mutant Env proteins were generated to evaluate whether Abs to the CD4-binding site are involved in the neutralizing activity of the two sera. The integrity of the wildtype and mutant proteins was tested for their reactivity to 2G12. Li *et al.* [2007b] (**binding affinity**)

- 2G12: 2G12 structure, binding, neutralization, and strategies that can be used for vaccine antigen design to elicit 2G12-like Abs, are reviewed in detail. Lin & Nara [2007] (**vaccine antigen design**, **review**, **structure**)
- 2G12: MBL, a lectin present in human serum that recognizes mannose-rich N-glycans, was shown to mediate increased HIV-1 infectivity, and to reduce 2G12-mediated neutralization of HIV-1. Marzi *et al.* [2007] (**neutralization**)
- 2G12: A chimeric protein entry inhibitor, L5, was designed consisting of an allosteric peptide inhibitor 12p1 and a carbohydrate-binding protein cyanovirin (CNV) connected via a flexible linker. The L5 chimera inhibited 2G12-gp120 interaction, as did CNV alone, indicating that the chimera has the high affinity binding property of the CNV molecule. McFadden *et al.* [2007]
- 2G12: This review summarizes data on possible vaccine targets for elicitation of neutralizing Abs and discusses whether it is more practical to design a clade-specific than a clade-generic HIV-1 vaccine. Development of a neutralizing Ab response in HIV-1 infected individuals is reviewed, including data that show no apparent division of different HIV-1 subtypes into clade-related neutralization groups. Also, a summary of the neutralizing activity of mAb 2G12 in different HIV-1 clades is provided. McKnight & Aasa-Chapman [2007] (**variant cross-recognition or cross-neutralization**, **review**)
- 2G12: Three MAbs, 2G12, 4E10 and 2F5, were administered to ten HIV-1 infected individuals treated with ART during acute and early infection, in order to prevent viral rebound after interruption of ART. MAb infusions were well tolerated with essentially no toxicity. Viral rebound was not prevented, but was significantly delayed in 8/10 patients. 2G12 activity was dominant among the MAbs used. Baseline susceptibility to 2G12 was inversely correlated with the time to viral rebound. Escape from 2G12 was associated with viral rebound. Long-term suppression of viremia was achieved in 3/10 patients. Mehandru *et al.* [2007] (**escape**, **immunotherapy**, **supervised treatment interruptions (STI)**)
- 2G12: 2G12-neutralized HIV-1 captured on Raji-DC-SIGN cells or immature monocyte-derived DCs (iMDDCs) was successfully transfered to CD4+ T lymphocytes, indicating that the 2G12-HIV-1 complex was disassembled upon capture by DC-SIGN-cells. van Montfort *et al.* [2007] (**neutralization**, **dendritic cells**)
- 2G12: HIV-1 passaged in the presence of chloroquine was observed to have lost two glycosylation sites imporatnt for 2G12 binding, at positions 332 and 397 in the gp120 region, indicating that the drug can alter the immunogenic properties of gp120. Naarding *et al.* [2007]
- 2G12: This review provides information on the HIV-1 glycoprotein properties that make it challenging to target with neutralizing Abs. 2G12 structure and binding to HIV-1 envelope and current strategies to develop versions of the Env spike with functional trimer properties for elicitation of broadly neutralizing Abs, such as 2G12, are discussed. In addition, approaches to target cellular molecules, such as CD4, CCR5, CXCR4, and MHC molecules, with therapeutic Abs are reviewed. Phogat *et al.* [2007] (**review**)
- 2G12: The ability of 2G12 to neutralize recently transmitted viruses was examined in four homosexual and two parenteral transmission couples. The vast majority of recently transmitted viruses from homosexual recipients were resistant to neutralization by 2G12, although viruses isolated later in the course of infection showed increased sensitivity to 2G12 in one of the patients. In the parenteral transmission, one of the recipients had early viruses resistant to 2G12 neutralization, and one had viruses somewhat sensitive to 2G12 neutralization. The neutralization sensitivity patterns of recipient viruses to 2G12 did not correlate to the neutralization sensitivity patterns of their donors in the homosexual couples, while the HIV-1 variants from the one of the two parenteral pairs were similarly resistant to neutralization by 2G12. 12% of 2G12 resistant viruses had all five PNGS of the 2G12 epitope. 88.5% of the 2G12 resistant viruses lacked at least one of the five PNGS, and viruses isolated later in infection that had become sensitive to 2G12 neutralization had restored the 2G12 epitope. Quakkelaar *et al.* [2007b] (**neutralization**, **acute/early infection**, **mother-to-infant transmission**)
- 2G12: Neutralization sensitivity of maternal and infant viruses to 2G12 close to transmission timepoint was shown to be poor. Even the viruses from one mother, that were shown to be sensitive to maternal Abs and pooled plasma, were not neutralized by 2G12, indicating that Abs in plasma are not directed to this Ab epitope. Rainwater *et al.* [2007] (**neutralization**, **mother-to-infant transmission**)
- 2G12: Chemical inhibition of mammalian glycoprotein synthesis with the plant alkaloid kifunensine resulted in an abundance of oligomannose-type glycans on the cell surface, and binding of 2G12 to previously non-antigenic self proteins and cells. Expression of gp120 in the presence of kifunensine also increased both binding and valency of gp120 to 2G12. Scanlan *et al.* [2007] (**antibody binding site definition and exposure**, **binding affinity**)
- 2G12: A reference panel of recently transmitted Tier 2 HIV-1 subtype B envelope viruses was developed representing a broad spectrum of genetic diversity and neutralization sensitivity. The panel includes viruses derived from male-to-male, female-to-male, and male-to-female sexual transmissions, and CCR5 as well as CXCR4 using viruses. The envelopes displayed varying degrees of neutralization sensitivity to 2G12, with 11 of 19 enevlopes sensitive to neutralization by this Ab. Schweighardt *et al.* [2007] (**neutralization**, **assay standardization/improvement**)
- 2G12: Pre-treatment of gp120 with 2G12 strongly inhibited induction of IL-10, indicating that interaction between gp120 and a mannose C-type lectin receptor is a critical trigger for IL-10 induction. Shan *et al.* [2007]
- 2G12: This Ab was used in the analysis of clade C gp140 (97CN54) antigenicity and was shown not to bind to this molecule, as the glycan epitope is absent. Sheppard *et al.* [2007b] (**binding affinity**)
- 2G12: Modeling of protein-protein interaction based on the gp120 crystal structure, X-ray crystal structure of 2G12 and its

complexes with glycans, suggested that the glycans attached to N295 and N302 from the V3 loop are the two most likely involved in the conformational epitope of 2G12. Sirois *et al.* [2007] (**review**, **structure**)

- 2G12: Infusion of a MAb cocktail (4E10, 2G12 and 2F5) into HIV-1 infected subjects was shown to be associated with increased levels of serum anti-cardiolipin and anti-phosphatidylserine Ab titers, and increased coagulation times. In the absence or in the presence of adult and neonate plasma, 2G12 did not bind to either phosphatidylserine nor to cardiolipin, and did not induce significant prolongations of clotting times in human plasma, indicating that infusion of 2G12 was not responsible for autoreactivity and prolonged clotting times. Vcelar *et al.* [2007] (**antibody interactions**, **autoantibody**, **binding affinity**, **immunotherapy**)
- 2G12: Synthetic monomeric D1 arm oligosaccharide, corresponding to the D1 arm of Man9 which has a high affinity to 2G12, and its fluorinated derivative interacted with 2G12 only weakly. However, when four units of synthetic D1 arm tetrasaccharide were introduced to a cyclic decapeptide template, it showed high affinity to 2G12. Introduction of two T-helper epitopes onto the template did not affect 2G12 binding, indicating that the construct could be used as a new type of immunogen for raising carbohydrate-specific neutralizing Abs against HIV. Wang *et al.* [2007b] (**mimotopes**, **vaccine antigen design**, **kinetics**, **binding affinity**)
- 2G12: Novel approaches based on sequential (SAP) and competitive (CAP) antigen panning methodiologies, and use of antigens with increased exposure of conserved epitopes, for enhanced identification of broadly cross-reactive neutralizing Abs are reviewed. Previously known broadly neutralizing human mAbs are compared to Abs identified by these methods. Zhang & Dimitrov [2007] (**review**)
- 2G12: 2G12 did not inhibit binding of Fc-gp120 to CD4, however, it inhibited binding of Fc-gp120, and of the virus itself, to the CCR5 coreceptor and to the DC-SIGN. Thus 2G12 probably inhibits HIV-1 by two mechanisms: blocking of gp120-CCR5 and of gp120-DC-SIGN interactions. Pre-incubation of virus with sCD4 did not affect its neutralization by 2G12. This Ab was also shown to effectively inhibit trans-infection of virus from primary monocyte-derived dendritic cells (MDDCs) to CD4+ T-cells. Attachment of Fc-gp120 to MDDCs and PBLs was partially inhibited by 2G12, while b12 and sCD4 did not inhibit binding to MDDCs but did inhibit binding to PBLs. The results indicate that Env attachment is mediated through DC-SIGN and other receptors on MDDCs while it is predominantly mediated by CD4 and CCR5 on PBLs. Binley *et al.* [2006] (**antibody binding site definition and exposure**, **co-receptor**, **neutralization**, **binding affinity**, **dendritic cells**)
- 2G12: Development of neutralizing Abs and changes to Env gp120 were analyzed in SHIV infected macaques during a period of 1 year. 4 macaques showed little viral divergence while the remaining 7 showed significant env divergence from the inoculum, associated with higher titers of homologous NAbs. In five of the 7 divergent animals, the glycosylation site N386, which is a part of the 2G12 epitope, was significantly added. Glycosylation sites N392, on the inner domain of gp120, and N295, on the silent face, also forma a part of the 2G12 epitope, and were found to be highly conserved. Blay *et al.* [2006] (**antibody binding site definition and exposure**)
- 2G12: Inhibition of 2G12 binding to gp120 by 2G12-like Abs in sera from long-term non-progressors (LTNP) was determined. 2G12-like Abs were present in almost all sera from LTNPs but at a lower levels than b12. Higher 2G12-like Ab levles were significantly associated with the broadest neutralizing activity in sera from LNTPs. Braibant *et al.* [2006] (**enhancing activity**, **neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2G12: Cloned Envs (clades A, B, C, D, F1, CRF01_AE, CRF02_AG, CRF06_cpx and CRF11_cpx) derived from donors either with or without broadly cross-reactive neutralizing antibodies were shown to be of comparable susceptibility to neutralization by 2G12. Cham *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2G12: Neutralization rates and rate constants for the neutralization of clade B primary isolates SF33, SF162 and 89.6 by this Ab were determined. Statistically significant neutralization was not observed for isolate SF162. It was shown that neutralization sensitivity is not associated with neutralization of cell-associated or free virus. Davis *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **kinetics**)
- 2G12: Macaques were immunized with SF162gp140, ΔV2gp140, ΔV2ΔV3gp140 and ΔV3gp140 constructs and their antibody responses were compared to the broadly reactive NAb responses in a macaque infected with SHIV SF162P4, and with pooled sera from humans infected with heterologous HIV-1 isolates (HIVIG). 2G12 recognized all four gp140 proteins equally. Low titers of Abs capable of blocking the binding of 2G12 were present in the sera from the SHIV-infected macaque, but were absent in the sera from the gp140-immunized animals. Derby *et al.* [2006] (**antibody binding site definition and exposure**)
- 2G12: Env-pseudotyped viruses were constructed from the gp160 envelope genes from seven children infected with subtype C HIV-1. 2G12 failed to neutralize any of the seven viruses, correlating with the absence of crucial N-linked glycans that define 2G12 epitope on these viruses. When this Ab was mixed with IgG1b12 and 2F5, the neutralization was similar as to IgGb12 alone, indicating that the majority of the pool activity was due to IgG1b12. When 4E10 was added to this mix, all isolates were neutralized. Gray *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **responses in children**, **mother-to-infant transmission**)
- 2G12: This review describes the effectiveness of the current HIV-1 immunogens in eliciting neutralizing antibody responses to different clades of HIV-1. It also summarizes different evasion and antibody escape mechanisms, as well as the most potent neutralizing MAbs and their properties. MAbs reviewed in this article are: 2G12, IgG1b12, 2F5, 4E10, A32, 447-52D and, briefly, D50. Novel immunogen design strategies are also discussed. Haynes & Montefiori [2006] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**, **escape**)

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- 2G12: Viruses with cleavage-competent 2G12-knockout Env and cleavage-defective Env able to bind 2G12 were constructed. The amount of Env precipitated by 2G12 was same when the two pseudotyped virus variants were mixed as with the wildtype alone, suggesting formation of heterotrimers consisting of both cleavage-competent and defective Envs. The presence of nonfunctional Envs on the surface of infectious virions did not affect the neutralization by 2G12. The neutralization by the CD4-binding agents was also unaffected by 2G12 binding to uncleaved Env indicating that the function of a trimer is unaffected sterically by the binding of an antibody to adjacent trimer. Herrera *et al.* [2006] (**neutralization**, **binding affinity**)
- 2G12: Inhibition of R5 HIV replication by monoclonal and polyclonal IgGs and IgAs in iMDDCs was evaluated. The neutralizing activity of 2G12 was higher in iMDDCs than in PHA-stimulated PBMCs. A 90% reduction of HIV infection was observed without induction of MDDC maturation by this mAb. Blockade of FcgammaRII on iMDDCs decreased the anti-HIV acitvity of 2G12 while increased expression of FcgammaRI increased inhibition of HIV by 2G12, suggesting the involvment of these receptors in the HIV-inhibitory activity of this Ab. Holl *et al.* [2006b] (**neutralization**, **dendritic cells**)
- 2G12: The ability of this Ab to inhibit viral growth was increased when macrophages and immature dendritic cells (iDCs) were used as target cells instead of PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication by this Ab for macrophages and iDCs can occur by two distinct mechanisms, neutralization of infectivity involving only the Fab part of the IgG, and, an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 2G12: Pharmacokinetic properties of this Ab were studied in HIV infected patients infused with high doses of 2G12. The Ab did not elicit an endogenous immune response and had distribution and systemic clearance values similar to other Abs. The elimination half-life was measured to 21.8 days, which is significantly longer than the elimination half-life of 4E10 and 2F5. Joos *et al.* [2006] (**kinetics**, **immunotherapy**)
- 2G12: This Ab was used as a control since its epitope is independent of either V1/V2 or V3 domains confirmed in its equal neutralization of SF162 and variants SF162(JR-FL V3), SF162(JR-FL V1/V2) and SF162(JR-FL V1/V2/V3). This Ab was also shown to neutralize viruses with V3 sequences from several different subtypes (B, F, A1, H, C, CRF02_AG and CRF01_AE). Krachmarov *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2G12: All subtype C env-pseudotyped clones derived from individuals in acute/early stage of HIV-1 infection were highly resistant to neutralization by this Ab, since each of the clones lacked a PNLG at one or more critical epitope positions. The sensitivity of clones to a mix of Abs IgG1b12, 2G12 and 2F5 was tracked to IgG1b12. Li *et al.* [2006c] (**neutralization**, **variant cross-recognition or cross-neutralization**, **acute/early infection**, **subtype comparisons**)
- 2G12: The gp140δCFI protein of CON-S M group consensus protein and gp140CFI and gp140CF proteins of CON6 and WT viruses from HIV-1 subtypes A, B and C were expressed in recombinant vaccinia viruses and tested as immunogens in guinea pigs. 2G12 was shown to bind specifically to all recombinant proteins except for the subtype B gp140δCF and subtype A gp140δCFI. The specific binding of this Ab to CON-S indicated that its conformational epitope was intact. This Ab also bound specifically to the two tested subtype B gp120 proteins. Liao *et al.* [2006] (**antibody binding site definition and exposure**, **vaccine antigen design**, **subtype comparisons**)
- 2G12: In addition to gp120-gp41 trimers, HIV-1 particles were shown to bear nonfunctional gp120-gp41 monomers and gp120-depleted gp41 stumps on their surface. 2G12 effectively neutralized wildype virus particles. 2G12 was found to bind to both nonfunctional monomers and to gp120-gp41 trimers. Binding of 2G12 to trimers correlated with its neutralization of wildtype virus particles. Monomer binding did not correlate with neutralization, but it did correlate with virus capture. It is hypothesized that the nonfunctional monomers on the HIV-1 surface serve to divert the Ab response, helping the virus to avoid neutralization. Moore *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- 2G12: SHIV SF162p4 virus used as challenge in ISCOM vaccinated macaques was shown to be highly sensitive to neutralization by this Ab. Pahar *et al.* [2006] (**neutralization**)
- 2G12: A carbohydrate mimetic peptide with central motif versions RYRY and YPYRY was shown to precipitate human IgG Ab that bind to gp120 and to immunoprecipitate gp120 from transfected cells. 2G12 showed significant binding only to the PYPY motif version of the peptide. Pashov *et al.* [2006] (**mimotopes**)
- 2G12: Binding of 2G12 to wt gp120 and two constructs with 5 and 9 residues deleted in the middle of the beta3-beta5 loop in the C2 region of gp120 was examined. The deletions of the loop residues did not affect the conformation of 2G12 epitope as 2G12 Ab binding and kinetics were identical for the wt gp120 and both constructs. Rits-Volloch *et al.* [2006] (**antibody binding site definition and exposure**, **kinetics**, **binding affinity**)
- 2G12: A fusion protein (FLSC R/T-IgG1) that targets CCR5 was expressed from a synthetic gene linking a single chain gp120-CD4 complex containing an R5 gp120 sequence with the hinge-Ch2-Ch3 portion of human IgG1. The fusion protein did not activate the co-receptor by binding. In cell-line based assays, the FLSC R/T-IgG1 was less potent in neutralizing R5 HIV-1 primary isolates than 2G12, while in PBMC assays they were comparable. Vu *et al.* [2006] (**neutralization**)
- 2G12: This Ab was used as a positive control in the neutralization assay. At the highest Ab concentrations, 2G12 was able to neutralize several primary isolates but not all, with a neutralization pattern similar to that of rabbit sera immunized with monovalent and polyvalent DNA-prime/protein-boost Env from different HIV-1 subtypes. At a reduced concentrations, 2G12 showed much weaker neutralizing activities. Wang *et al.* [2006a] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

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- 2G12: Viruses with wild-type HIV-1JR-FL Envs were neutralized by this Ab at much lower concentrations than HIV-1 YU2 Env viruses. Yang *et al.* [2006] (**neutralization**, **binding affinity**)
- 2G12: No significant levels of 2G12 were shown to bind to HA/gp41 expressed on cell surfaces and this Ab did not stain cells expressing HA/gp41 in a fluorescence assay. However, it did bind to HIV 89.6 Env expressing cells. Ye *et al.* [2006] (**antibody binding site definition and exposure**, **binding affinity**)
- 2G12: Interactions of this Ab with gp120 monomer and two cleavage-defective gp140 trimers were studied. It was shown that 2G12 interactions with the soluble monomers and trimers were minimally affected by GA cross-linking of the proteins, indicating that the 2G12 epitope was maintained after cross-linking. This Ab was associated with a small entropy change upon gp120 binding. This Ab was shown to have a kinetic advantage as it bound to gp120 faster than other less neutralizing Abs. Yuan *et al.* [2006] (**antibody binding site definition and exposure**, **antibody interactions**, **kinetics**, **binding affinity**)
- 2G12: The major infectivity and neutralization differences between a PBMC-derived HIV-1 W61D strain and its T-cell line adapted counterpart were conferred by the interactions of three Env amino acid substitutions, E440G, D457G and H564N. Chimeric Env-pseudotyped virus Ch5, containing all three of the mutations, was equally neutralization sensitive to 2G12 as Ch2, which did not contain any of these mutations. Beddows *et al.* [2005b] (**neutralization**)
- 2G12: A panel of 60 HIV-1 isolates, with complete genome sequences available, was formed for neutralization assay standardization. It comprises of 10 isolates from each of the subtypes A, B, C, D, CRF01_AE and CRF02AG, with majority of the viruses being of R5 phenotype and few of X4 phenotype. Neutralization profile of each isolate was assessed by measuring neutralization by sCD4, a cocktail of MAbs including 2G12, 2F5 and IgG1b12, and a large pool of sera collected from HIV-1 positive patients. The MAb cocktail neutralized with >50% a large portion of the isolates (51/60) including: 10 subtype A isolates, 8 subtype B isolates, 8 subtype C isolates, 9 subtype D isolates, 7 CRF-01_AE isolates, and 9 CRF_02AG isolates. Brown *et al.* [2005] (**neutralization**, **subtype comparisons**, **assay standardization/improvement**)
- 2G12: Four primary isolates (PIs), Bx08, Bx17, 11105C and Kon, were tested for binding and neutralization by 2G12. 2G12 was only able to neutralize Bx08, but bound well to both Bx08 and Bx17 and less well to 11105C and Kon. There was no direct correlation between binding and neutralization of the four PIs by 2G12. CD4-induced gp120 shedding resulted in a decrease of 2G12 binding to Bx08. Presence of gp160 depleted of the principal immunodominant domain (PID) significantly decreased capture of Bx17 and Kon by 2G12. Presence of both gp160ΔPID and PID slightly improved the inhibition of virus capture compared to PID peptide alone, revealing an additive effect. Burrer *et al.* [2005] (**neutralization**, **binding affinity**)
- 2G12: The unique structure of the 2G12 MAb, and the reasons for its unique ability to recognize oligomannose chains on the silent face of the gp120, are reviewed. Engineering of Abs based on revealed structures of broadly neutralizing MAbs is discussed. Burton *et al.* [2005] (**antibody binding site definition and exposure**, **review**, **structure**)
- 2G12: Precise characterization of 2G12 binding to carbohydrate was undertaken; the 2G12 Fab was co-crystallized with four oligomannose derivatives, Man4, Man5, Man7 and Man8. 2G12 recognizes the terminal Manα1-2Man both in the context of the D1 arm (Manα1-2Manα1-2Man) and D3 arm (Manα1-2Manα1-6Man) of the Man9GlcNAc2 moiety, but not the D2 arm. This gives the 2G12 more binding flexibility than previously thought, as only the D1 arm binding had been shown previously. Calarese *et al.* [2005] (**antibody binding site definition and exposure**, **structure**)
- 2G12: The lack of glycosylation sites at residues Asn 295 and Thy 394 within C-clade gp120s generally causes the loss of 2G12 recognition. Introduction of glycans in the subtype C strain HIV-1CN54 at these positions restored 2G12 binding, and addition of just a single glycan partially restored binding (V295N + A394T » V295N > A395T). 2G12 epitope recovery decreased b12 binding. Chen *et al.* [2005] (**antibody binding site definition and exposure**)
- 2G12: 2G12 was investigated in differnt neutralization formats, including the standard format that measures activity over the entire infection period and several formats that emphasize various stages of infection. The activity of 2G12 was induced in the post-CD4 format and was less pronounced in the standard format. 2G12 did not neutralize after CD4/CCR5 engagement. HIV-1 + human plasma mediated high-levels of post-CD4 neutralization indicating presence of b12 and 2G12 -like Abs. Crooks *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **assay standardization/improvement**)
- 2G12: SFV-gp140(-GCN4) was constructed for analysis of its immunogenic properties in animal models. Both gp120 and gp140(-GCN4) secreted from rSFV-infected cells were recognized by 2G12, suggesting that the proteins retained their native folding. Forsell *et al.* [2005] (**antibody binding site definition and exposure**)
- 2G12: Monomeric gp120 and trimeric gp140CF proteins synthesized from an artificial group M consensus Env gene (CON6) bound efficiently to 2G12, indicating correct exposure of the 2G12 epitope. A mix of 2G12, 2F5 and b12 MAbs (TriMab2) was used for neutralization assessment of some subtype B isolates, but showed no significant neutralization. Gao *et al.* [2005a] (**antibody binding site definition and exposure**, **neutralization**)
- 2G12: 2909 is a human anti-Env NAb that was selected by a neutralization assay and binds to the quaternary structure on the intact virion. ELISA-based competition assays and subsequent mutational analysis determined that the CD4BS and V2 and V3 loops contribute to the 2909 epitope: 2909 binding was inhibited by MAbs 447-52d (anti-V3), 830A (anti-V2), and IgG1b12 (anti-CD4BS) and sCD4. 2909 was not inhibited by MAbs 670, 1418, nor 2G12; in fact, 2G12 enhanced 2909 binding. Gorny *et al.* [2005]
- 2G12: 2G12 neutralized viral isolates HXBc2, SF162, 89.6 and BaL. ADA isolate was poorly neutralized and the YU2 isolate was not neutralized. Neutralization was concentration dependent, as higher MAb concentration resulted in higher %

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of neutralization. The exception was the YU2 isolate, where higher concentration of 2G12 resulted in enhancement of viral infection. Grundner *et al.* [2005] (**enhancing activity**, **neutralization**)

- 2G12: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. Unlike the other three broadly neutralizing human anti-HIV-1 MAbs, 2G12 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)
- 2G12: This review summarizes data on the polyspecific reactivities to host antigens by the broadly neutralizing MAbs IgG1b12, 2G12, 2F5 and 4E10. It also hypothesizes that some broadly reactive Abs might not be routinely made because they are derived from B cell populations that frequently make polyspecific Abs and are thus subjected to B cell negative selection. Haynes *et al.* [2005b] (**antibody generation**, **antibody interactions**, **review**)
- 2G12: 2G12 bound with a higher maximal mean fluorescence intensity (MFI) to Env protein on the surface of cells producing gp140Δct-pseudotyped neutralization resistant 3.2P strain, than to the Env of pseudotyped neutralization sensitive HXBc2. Neutralization assays with the pseudotyped viruses showed that 2G12 neutralized both viruses with same potency. Furin co-transfection did not have an effect on the reactivity of pseudoviruses with 2G12 or on their neutralization sensitivity. Presence or absence of sialic acid residues did not affect Env reactivity with 2G12. Herrera *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- 2G12: Why broadly neutralizing Abs, such as 2G12, 2F5 and 4E10, are extremely rare, and their protective abilities and potential role in immunotherapy are discussed. Jülg & Goebel [2005] (**neutralization**, **immunotherapy**, **review**)
- 2G12: Point mutations in the highly conserved structural motif LLP-2 within the intracytoplasmic tail of gp41 resulted in conformational alternations of both gp41 and gp120. The alternations did not affect virus CD4 binding, coreceptor binding site exposure, or infectivity of the virus, but did result in increased relative neutralization resistance of the LLP-2 mutant virus to 2G12, compared with wildtype virus. The increased neutralization resistance of LLP-2 virus was associated with decreased 2G12 binding to its epitope. Kalia *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- 2G12: A series of genetically modified Env proteins were generated and expressed in both insect and animal cells to be monitored for their antigenic characteristics. For 2G12, two of the modified proteins expressed in insect cells, dV1V2 mutant (V1V2 deletions) followed by the dV2 mutant, showed higher binding to the Ab than the wildtype Env did, indicating that V1V2 deletion exposes epitopes against 2G12 better than other proteins. Unlike for most of the other MAbs, 3G mutant (mutations in 3 glycosylation sites) did not show a higher binding affinity to 2G12. When expressed in animal cells, only dV2 mutant resulted in higher binding to 2G12, while all other modified proteins showed lower binding compared to the wildtype. Kang *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)
- 2G12: Sera from subtype A infected individuals from Cameroon have antibodies that react strongly with subtype A and subtype B V3 loops in fusion proteins, and neutralize SF162 pseudotypes, while sera from 47 subtype B infected individuals reacted only with subtype B V3s. Sera from Cameroon did not neutralize primary A or B isolates, due to indirect masking by the V1/V2 domain rather than due to loss of the target epitope. Neutralization by Cameroonian sera MAbs was blocked by Clade A and B V3 loop fusion proteins, while NAbs to non-V3 epitopes, 2F5, 2G12, and b12, were not blocked. Krachmarov *et al.* [2005] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2G12: Full-length gp160 clones were derived from acute and early human HIV-1 infections and used as env-pseudotyped viruses in neutralization assays for their characterization as neutralization reference agents. 12 out of 19 pseudoviruses were neutralized by 2G12, as were SF162.LS and IIIB strains but not the MN strain. Resistance to 2G12 was generally associated with lack of N-glycosylation sites, except in one case, where the clone was resistant to neutralization in spite of presence N-glycosylation sites. Two clones lacked N-glycosylation at residues 339 and 386, but remained sensitive to 2G12. A mixture of IgG1b12, 2F5 and 2G12 (TriMab) exhibited potent neutralizing activity against all Env-pseudotyped viruses except one. 7 out of 12 Env-pseudotyped viruses were more sensitive to neutralization by 2G12 than their uncloned parental PBMC-grown viruses. Li *et al.* [2005a] (**neutralization**, **assay standardization/improvement**)
- 2G12: Pseudoviruses expressing HIV-1 envelope glycoproteins from BL01, BR07 and 89.6 strains were compared in neutralization assays to replication competent clone derived from transfection of 293T cells (IMC-293T) and to the IMC-293T derived from a single passage through PBMC (IMC-PBMC). The neutralization responses of pseudoviruses and corresponding IMC-293T to 2G12 were similar, while a significant decrease in viral neutralization sensitivity to 2G12 was observed for all three IMC-PBMC viruses. The decrease was associated with an increase in average virion envelope glycoprotein content on the PBMC-derved virus. Louder *et al.* [2005] (**neutralization**, **assay standardization/improvement**)
- 2G12: Nine anti-gp41 bivalent Fabs that interacted with either or both of the six-helix bundle and the internal coiled-coil of N-helices of gp41 were selected from a non-immune human phage display library. The IC50 the range for the inhibition of LAV ENV-mediated cell-fusion was 6-61 ug/ml – for context, 2F5 and 2G12 (IC50s of 0.5-1.5 ug/ml) were about an order of magnitude more potent in this assay than the best Fabs generated here. Louis *et al.* [2005] (**neutralization**)
- 2G12: The HIV-1 Bori-15 variant was adapted from the Bori isolate for replication in microglial cells. Bori-15 had increased replication in microglial cells and a robust syncytium-forming phenotype, ability to use low levels of CD4 for infection, and increased sensitivity to neutralization by sCD4 and

17b. Four amino acid changes in gp120 V1-V2 were responsible for this change. Protein functionality and integrity of soluble, monomeric gp120-molecules derived from parental HIV-1 Bori and microglia-adapted HIV-1 Bori-15 was assessed in ELISA binding assays using CD4BS MAbs F105 and IgG1b12, glycan-specific 2G12, and V3-specific 447-52D, and were unchanged. Association rates of sCD4 and 17b were not changed, but dissociation rates were 3-fold slower for sCD4 and 14-fold slower for 17b. Martín-García *et al.* [2005] (**antibody binding site definition and exposure**)

- 2G12: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **antibody interactions**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **immunotherapy**, **review**, **structure**)
- 2G12: Viruses containing substitutions at either L568 or K574 of the gp41 hydrophobic pocket were resistant to D5-IgG1 but were as sensitive to 2G12 as the wildtype virus. Miller *et al.* [2005]
- 2G12: This short review summarizes recent findings of the role of neutralizing Abs in controlling HIV-1 infection. Certain neutralizing MAbs and their potential role in immunotherapy and vaccination, as well as the reasons for their poor immunogenicity, are discussed. Montefiori [2005] (**antibody binding site definition and exposure**, **therapeutic vaccine**, **escape**, **immunotherapy**)
- 2G12: A short review of 2F5 and 4E10 interaction with autoantigens, epitope accessibility, structure, neutralizing capability, and the reasons for their infrequent appearance in nature. Immunotherapy and escape to 2G12 is also discussed. Nabel [2005] (**escape**, **immunotherapy**, **review**)
- 2G12: Passive immunization of 8 HIV-1 infected patients with 4E10, 2F5 and 2G12 (day 0, 4E10; days 7, 14 and 21 4E10+2G12+2F5; virus isolated on days 0 and 77) resulted in 0/8 patients with virus that escaped all three NAbs. Three patients had viruses that escaped 2G12, and two of these were sequenced. Each had lost two of the glycosylation sites required for 2G12 binding (one had 295 N->D and 332 N->T changes, the other had 295 N->T and 392 N->T changes). In a companion in vitro study, resistance to a single MAb emerged in 3-22 weeks, but triple combination resistance was slower and characterized by decreased viral fitness. In contrast to the in vivo escape study, only one N was lost in the in vitro experiments, a 386 N->K change in a triple resistant mutant. The lack of resistance to the combination of MAbs in vivo and the reduced fitness of the escape mutants selected in vitro suggests passive immunotherapy may be of value in HIV infection. Nakowitsch *et al.* [2005] (**escape**, **immunotherapy**)
- 2G12: 2G12 neutralized JR-FL, but not YU2 HIV-1 strain. 2G12 and other neutralizing mAbs recognized JR-FL cleavage-competent and cleavage-defective env glycoproteins, while non-neutralizing Abs only recognized JR-FL cleavage-defective glycoproteins. It is suggested that an inefficient env glycoprotein precursor cleavage exposes non-neutralizing determinants, while only neutralizing regions remain accessible on efficiently cleaved spikes. For YU2, both cleavage-competent and -defective glycoproteins were recognized by both neutralizing and non-neutralizing Abs. Pancera & Wyatt [2005] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- 2G12: Concanavalin A (ConA) binds to mannose and blocks 2G12 binding, but 2G12 does not block ConA binding. ConA binding is less sensitive to mutations in glycosylation sites than 2G12. Furthermore, ConA neutralizes HIV-1 at a post-CD4 binding step. Thus, this report indicates that designing antigens based on the HIV-1 mannose residues that bind ConA may be an effective vaccine strategy, as antibodies elicited might be broadly cross-reactive. Pashov *et al.* [2005b] (**vaccine antigen design**)
- 2G12: 2G12 was used as isolating template for screening of a phage library in order to develop mimotopes that target carbohydrate antigens of gp120. Specific binding of 2G12 to three phages expressing peptides was observed, however, 2G12 did not bind to the peptides themselves. Pashov *et al.* [2005a] (**assay development**)
- 2G12: This study is about the V2 MAb C108g, that is type-specific and neutralizes BaL and HXB2. JR-FL is a neutralization resistant strain; modification of JRFL at V2 positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potently neutralize the modified JR-FL. The modification in V2 also increased neutralization sensitivity to V3 MABs 4117c, 2219, 2191, and 447-52D, but only had minor effects on neutralization by CD4BS MAb 5145A, and broadly neutralizing MAbs IgG1b12, 2G12, and 2F5. Pinter *et al.* [2005] (**antibody binding site definition and exposure**)
- 2G12: Virions containing a single point mutation Y706C in gp41 had a 10-fold increase in binding to 2G12 compared to wildtype. This, together with the same p24 supernatant levels after transfection with wildype and mutant virus, indicated that the mutant virions contained more envelope on a per-particle basis. Poon *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)
- 2G12: Retrovirus inactivation for vaccine antigen delivery was explored through lipid modification by hydrophobic photoinduced alkylating probe 1.5 iodonaphthylazide (INA). The viral proteins were shown to be structurally intact in the treated non-infectious virus, through the preservation of antibody binding sites for polyclonal anti-gp120 serum, and for broadly neutralizing MAbs 2G12, b12 and 4E10, although the modifications of the lipid disabled viral infection. Raviv *et al.* [2005] (**vaccine antigen design**)
- 2G12: Escape mutations in HR1 of gp41 that confer resistance to Enfuvirtide reduced infection and fusion efficiency and also delayed fusion kinetics of HIV-1. They also conferred increased neutralization sensitivity to a subset of neutralizing MAbs that target fusion intermediates or with epitopes exposed following receptor interactions. Enhanced neutralization correlated with reduced fusion kinetics. None of the mutations had a significant effect on 2G12 neutralization

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of virus. Reeves *et al.* [2005] (**antibody binding site definition and exposure**, **drug resistance**, **neutralization**, **escape**, **HAART, ART**)

- 2G12: There was no difference found in the neutralization sensitivity of viruses isolated from acutely and from chronically infected HIV-1 patients to this Ab, suggesting that the glycosylation sites manifesting the epitope of 2G12 are well conserved throughout the course of infection. Rusert *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **acute/early infection**)
- 2G12: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. 2G12 had diminished binding to both antigen constructs. Selvarajah *et al.* [2005] (**vaccine antigen design**, **vaccine-specific epitope characteristics**)
- 2G12: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **binding affinity**, **immunotherapy**, **review**, **structure**)
- 2G12: Six acutely and eight chronically infected patients were passively immunized with a mix of 2G12, 2F5 and 4E10 neutralizing Abs during treatment interruption. Two chronically and four acutely infected individuals showed evidence of a delay in viral rebound during Ab treatment suggesting that NAbs can contain viremia in HIV-1 infected individuals. All subjects with virus sensitive to 2G12 developed Ab escape mutants resulting in loss of viremia and failure to treatment. In several cases resistance to 2G12 emerged rapidly. Plasma levels of 2G12 were substantially higher than those of 2F5 and 4E10, and the 2G12 levels exceeded the in vitro required 90% inhibitory doses by two orders of magnitude in subjects that responded to Ab treatment. This suggested that high levels of NAbs are required for inhibition in vivo. Trkola *et al.* [2005] (**neutralization**, **acute/early infection**, **escape**, **immunotherapy**, **early treatment**, **HAART, ART**, **supervised treatment interruptions (STI)**)
- 2G12: Ab neutralization of viruses with mixtures of neutralization-sensitive and neutralization-resistant envelope glycoproteins was measured. It was concluded that binding of a single Ab molecule is sufficient to inactivate function of an HIV-1 glycoprotein trimer. The inhibitory effect of the Ab was similar for neutralization-resistant and -sensitive viruses indicating that the major determinant of neutralization potency of an Ab is the efficiency with which it binds to the trimer. It was also indicated that each functional trimer on the virus surface supports HIV-1 entry independently, meaning that every trimer on the viral surface must be bound by an Ab for neutralization of the virus to be achieved. Yang *et al.* [2005c] (**neutralization**)
- 2G12: A substantial fraction of soluble envelope glycoprotein trimers contained inter-subunit disulfide bonds. Reduction of these disulfide bonds had little effect on binding of the 2G12 to the glycoprotein, indicating that the inter-S-S bonds had no impact on the exposure of 2G12 epitope. Yuan *et al.* [2005] (**antibody binding site definition and exposure**)
- 2G12: This review summarizes data that indicate that the V3 region of HIV-1 may be an epitope to target for the induction of protective Abs. Data shows that the V3 region can induce broadly-reactive, cross-neutralizing Abs, that it is partially exposed during various stages of the infectious process, and that it is immunogenic. 2G12 is the only highly neutralizing MAb targeting the carbohydrate region of gp120, suggesting that this region does not induce protective Abs. The carbohydrate epitope is poorly immunogenic and 2G12 has an aberrant structure probably extremely rare in the human Ab repertoire. Zolla-Pazner [2005] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **review**)
- 2G12: 93 viruses from different clades were tested for their neutralization cross-reactivity using a panel of HIV antibodies. 2G12 primarily neutralized B clade viruses with sporadic neutralization of A, D, and two AC recombinants, and no C or CRF01 (E) isolates. Envelopes from subtypes C and E have generally lost critical glycans for 2G12 binding. Binley *et al.* [2004] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2G12: The peptide 12p1 (RINNIPWSEAMM) inhibits direct binding of YU2 gp120 or Env trimer to CD4, CCR5 and MAb 17b in a concentration-dependent allosteric manner. 12p1 is thought to bind to unbound gp120 near the CD4 binding site, with a 1:1 stoichiometry. 12p1 also inhibited MAb F105 binding. presumably because F105 favors an unactivated conformation, but not MAbs 2G12 or b12. The 1:1 stoichiomtry, the fact that the peptide binding site is accessible on the trimer, the non-CD4 like aspect of the binding, and an ability to inhibit viral infection in cell cultures make it a promising lead for therapeutic design. Biorn *et al.* [2004]
- 2G12: Env sequences were derived from 4 men at primary infection and four years later; the antigenicity in terms of the ability to bind to 2G12, 2F5 and IgG1b12 was determined. 2G12 bound primarily to late clones in 3 of the 4 patients, and to both early and late in the other patient. Neither 2F5 nor IgG1b12 showed a difference in binding affinity to early or late envelopes. The number of glycosylation sites increased in the three patients. The ability to bind to 2G12 correlated perfectly with having all three sites known to be important for binding: N295 in C2, N332 in C3, and N392 in the V4 loop. Dacheux *et al.* [2004] (**antibody binding site definition and exposure**, **acute/early infection**, **kinetics**)
- 2G12: Neonatal rhesus macaques were exposed orally to a pathogenic SHIV, 89.6P. 4/8 were given an intramuscular, passive immunization consisting of NAbs 2G12, 2F5 and 4E10, each given at a different body sites at 40 mg/kg per Ab, at one hour and again at 8 days after exposure to 89.6P. The four animals that were untreated all died with a mean survival time of 5.5 weeks, the four animals that got the NAb combination

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were protected from infection. This model suggests Abs may be protective against mother-to-infant transmission of HIV. Ferrantelli *et al.* [2004b] (**mother-to-infant transmission**)

- 2G12: Nabs against HIV-1 M group isolates were tested for their ability to neutralize 6 randomly selected HIV-1 O group strains. 2G12 didn't neutralizeO group strains, although it was included in a quadruple combination of b12, 2F5, 2G12, and 4E10, that neutralized the six Group O viruses between 62-97%. Ferrantelli *et al.* [2004a] (**variant cross-recognition or cross-neutralization**)
- 2G12: This paper is a reviw of anti-HIV-1 Envelope antibodies. This unique epitope is formed from carbohydrates. The mechanism of MAb neutralization is thought to be steric inhibition of CCR5 binding. 2G12 neutralizes many TCLA strains and about 40% of primary isolates tested. Gorny & Zolla-Pazner [2004] (**review**)
- 2G12: A set of oligomeric envelope proteins were made from six primary isolates for potenial use as vaccine antigens: 92/UG/037 (clade A), HAN2/2 (clade B), 92/BR25/025 (clade C), 92/UG/021 (clade D), 93/BR/029 (clade F) and MVP5180 (clade O). This was one of a panel of MAbs used to explore folding and exposure of well characterized epitopes. The clade C isolate BR25 is apparently misfolded, as conformation-dependent antibodies did not bind to it. 2G12 bound to clade A, B, D and F HIV-1 primary isolates. Polyclonal sera raised in rabbits against these antigens cross-bound the other antigens, but none of the sera had neutralizing activity. Jeffs *et al.* [2004] (**vaccine antigen design**, **subtype comparisons**)
- 2G12: 2G12 was used as a positive control in a study that showed that A32-rgp120 complexes open up the CCR5 co-receptor binding site, but did not induce neutralizing antibodies with greater breadth among B subtype isolates than did uncomplexed rgp120 in vaccinated guinea pigs. Liao *et al.* [2004] (**vaccine antigen design**)
- 2G12: Mice susceptible to MV infection were intraperitoneally immunized with native HIV-1 89.6 env gp160 and gp140 and δV3 HIV-1 89.6 mutants expressed in live attenuated Schwarz measles vector (MV). The gp160ΔV3 construct raised more cross-reactive NAbs to primary isolates. A HIVIG/2F5/2G12 combination was used as a positive control and could neutralize all isolates. Lorin *et al.* [2004] (**vaccine antigen design**)
- 2G12: A set of HIV-1 chimeras that altered V3 net charge and glycosylation patterns in V1V2 and V3, involving inserting V1V2 loops from a late stage primary isolate taken after the R5 to X4 switch, were studied with regard to phenotype, co-receptor usage, and MAb neutralization. The loops were cloned into a HXB2 envelope with a LAI viral backbone. It was observed that the addition of the late-stage isolate V1V2 region and the loss of V3-linked glycosylation site in the context of high positive charge gave an X4 phenotype. R5X4 viruses were more sCD4 and 2G12 neutralization resistant than either R5 or X4, but the opposite pattern was observed for b12. Addition of the late stage V1V2 altered neutralization for both MAbs, but this alteration was reversed with the loss of the V3 glycan. Nabatov *et al.* [2004] (**antibody binding site definition and exposure**, **co-receptor**)
- 2G12: An antigen panel representing different regions of gp41 was generated, and sera from 23 individuals were screened. 2G12 was a control, binding to gp120 but to none of the gp41 peptides in the experiment. Opalka *et al.* [2004] (**assay development**, **assay standardization/improvement**)
- 2G12: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it binds to the neutralizing MAb 2G12. It masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- 2G12: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neturalization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. 2G12 was the only MAb that neutralized JRFL more efficiently than SF162, with a 6-fold lower ND50 for JRFL. 2G12 also had ahigher affinity for JRFL. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 2G12: A primary isolate, CC1/85, was passaged 19 times in PBMC and gradually acquired increased sensitivity to FAb b12 and sCD4 that was attributed to changes in the V1V2 loop region, in particular the loss of a potential glycosylation site. The affinity for sCD4 was unchanged in the monomer, suggesting that the structural impact of the change was manifested at the level of the trimer. The passaged virus, CC-con19, retained an R5 phenotype and its neutralization susceptibility to other Abs was essentially the same as CC1/85. The IC50 for 2G12 was 1.8 for CC1/85, and was 4.2 for CC-con19, so both the primary and passaged viruses were neutralized. Pugach *et al.* [2004] (**variant cross-recognition or cross-neutralization**, **viral fitness and reversion**)
- 2G12: This review discusses research presented at the Ghent Workshop of prevention of breast milk transmission and immunoprophylaxis for HIV-1 in pediatrics (Seattle, Oct. 2002), and makes the case for developing passive or active immunoprophylaxis in neonates to prevent mother-to-infant transmission. Macaque studies have shown that passive transfer of NAb combinations (for example, IgG1b12, 2G12, 2F5, and 4E10; or 2G12 and 2F5) can confer partial or complete protection to infant macaques from subsequent oral SHIV challenge. Safrit *et al.* [2004] (**immunoprophylaxis**, **mother-to-infant transmission**)
- 2G12: Synthetic mannose Man9 clusters arranged on a scaffold were used to mimic the epitope of 2G12. Bi-, tri, and tetra-valent clusters had a 7-, 22-, and 73-fold higher affinities for 2G12 than the monomers, suggesting that 2G12 binds best to multiple carbohydrate moieties. 2G12 bound larger mannose oligosaccharides with higher affinity: Ma9GlcNAc bound 210- and 74-fold more effectively that Man6GlcNac

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and Man5GlcNAc, respectively. Wang *et al.* [2004] (**antibody binding site definition and exposure**)

- 2G12: SOS-Env is a mutant protein engineered to have a disulfid bond between gp120 and gp41. Cells expressing SOS-Env due not fuse with target cells expressing CD4 and CCR5, although the fusion process proceeds to an intermediate state associated with CD4 and co-receptors, prior to the formation of the six helix bundle that allows fusion.2G12 was used to monitor surface expression of SOS-Env compared to wildtype. Abrahamyan *et al.* [2003] (**co-receptor**, **vaccine antigen design**)
- 2G12: 2G12 was used as a positive control to test for a NAb activity in mice intranasally immunized with gp120 or gp140 with IL-12 and Cholera Toxin B. Albu *et al.* [2003]
- 2G12: The SOS mutant envelope protein introduces a covalent disulfide bond between gp120 surface and gp41 transmembrane proteins into the R5 isolate JR-FL by adding cysteines at residues 501 and 605. Pseudovirions bearing this protein bind to CD4 and co-receptor bearing cells, but do not fuse until treatment with a reducing agent, and are arrested prior to fusion after CD4 and co-receptor engagement. 2G12 is able to neutralize both the wildtype and SOS protein comparably, but 2G12 could not neutralize SOS when added post-attachment. Binley *et al.* [2003] (**vaccine antigen design**)
- 2G12: Crystal structure analysis of Fab 2G12 alone or complexed with Manα1-2Man or Man9GlcNac2 demonstrates that the exchange of VH domains forms stable dimers for gp120 binding. Two Fabs assemble in an interlocked VH domain swapped dimer, providing an extended surface for multivalent interaction with the cluster of oligomannose on gp120, allowing high-affinity recognition of repeated epitopes in the carbohydrate structure. Ala substitutions of the 2G12 VH/VH' interface residues Ile H19, Arg H57, Phe H77, Tyr H80, Val H84 and Pro H113 result in the loss of 2G12-gp120 JR-FL binding. Calarese *et al.* [2003] (**antibody binding site definition and exposure**, **antibody sequence variable domain**, **structure**)
- 2G12:The MAb B4e8 binds to the base of the V3 loop, neutralizes multiple primary isolates and was studied for interaction with other MAbs. B4e8 and 2G12 enhanced each others binding, and gave synergistic neutralization. B4e8 could neutralize R5X4 virus 92HT593 better than 2G12, while 2G12 was better at neutralizing R5 virus 92US660. Cavacini *et al.* [2003] (**antibody interactions**)
- 2G12: 2G12 was used as a negative control to investigate the relationship of MAb 412d epitope to the CCR5 binding site of gp120. These two MAbs were incubated with soluble CD4 and ADA gp120 in the presence of a peptide shown to block the association of gp120-CD4 with CCR5. As expected, the presence of the peptide did not inhibit precipitation of gp120 by 2G12, since it binds an epitope distinct from the CCR5 binding domain, while it did inhibit the 412d. Choe *et al.* [2003] (**antibody binding site definition and exposure**)
- 2G12: A sCD4-17b single chain chimera was made that can bind to the CD4 binding site, then bind and block co-receptor interaction. This chimeric protein is a very potent neutralizing agent, more potent than IgG1b12, 2G12 or 2F5 against Ba-L infection of CCR5-MAGI cells. It has potential for prophylaxis or therapy. Dey *et al.* [2003] (**co-receptor**)
- 2G12: Four newborn macaques were challenged with pathogenic SHIV 89.6 and given post exposure prophylaxis using a combination of NAbs 2F5, 2G12, 4E10 and IgG1b12. 2/4 treated animals did not show signs of infection, and 2/4 macaques maintained normal CD4+ T cell counts and had a lower delayed peak viremia compared to the controls. Ferrantelli *et al.* [2003] (**immunoprophylaxis**, **mother-to-infant transmission**)
- 2G12: This study investigates the effects of glycosylation inhibitors on the binding between HIV-1 gp120 and mannose-binding lectin (MBL). Mannosidase I inhibitor deoxymannojirimycin (dMM) inhibits formation of complex and hybrid N-linked saccharides and yields virus with more mannose residues. dMM added during viral production significantly enhanced the binding 2F5 and 2G12, but not IgG1b12 in a viral capture assay. Hart *et al.* [2003] (**antibody binding site definition and exposure**)
- 2G12: CD4BS MAbs b12 (neutralizing) and 205-42-15, 204-43-1, 205-46-9 (non-neutralizing) all cross-competed for binding to monomeric gp120, indicating the topological proximity of their epitopes, however, the non-neutralizing CD4BS MAbs did not interfere with the neutralization activity of MAb b12 – 2G12 was used to normalize and as a control in these experiments. Herrera *et al.* [2003] (**antibody interactions**)
- 2G12: MAbs IgG1b12, 2G12, 2F5 and 4E10 were tested for their ability to neutralize two primary HIV-1 clade A isolates (UG/92/031 and UG/92/037) and two primary HIV-1 clade D isolates (UG/92/001 and UG/92/005). 4E10 demonstrated the most potent cross-neutralization activity. Quadruple administration of MAbs IgG1b12, 2G12, 2F5, and 4E10 induced strong synergistic neutralization of 4 clade A isolates (UG/92/031, UG/92/037, RW/92/020 and RW/92/025) as well as 5 clade D isolates (UG/92/001,UG/9/005, /93/086/RUG/94/108, UG/94/114). The authors note this combination of 4 MAbs neutralizes primary HIV A, B, C, and D isolates. Kitabwalla *et al.* [2003] (**antibody interactions**, **immunoprophylaxis**, **variant cross-recognition or cross-neutralization**, **mother-to-infant transmission**, **subtype comparisons**)
- 2G12: Polyclonal Abs raised against soluble trivalently linked N35CCG-N13 and N34CCG, the internal trimeric core of the coiled-coil ectodomain, inhibit HIV-1 Env-mediated cell fusion at levels comparable to 2G12. Louis *et al.* [2003] (**vaccine antigen design**)
- 2G12: This review dicusses the importance and function of protective antibody responses in animal model studies in the context of effective vaccine development. SHIV models have shown protection using high levels of MAbs can prevent infection, and partial protection that can influence disease course can be obtained from modest levels of NAbs. SHIV challenges studies conducted with infusions of combinations of MAbs b12, 2G12, and 2F5 are reviewed. Mascola [2003] (**immunoprophylaxis**, **review**)
- 2G12: Infusions of 2F5 and 2G12 intravenously administered 24h prior to vaginal SHIV-89.P challenge are able to protect macaques from infections. Animals that recieve a IL-2 adjuvanted DNA immunization SIV Gag and HIV Env have T-cell responses and lower viral loads, but were not protected. Suboptimal levels of 2F5 and 2G12 were not able to confer sterile

protection in combination with the T-cell responses stimulated by DNA immunizations. Mascola *et al.* [2003]

- 2G12: AC10 is a subject who was given treatment early after infection, and had a viral rebound after cessation of therapy, which then declined to a low level. The polyclonal sera from AC10 could potently neutralize the rebound virus, and NAb escape followed with a neutralizing response against the escape variant and subsequent escape from that response. Viral loads remained low in this subject despite escape. The rebound isolate that was potently neutralized by autologous sera was not particularly neutralization sensitive, as it resisted neutralization by sCD4 and MAbs IgG1b12, 2G12 and 2F5, and was only moderately sensitive to sera from other HIV+ individuals that had high titers of NAbs to TCLA strains. Montefiori *et al.* [2003] (**acute/early infection**, **escape**)
- 2G12: Env genes derived from uncultured brain biopsy samples from four HIV-1 infected patients with late-stage AIDS were compared to env genes from PBMC samples. Brain isolates did not differ in the total number or positions of N-glycosylation sites, patterns of coreceptor usage, or ability to be recognized by gp160 and gp41 MAbs. 2G12 was the only MAb tested to recognize all blood and brain isolates from all four patients by gp120 immunoprecipitation. Ohagen *et al.* [2003] (**variant cross-recognition or cross-neutralization**)
- 2G12: Alanine scanning mutagenesis was used to compare substitutions that affected anti-CD4BS NAb b12 – rec gp120s were engineered to contain combinations of Alanine substitutions that enhanced b12 binding, and while binding of b12 to these gp120 monomers was generally maintained or increased, binding by five non-neutralizing anti-CD4bs MAbs (b3, b6, F105, 15e, and F91) was reduced or completely abolished – 2G12 binding was largely unperturbed, indicating these proteins were not grossly misfolded. Pantophlet *et al.* [2003a] (**antibody binding site definition and exposure**)
- 2G12: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- 2G12: This paper shows that binding of CD4BS MAbs to Env blocks the conformational shift that allows co-receptor CCR5 binding and CD4-independent mediated cell fusion. CD4BS MAbs IgG1b12, F91 and F105 and their Fab counterparts (except for C11, used as a negative control) inhibited CD4-independent JR-FL and YU-2 gp120-CCR5 binding to CCR5-expressing Cf2Th cells and syncytium formation. The carbohydrated binding MAb 2G12 also inhibited CD4-independent syncytium formation. Raja *et al.* [2003] (**co-receptor**)
- 2G12: Most plasma samples of patients from early infection had NAb responses to early autologous viruses, and NAbs against heterologous strains tended to be delayed. Serial plasma samples were tested against serial isolates, and neutralization escape was shown to be rapid and continuous throughout infection. Autologous neutralization-susceptible and resistant viruses from four patients were tested for susceptability to neutralizing Ab responses using MAbs 2G12, IgG1b12 and 2F5. No correlation was established, all viruses tested were susceptible to at least one of the neutralizing MAbs. Two patients that did not have an autologous NAb response also did not evolve changes in susceptibility to these MAbs, while one patient with a pattern of autologous neutralization and escape acquired a 2G12 sensitive virus at month 6, and lost IgG1b12 sensitivity at month 21. Richman *et al.* [2003] (**autologous responses**, **acute/early infection**, **escape**)
- 2G12: To begin to design vaccine antigens that can mimic the carbohydrate structure, the gp120 peptide 336-342 was synthesized with Man(9), Man(6), and Man(5) moieties attached. Singh *et al.* [2003] (**vaccine antigen design**)
- 2G12: Review of current neutralizing antibody-based HIV vaccine candidates and strategies of vaccine design. Strategies for targeting of the epitopes for NAbs 2F5, 2G12, 4E10, b12, and Z13 are described. They have shown that both N-glycans, at 295N and 332N are required for 2G12 binding, emphasizing the oligosaccharide cluster nature of the epitope, and suggest the uniqueness of the target structure may not result in autoimmune reactions. Wang [2003] (**vaccine antigen design**, **review**)
- 2G12: The broadly neutralizing antibodies 2F5 and 2G12 were class-switched from IgG to IgA and IgM isotypes. Neutralizing potency was increased with valence for 2G12 so the IgM form was most potent, but for 2F5 the IgG form was most potent. Eight primary isolates were tested including two subtype A isolates. The polymeric IgM and IgA Abs, but not the corresponding IgGs, could interfere with HIV-1 entry across a mucosal epithelial layer, although they were limited in a standard neutralization assay. All isotypes could interact with activated human sera, presumably through complement, to inhibit HIV replication. Wolbank *et al.* [2003] (**complement**, **isotype switch**, **variant cross-recognition or cross-neutralization**, **mucosal immunity**, **subtype comparisons**)
- 2G12: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. 2G12 had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
- 2G12: A phase I trial in seven HIV+ individuals was conducted with MAbs 2F5 and 2G12 – no clinical or laboratory abnormalities were observed throughout the study – eight infusions were administered over a 4-week period (total dose 14 g) – the elimination half-life ($t_{1/2}$) was calculated to be 7.94 (range, 3.46–8.31) days for 2F5 and 16.48 (range, 12.84–24.85) days for 2G12. Armbruster *et al.* [2002] (**kinetics**, **immunotherapy**)
- 2G12: IgG1b12 neutralized many South African (5/8) and Malawian (4/8) clade C primary HIV-1 isolates, being more effective than 2F5 which neutralized only two Malawian and no South African isolates. 2G12 did not neutralize any of the 16 isolates. Bures *et al.* [2002] (**subtype comparisons**)
- 2G12: This study examined Ab interactions, binding and neutralization with a B clade R5 isolate (92US660) and R5X4

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isolate (92HT593). Abs generally bound and neutralized the R5X4 isolate better than the R5 isolate. Anti-gp41 MAb F240 did not affect binding of 2G12 to either R5X4 and R5 isolates, and anti-V3 MAb B4a1 increased 2G12 binding to R5X4 virions but not R5. Neutralization with B4al and 2G12 was additive for the R5X4 virus, and was enhanced for the R5 virus. Cavacini *et al.* [2002] (**antibody interactions**, **co-receptor**, **variant cross-recognition or cross-neutralization**)

- 2G12: A modified gp140 (gp140deltaCFI), with C-term mutations intended to mimic a fusion intermediate and stabilize trimer formation, retained antigenic conformational determinants as defined by binding to CD4 and to MAbs 2F5, 2G12, F105, and b12, and enhanced humoral immunity without diminishing the CTL response in mice injected with a DNA vaccine. Chakrabarti *et al.* [2002] (**vaccine antigen design**)
- 2G12: Truncation of the gp41 cytoplasmic domain of X4, R5, and X4R5 viruses forces a conformation that more closely resembles the CD4 bound state of the external Envelope, enhancing binding of CD4i MAbs 17b and 48d and of CD4BS MAbs F105, b12, and in most cases of glycosylation site dependent MAb 2G12 and the anti-gp41 MAb 246D – in contrast, binding of the anti-V2 MAb 697D and the anti-V3 MAb 694/98D were not affected – viruses bearing the truncation were more sensitive to neutralization by MAbs 48d, b12, and 2G12 – the anti-C5 MAb 1331A was used to track levels of cell surface expression of the mutated proteins. Edwards *et al.* [2002] (**antibody binding site definition and exposure**)
- 2G12: Review of NAbs that notes 2G12 alone or in combination with other MAbs can protect some macaques against SHIV infection, that it has strong ADCC activity, and that it is safe and well tolerated in humans. Ferrantelli & Ruprecht [2002] (**immunoprophylaxis**)
- 2G12: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – the preincubation 31.5 C step did not alter the inhibitory activity of neutralizing Abs anti-gp41 2F5, or anti-gp120 2G12, IG1b12, 48d, and 17b. Golding *et al.* [2002b] (**antibody binding site definition and exposure**)
- 2G12: UK1-br and MACS2-br are R5 isolates derived from brain tissue samples from AIDS patients with dementia and HIV-1 encephalitis; both are neurotropic, but only UK1-br induced neuronal apoptosis and high levels of syncytium formation in macrophages. UK1-br Env had a greater affinity for CCR5 than MACS-br, and required low levels of CCR5 and CD4 for cell-to-cell fusion and single round infection. PBMC infected with UK1-br and MACS2-br virus isolates were resistant to neutralization by MAb 2G12. UK1-br was more sensitive than MACS2-br to IgG1b12, 2F5 and CD4-IgG2 neutralization. Gorry *et al.* [2002] (**brain/CSF**, **co-receptor**)
- 2G12: HIV-1 gp160deltaCT (cytoplasmic tail-deleted) proteoliposomes (PLs) containing native, trimeric envelope glycoproteins from R5 strains YU2 and JRFL, and X4 strain HXBc2, were made in a physiologic membrane setting as candidate immunogens for HIV vaccines – 2F5 bound to gp160deltaCT with a reconstituted membrane ten-fold better than the same protein on beads, while such an affinity difference was not seen with F105 and 2G12 – anti-CD4BS MAbs IgG1b12 and F105, A32 (C1-C4), C11 (C1-C5), and 39F (V3) MAbs bound gp160deltaCT PLs indistinguishably from gp160deltaCT expressed on the cell surface. Grundner *et al.* [2002] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- 2G12: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, except for 2G12, which might not have bound well to the carbohydrate additions on the Drosophila expressed core. Enthalpy and entropy changes were divergent, but compensated. Not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs (17b, 48d, 1.5e, b6, F105 and F91) had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, but the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. The high values suggest surface burial or protein folding an ordering of amino acids. 2G12 had an entropy value of -1.6. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- 2G12: Review of NAbs that discusses mechanisms of neutralization, passive transfer of NAbs and protection in animal studies, and vaccine strategies. Liu *et al.* [2002] (**review**)
- 2G12: Rhesus macaques were better protected from vaginal challenge with SHIV89.6D (MAb 2G12, 2/4; MAbs 2F5/2G12, 2/5; and HIVIG/2F5/2G12, 4/5 infected) than from intravenous challenge (MAb 2G12, 0/3; MAbs 2F5/2G12, 1/3; and HIVIG/2F5/2G12, 3/6 infected)– the animals that were infected by vaginal challenge after Ab infusion had low or undetectable viral RNA levels and modest CD4 T-cell decline. Mascola [2002] (**immunoprophylaxis**, **mucosal immunity**)
- 2G12: The 2G12 epitope is composed of carbohydrates involving high-mannose and hybrid glycans of residues 295, 332, and 392, with peripheral glycans from 386 and 448 contributing on either flank, and with little direct gp120 protein surface involvement – these mannose residues are proximal to each other near the chemokine receptor binding surface. Sanders *et al.* [2002] (**antibody binding site definition and exposure**)
- 2G12: Alanine scanning mutagenesis used in conjunction with competition and replacement studies of N-linked carbohydrates and sugars suggest that the 2G12 epitope is formed from mannose residues contributed by the glycans attached to N295 and N332, with the other N-linked carbohydrates in positions N339, N386, and N392 playing a role in maintaining conformation relevant to 2G12 binding – N295A and N332A mutants showed essentially unchanged anti-CD4BS NAb b12 binding affinities, while N339A, N386A and N392A mutants

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displayed significantly lowered b12 affinity, presumably due to conformational changes. Scanlan *et al.* [2002] (**antibody binding site definition and exposure**)

- 2G12: Ab binding characteristics of SOS gp140 were tested using SPR and RIPA – SOS gp140 is gp120-gp41 bound by a disulfide bond – NAbs 2G12, 2F5, IgG1b12, CD4 inducible 17b, and 19b bound to SOS gp140 better than uncleaved gp140 (gp140unc) and gp120 – non-neutralizing MAbs 2.2B (binds to gp41 in gp140unc) and 23A (binds gp120) did not bind SOS gp140 – 2G12 complexes with SOS gp140 or with gp120 had a very unusual linear structure. Schulke *et al.* [2002] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- 2G12: The antiviral response to intravenously administered MAbs 2F5 and 2G12 was evaluated in 7 HAART-naïve asymptomatic HIV-1 infected patients during a treatment period of 28 days. MAb therapy reduced plasma HIV RNA in 3/7 patients during the treatment period, and transiently reduced viral load in two more. CD4 counts were up in 3/7 through day 28, and transiently increased in three more. Vigorous complement activation was observed after 48/56 Ab infusions. Virus derived from 2/7 patients could be neutralized by 2G12, and escape from 2G12 was observed in both cases after infusion; one year after the infusion, isolates were again sensitive to 2G12. Stiegler *et al.* [2002] (**complement**, **variant cross-recognition or cross-neutralization**, **escape**, **immunotherapy**)
- 2G12: Passive immunization of neonate macaques with a combination of F105+2G12+2F5 conferred complete protection against oral challenge with SHIV-vpu+ or – the combination b12+2G12+2F5 conferred partial protection against SHIV89.6 – such combinations may be useful for prophylaxis at birth and against milk born transmission – the synergistic combination of IgG1b12, 2G12, 2F5, and 4E10 neutralized a collection of HIV clade C primary isolates. Xu *et al.* [2002] (**antibody interactions**, **immunoprophylaxis**, **mother-to-infant transmission**)
- 2G12: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibritin – stabilized oligomer gp140 delta683(-FT) showed strong preferential recognition by NAbs IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAbs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and MAbs C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002] (**antibody binding site definition and exposure**)
- 2G12: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002] (**antibody binding site definition and exposure**)
- 2G12: SF162DeltaV2 is a virus that has a 30 amino acids deletion in the V2 loop that does not abrogate its infectivity but renders it highly susceptible to neutralization – when incorporated into a codon-optimized DNA vaccine with a CMV promoter and delivered by gene gun, SF162DeltaV2 gave higher neutralizing Ab titers against SF162 than did SF162 itself, and Abs that cross-neutralized non-homologous primary isolates were obtained only when SF162DeltaV2, but not intact SF162, was used as the immunogen – Control MAbs 2F5 and 2G12 could neutralize all of the following primary isolates: 91US056(R5), 92US714(R5), 92US660(R5), 92HT593(R5X4), and BZ167(R5X4), while after the first protein boost, the sera from two SF162DeltaV2 immunized macaques could neutralize 91US056(R5), 92US714(R5), 92US660(R5) and ADA(R5), but not 92HT593(R5X4) or 92US657(R5) – the pattern of cross-recognition shifted after the second boost. Barnett *et al.* [2001] (**vaccine antigen design**)
- 2G12: A combination of MAbs IgG1b12, 2F5, and 2G12 was given postnatally to four neonates macaques that were then challenged with highly pathogenic SHIV89.6P – one of the four infants remained uninfected after oral challenge, two infants had no or a delayed CD4(+) T-cell decline. Hofmann-Lehmann *et al.* [2001] (**immunoprophylaxis**, **mother-to-infant transmission**)
- 2G12: Review of studies in macaques that have shown immune control of pathogenic SHIV viremia, improved clinical outcome, and protection, and the implications of the observations for HIV vaccines. Mascola & Nabel [2001] (**review**)
- 2G12: Moore and colleagues review structural aspects of gp120 and how they relate to antigenic domains, and review the data concerning the lack of a clear relationship between genetic subtype and serotype – an exception exists for human MAb 2G12, which does not recognize CRF01 envelopes because of an unusual additional disulfide bond in the V4 loop region that appears to be unique to the subtype E, CRF01 gp120 protein. Moore *et al.* [2001] (**antibody binding site definition and exposure**, **review**)
- 2G12: Structural aspects of the interaction of neutralizing Abs with HIV-1 Env are reviewed – Env essentially has three faces, one is largely inaccessible on the native trimer, and two that exposed but have low immunogenicity on primary viruses – neutralization is suggested to occur by inhibition of the interaction between gp120 and the target cell membrane receptors as a result of steric hindrance and it is noted that the attachment of approximately 70 IgG molecules per virion is required for neutralization, which is equivalent to about one IgG molecule per spike – the 2G12, 17b and b12 epitopes are discussed in detail – although it is potently neutralizing, 2G12 does not interfere with CD4 and coreceptor binding, and this Ab specificity is uncommon in sera from HIV-1-infected individuals. Poignard *et al.* [2001] (**antibody binding site definition and exposure**, **review**)
- 2G12: Chloroquine reduces the HIV-1-infectivity of H9 IIIB cells, apparently through altering the conformation of envelope – there is a reduction of reactivity of 2G12 to its epitope in

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chloroquine treated cultures. Savarino *et al.* [2001] (**antibody binding site definition and exposure**)

- 2G12: SHIV-HXBc2 is a neutralization sensitive non-pathogenic virus, and several *in vivo* passages through monkey's yielded highly pathogenic SHIV KU-1 – HXBc2 and the KU-1 clone HXBc2P3.2 differ in 12 amino acids in gp160 – substitutions in both gp120 and gp41 reduced the ability of sCD4, IgG1b12, F105 and AG1121 to Env achieve saturation and full occupancy, and neutralize KU-1 – 17b and 2F5 also bound less efficiently to HXBc2P3.2, although 2G12 was able to bind both comparably. Si *et al.* [2001]
- 2G12: A luciferase-reporter gene-expressing T-cell line was developed to facilitate neutralization and drug-sensitivity assays – luciferase and p24 antigen neutralization titer end points were found comparable using NAb from sera from HIV+ donors, and MAbs 2F5, 2G12 and IgG1b12. Spenlehauer *et al.* [2001] (**assay development**)
- 2G12: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001] (**antibody interactions**)
- 2G12: Twenty HIV clade C isolates from five different countries were susceptible to neutralization by anti-clade B MAbs in a synergistic quadruple combination of mAbs IgG1b12, 2G12, 2F5, and 4E10. Xu *et al.* [2001] (**antibody interactions**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2G12: Neutralizing synergy between MAbs 1b12, 2G12 and 2F5 was studied using surface plasmon resonance to determine the binding kinetics for these three MAbs with respect to monomeric and oligomeric Env protein gp160 IIIB – the 2G12 epitope is highly accessible on both monomeric and oligomeric Envs, 1b12 is highly accessible on monomers but not oligomers, and 2F5 on neither form – binding of 2G12 exposes the 2F5 epitope on gp160 oligomers – 2G12-gp160 oligomer interactions were best fitted to a two state model, with the first complex having a high association constant and fast dissociation, stabilized by conformational changes induced by the binding of a second MAb. Zeder-Lutz *et al.* [2001] (**antibody binding site definition and exposure**, **antibody interactions**, **kinetics**)
- 2G12: Neutralization synergy between anti-HIV NAbs b12, 2G12, 2F5, and 4E10 was studied – a classic fixed-ratio method was used, as well as a method where one Ab was fixed at a low neutralization titer and the other was varied – using primary isolates, a two-four fold enhancement of neutralization was observed with MAb pairs, and a ten-fold enhancement with a quadruple Ab combination – no synergy was observed with any MAb pair in the neutralization of TCLA strain HXB2 – there was no evidence for cooperativity of binding between b12 and 2G12 to envelope spikes expressed on the cell surface of TCLA or primary isolates. Zwick *et al.* [2001c] (**antibody interactions**)
- 2G12: A triple combination of 2F5, F105 and 2G12 effectively neutralized perinatal infection of macaque infants when challenged with SHIV-vpu+ – the mean plasma half-life was 14.0 +/- 7.9 days, the longest of the three Abs. Baba *et al.* [2000] (**immunoprophylaxis**, **mother-to-infant transmission**)
- 2G12: To determine the antigenicity of virus killed by thermal and chemical inactivation, retention of conformation-dependent neutralization epitopes was examined, and exposure of CD4BS epitopes was found to be enhanced (MAbs IgG1b12, 205-46-9, and 205-43-1) – binding to 2G12 and 447-52D epitopes was essentially unaltered – the 17b CD4i epitope was also exposed. Grovit-Ferbas *et al.* [2000] (**vaccine antigen design**)
- 2G12: Because HIV-1 is most often transmitted across mucosal surfaces, the ability of passive transfer of infused HIVIG/2F5/2G12 to protect against mucosal exposure of macaques to pathogenic SHIV 89.6PD was studied – HIVIG/2F5/2G12 protected 4/5 animals against vaginal challenge, 2F5/2G12 combined protected 2/5 animals, and 2G12 alone protected 2/4 animals – in contrast, Mascola and coworkers had previously shown single MAbs could not protect against intervenous challenge – Ab treated animals that got infected through vaginal innoculation had low viral loads and only modest declines in CD4 counts – the infused Abs were detected in the nasal, vaginal, and oral mucosa. Mascola *et al.* [2000] (**immunoprophylaxis**, **mucosal immunity**)
- 2G12: Six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – 2G12 was an exception and could not neutralize MN in either form. Park *et al.* [2000]
- 2G12: A mini-review of observations of passive administration of IgG NAbs conferring protection against intervenous or vaginal SHIV challenge, that considers why IgG MAbs might protect against mucosal challenge. Robert-Guroff [2000] (**immunoprophylaxis**, **mucosal immunity**, **review**)
- 2G12: A Semliki Forest virus (SFV) expression system carrying BX08 Env was used to study the conformation of gp120 Env – intracytoplasmic gp120 was recognized by the anti-V3 MAbs K24 and F5.5, while gp120 at the plasma membrane was detected only by conformation dependent MAbs 2G12, 670-D and 694/98D and not V3 MAbs – expression in rat brain also showed that surface expressed Env was recognized only by the conformation-dependent Abs and not by anti-V3 Abs. Altmeyer *et al.* [1999]
- 2G12: rgp120 derived from a R5X4 subtype B virus was used to vaccinate healthy volunteers and the resulting sera were compared with sera from HIV-1 positive subjects and neutralizing MAbs – 2G12 was able to bind with low affinity to the rgp120 monomer HIV-1 W61D. Beddows *et al.* [1999]
- 2G12: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by

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NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999] (**antibody binding site definition and exposure**, **vaccine antigen design**)

- 2G12: Neutralization assays with rsCD4, MAbs, and serum samples from SHIV-infected macaques and HIV-1 infected individuals were used to characterize the antigenic properties of the env glycoprotein of six primary isolate-like or TCLA SHIV variants. 2G12 neutralized the five SHIV strains tested, HXBc2, KU2, 89.6, 89.6P and KB9, in MT-2 cells. Crawford *et al.* [1999] (**variant cross-recognition or cross-neutralization**)
- 2G12: Combinations of HIVIG, 2F5, 2G12 were administered in passive-transfer experiments 24 hours prior to challenge with pathogenic SHIV 89.6PD – 3/6 animals given HIVIG/2F5/2G12 were completely protected, the others had reduced viremia and normal CD4 counts – 1/3 monkeys given 2F5/2G12 showed transient infection, the other two had reduced viral load – all monkeys that received HIVIG, 2F5, or 2G12 alone became infected and developed high-level plasma viremia, although animals that got HIVIG or 2G12 had a less profound CD4 T cell decline. Mascola *et al.* [1999] (**antibody interactions**)
- 2G12: A meeting summary presented results regarding neutralization –MAbs 2G12 and 2F5 tested for their ability to neutralize primary isolate infection of genetically engineered cell lines (cMAGI and others, presented by T. Matthews, A. Trkola, J. Bradac) – an advantage of such cells lines over PBMCs is that markers (X-Gal) can be added for staining to simplify the assay – the consensus of the meeting was that these engineered cell lines did not improve the sensitivity of detection of primary isolate neutralization – D. Burton and J. Mascola presented results concerning passive immunization and protection of hu-PBL-SCID mice and macaques, respectively, and both found combinations of MAbs that were able to achieve 99% neutralization *in vitro* corresponded to efficacy *in vivo*. Montefiori & Evans [1999] (**review**)
- 2G12: Review of the neutralizing Ab response to HIV-1. Parren *et al.* [1999] (**review**)
- 2G12: Hu-PBL-SCID mice were infected with HIV-1s JRCSF and SF162 to study the effect of NAbs on an established infection – no significant differences in the initial rate of decrease in viral load or the plateau levels of viral RNA between the b12 treated and control mice were seen – in most of the Ab treated mice b12 escape mutants were observed with varying patterns of mutations – a combination of b12, 2G12 and 2F5 protected 1/3 mice, and an isolate from one of the other two was resistant to neutralization by all three MAbs. Poignard *et al.* [1999] (**antibody interactions**, **escape**)
- 2G12: Post-exposure prophylaxis was effective when MAb 694/98-D was delivered 15 min post-exposure to HIV-1 LAI in hu-PBL-SCID mice, but declined to 50% if delivered 60 min post-exposure, and similar time constraints have been observed for HIVIG, 2F5 and 2G12, in contrast to MAb BAT123 that could protect when delivered 4 hours post infection. Andrus *et al.* [1998] (**immunoprophylaxis**)
- 2G12: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer – MAb 2G12 was the only exception to this, showing reduced binding efficiency. Binley *et al.* [1998] (**antibody binding site definition and exposure**)
- 2G12: Ab from gp120 vaccinated individuals prior to infection, who subsequently became HIV infected, could not achieve 90% neutralization of the primary virus by which the individuals were ultimately infected – these viruses were not particularly refractive to neutralization, as determined by their susceptibility to neutralization by MAbs 2G12, IgG1b12, 2F5 and 447-52D. Connor *et al.* [1998]
- 2G12: Notes that 2G12 and 2F5, potent neutralizing antibodies, were identified by screening for cell surface (oligomeric Envelope) reactivity. Fouts *et al.* [1998] (**antibody binding site definition and exposure**)
- 2G12: Infection of dendritic cells cultured from CD14+ blood cells or from cadaveric human skin was blocked by neutralizing MAbs IgG1b12, or 2F5 and 2G12 delivered together, but not by control non-neutralizing anti-gp120 MAb 4.8D, indicating that NAbs could interrupt early mucosal transmission events. Frankel *et al.* [1998] (**mucosal immunity**)
- 2G12: The complete V, J and D(H) domain was sequenced – unlike non-neutralizing anti-gp41 MAb 3D6, five neutralizing MAbs (2F5, 2G12, 1B1, 1F7, and 3D5) showed extensive somatic mutations giving evidence of persistent antigenic pressure over long periods – 2G12 D(H) has the best homology to a D(H) segment between D3-22 and D4-23, a region not usually considered for heavy-chain rearrangement because it lacks associated recombination signals in the flanking regions, Kunert *et al.* suggest this may be why Abs that compete with 2G12 are rare. Kunert *et al.* [1998] (**antibody sequence variable domain**)
- 2G12: Neutralization synergy was observed when the MAbs 694/98-D (V3), 2F5 (gp41), and 2G12 (gp120 discontinuous) were used in combination, and even greater neutralizing potential was seen with the addition of a fourth MAb, F105 (CD4 BS). Li *et al.* [1998] (**antibody interactions**)
- 2G12: Enhances Hx10 binding to CD4 positive or negative HeLa cells, but inhibited binding to CD4+ T-cell line A3.01 – neutralizes Hx10 infection of the HeLa cells. Mondor *et al.* [1998]
- 2G12: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**antibody binding site definition and exposure**)
- 2G12: MAbs 2G12, 2F5 and b12 are broadly neutralizing, as are some human polyconal sera, but this paper describes a set of primary isolates that are resistant to all three MAbs and

2 broadly neutralizing sera – results indicate that resistance levels of pediatric isolates might be higher than adult isolates – resistance in general did not seem to be conferred by a loss of binding affinity for gp120 or gp41, rather by a more global perturbation of oligomeric Envelope. Parren *et al.* [1998b] (**variant cross-recognition or cross-neutralization**)

- 2G12: In a study of the influence of the glycan at position 306 of the V3 loop on MAb recognition, 2G12 was found to neutralize an HIV-BRU mutant virus that lacks the V3 loop glycan and has a mutation at the tip of the loop more efficiently than it neutralizes HIV-BRU. Schonning *et al.* [1998] (**antibody binding site definition and exposure**)
- 2G12: Does not compete with binding of MAb generated in response to gp120-CD4 complex, CG10. Sullivan *et al.* [1998b] (**antibody interactions**)
- 2G12: Induces complement-mediated lysis in MN but not primary isolates – primary isolates are refractive to CML. Takefman *et al.* [1998] (**complement**, **variant cross-recognition or cross-neutralization**)
- 2G12: A wide range of neutralizing titers was observed that was independent of co-receptor usage. Trkola *et al.* [1998] (**co-receptor**, **variant cross-recognition or cross-neutralization**)
- 2G12: Summary of the implications of the crystal structure of gp120 combined with what is known about mutations that reduce NAb binding – probable mechanism of neutralization by 2G12 is unknown, but dependent on proper glycosylation and 2G12 is predicted to be oriented toward the target cell when bound, so neutralization may be due to steric hindrance – mutations in positions N 295, T 297, S 334, N 386, N 392 and N 397 HXBc2 (IIIB) decrease 2G12 binding, and the binding region is 25 angstroms from the CD4 binding site – probably the Ab binds in part to carbohydrates, which may account for both its broad reactivity and the scarcity of Abs in the same competition group. Wyatt *et al.* [1998] (**antibody binding site definition and exposure**)
- 2G12: Review of the antigenic and receptor binding-domains of gp120 in relation to the structure of the molecule – MAbs are discussed by category (anti-V2, anti-V3, CD4i, CD4BS...), however as 2G12 binds to a rarely immunogenic region, and it is dependent on glycosylation, it was discussed individually. Wyatt & Sodroski [1998] (**review**)
- 2G12: Review that discusses this MAb – reacts with residues at the base of the V3 loop and V4, and most of the changes that reduce binding are glycosylation sites – it is not clear whether the binding site is peptidic or direct carbohydrate. Burton & Montefiori [1997] (**antibody binding site definition and exposure**, **review**)
- 2G12: In a multilab evaluation of monoclonal antibodies, only IgG1b12, 2G12, and 2F5 could neutralize at least half of the 9 primary test isolates at a concentration of < 25 mug per ml for 90% viral inhibition – neutralized 6 of 9 primary isolates. D'Souza *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- 2G12: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – 2G12 bound monomer, and weakly bound oligomer and neutralized JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
- 2G12: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB Env – 2G12 was a strong neutralizer of SHIV-vpu+ – all Ab combinations tested showed synergistic neutralization – 2G12 has synergistic response with MAbs 694/98-D (anti-V3), 2F5, F105, and b12. Li *et al.* [1997] (**antibody interactions**)
- 2G12: Using concentrations of Abs achievable *in vivo*, the triple combination of 2F5, 2G12 and HIVIG was found to be synergistic to have the greatest breadth and magnitude of response against 15 clade B primary isolates. Mascola *et al.* [1997] (**antibody interactions**, **variant cross-recognition or cross-neutralization**)
- 2G12: A JRCSF variant that was selected for IgG1b12 resistance remained sensitive to MAbs 2G12 and 2F5, for combination therapy. Mo *et al.* [1997] (**escape**)
- 2G12: Review: MAbs 2F5, 2G12 and IgG1b12 have potential for use in combination with CD4-IgG2 as an immunotherapeutic or immunoprophylactic – homologous MAbs to these are rare in humans and vaccine strategies should consider including constructs that may enhance exposure of these MAbs' epitopes. Moore & Trkola [1997] (**immunoprophylaxis**, **immunotherapy**, **review**)
- 2G12: Neutralizes TCLA strains and primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 2G12: Viral binding inhibition by 2G12 was strongly correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5). Ugolini *et al.* [1997] (**antibody binding site definition and exposure**)
- 2G12: Neutralizes primary isolates, HXB2, and chimeric virus with gp120 from primary isolates in an HXB2 background. McKeating *et al.* [1996] (**variant cross-recognition or cross-neutralization**)
- 2G12: Binding weakly enhanced by some anti-C1, -C4, -V3, and CD4 binding site MAbs – unusual in that 2G12 binding neither enhanced or inhibited the binding of other MAbs included in the study. Moore & Sodroski [1996] (**antibody interactions**)
- 2G12: Review: exceptional capacity to neutralize primary isolates in terms of both breadth and potency – one of three MAbs (IgG1b12, 2G12, and 2F5) generally accepted as having significant potency against primary isolates. Poignard *et al.* [1996b] (**variant cross-recognition or cross-neutralization**, **review**)
- 2G12: Review: Only four epitopes have been described which can stimulate a useful neutralizing response to a broad spectrum of primary isolates, represented by the binding sites of MAbs: 447-52-D, 2G12, Fab b12, and 2F5. Sattentau [1996] (**review**)
- 2G12: Conformationally sensitive epitope destroyed by mutations altering the N-linked glycosylation sites near the base of the V3 loop and the amino-terminal flank of the V4 loop. Trkola *et al.* [1996b] (**antibody binding site definition and exposure**)
- 2G12: Neutralizes JR-FL – inhibits gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a] (**co-receptor**)

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- 2G12: Review: binding site is distinct from CD4BS MAbs epitope and is unique among known gp120 MAbs, human or rodent. Moore & Ho [1995] (**review**)
- 2G12: Highly potent Cross-clade neutralizing activity. Trkola *et al.* [1995] (**subtype comparisons**)
- 2G12: Human MAb generated by electrofusion of PBL from HIV-1 + volunteers with CB-F7 cells. Buchacher *et al.* [1994] (**antibody generation**)

No. 899
MAb ID 3074
HXB2 Location Env
Author Location gp120
Epitope
Subtype CRF02_AG
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
References Wu *et al.* 2008; Krachmarov *et al.* 2006; Gorny *et al.* 2006
Keywords binding affinity, neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- 3074: To test whether the conformation change of Env induced by CD4 affects the breadth and potency of 3074 neutralization, 3074 was tested in the presence or absence of sCD4 in neutralization of a panel of 12 subtype B and 12 subtype C Env-pseudoviruses. Without sCD4, 3074 neutralized 2 subtype B and 2 subtype C viruses. With sCD4 present, 3074 neutralized 7 subtype B and 5 subtype C viruses, indicating that neutralization resistance of some viruses to 3074 is due to a lack of exposure of the V3 loop. Neutralization of JRFL, ADA, and YU2 isolates by 3074 increased with increased dose of sCD4. Wu *et al.* [2008] (**neutralization**, **variant cross-recognition or cross-neutralization**)
- 3074: This MAb was derived from plasma from a patient with env clade A virus with the GPGQ V3 motif. When cross-reactivity was tested, this Ab bound to both the V3subtypeB-fusion protein containing GPGR motif and V3subtypeA-fusion protein containing GPGQ motif. This Ab was also shown to be able to neutralize both clade B psSF162 (GPGR) and clade C psMW965 (GPGQ) virus, and two of subtype B and four of non-B primary isolates. Gorny *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)
- 3074: This Ab was shown to neutralize SF162 and the neutralization sensitivity increased in the SF162 variant with a JR-FL V3 loop, SF162(JR-FL V3). In contrast, no neutralization was observed of the SF162(JR-FL V1/V2) variant and was somewhat restored in the SF162(JR-FL V1/V2/V3) variant, indicating that the masking of the V1/V2 loop plays a much greater role in restricting neutralization sensitivity than the variations in V3. This Ab was shown to neutralize viruses with V3 sequences from several different subtypes (B, F, A1, H, C, CRF02_AG and CRF01_AE) and SF162(JR-FL V1/V2) with V3 derived from different HIV-1 clades. The effect on the neutralization sensitivity of the residue at the crown of the V3 loop (position 18) was shown to be low for this Ab. Krachmarov *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 900
MAb ID 30D
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen
Species (Isotype)
References Yang *et al.* 2002

- 30D: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibritin—stabilized oligomer gp140Δ683(-FT) showed strong preferential recognition by NAbs IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAbs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002]

No. 901
MAb ID 31710B
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen
Species (Isotype) human (IgG1)
References Alsmadi & Tilley 1998

- 31710B: A study of 6 anti-Env MAbs and their ability to bind or direct ADCC against target cells infected with IIIB, MN, SF-2, and RF – bound and directed lysis against all four strains. Alsmadi & Tilley [1998]

No. 902
MAb ID 3224
HXB2 Location Env
Author Location gp120
Epitope
Subtype CRF02_AG
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
References Krachmarov *et al.* 2006; Gorny *et al.* 2006
Keywords binding affinity, neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- 3224: This MAb was derived from plasma from a patient with env clade A virus with the GPGQ V3 motif. When cross-reactivity was tested, this Ab bound to both the V3subtypeB-fusion protein containing GPGR motif and V3subtypeA-fusion protein containing GPGQ motif. This Ab was also shown to be able to neutralize both clade B psSF162 (GPGR) and clade C psMW965 (GPGQ) virus, and two of subtype B and three of non-B primary isolates. Gorny *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)

- 3224: This Ab was shown to neutralize SF162 and the neutralization sensitivity increased in the SF162 variant with a JR-FL V3 loop, SF162(JR-FL V3). In contrast, no neutralization was observed of the SF162(JR-FL V1/V2) variant and was somewhat restored in the SF162(JR-FL V1/V2/V3) variant, indicating that the masking of the V1/V2 loop plays a much greater role in restricting neutralization sensitivity than the variations in V3. This Ab was shown to neutralize viruses with V3 sequences from several different subtypes (B, F, A1, H, C, CRF02_AG and CRF01_AE). Krachmarov *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 903
MAb ID 38B5/C9
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References He *et al.* 2002

- 38B5/C9: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—38B5/C9 bound to most R5 and X4 B clade viruses, as well as one of two E clade viruses. He *et al.* [2002]

No. 904
MAb ID 39H10/A11
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Tuen *et al.* 2005; He *et al.* 2002
Keywords antibody interactions, binding affinity

- 39H10/A11: This Ab bound with intermediate affinity to gp120IIIb. 39H10/A11 did not fully disassociate from gp120 at acidic pH, but it had no inhibitory effect on gp120 antigen presentation by MHC class II. 39H10/A11 had minimal effect on the rate of gp120 fragmentation by lysosomal enzyme digestion. Tuen *et al.* [2005] (**antibody interactions**, **binding affinity**)
- 39H10/A11: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—39H10/A11 bound to three R5 and three X4 B clade viruses, as well as two E clade viruses. He *et al.* [2002]

No. 905
MAb ID 3C9
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing L
Immunogen vaccine
Strain: B clade SF2
Species (Isotype) mouse
References Kang *et al.* 1992
Keywords anti-idiotype, vaccine antigen design, variant cross-recognition or cross-neutralization

- C39: Murine antibodies were raised against human polyclonal antibodies against gp120, pooled from HIV-1 infected individuals. One anti-idiotype MAb was shown to bind to the CD4-binding site, and this MAb could raise anti-anti-idiotype antibodies when injected into cygnomolgous monkeys. The monkey MAbs neutralized laboratory strains MN, RF, and IIIB. Kang *et al.* [1992] (**anti-idiotype**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 906
MAb ID 3D5
HXB2 Location Env
Author Location Env
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human
Research Contact Herman Katinger, Inst. Appl. Microbiol. University of Agricultural Science, Vienna, Austria
References Kunert *et al.* 1998; Purtscher *et al.* 1994; Buchacher *et al.* 1994

- 3D5: The complete V, J and D(H) domain was sequenced – unlike non-neutralizing anti-gp41 MAb 3D6, five neutralizing MAbs (2F5, 2G12, 1B1, 1F7, and 3D5) showed extensive somatic mutations giving evidence of persistent antigenic pressure over long periods. Kunert *et al.* [1998]

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- 3D5: Generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994]

No. 907
MAb ID 3F8
HXB2 Location Env
Author Location Env
Epitope
Subtype C
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* C clade 97CN54 *HIV component:* Other
Species (Isotype) mouse (IgG2a)
References Chen *et al.* 2008a
Keywords neutralization, variant cross-recognition or cross-neutralization

- 3F8: Mice were immunized with a construct of the outer domain (OD) of gp120 of subtype C fused with Fc, and MAbs specific for the CN54 OD were derived by exhaustive screening of the mice sera. The OD-specific 3F8 MAb did not cross-compete with any of the other newly identified OD-specific MAbs: 4E1, 1G12, 3F9, 4D3 (bridging sheet) or the V3-specific 2B7 and 4E5. 3F8 showed weak neutralization of the three isolates tested, CN54, MN, and 93MW965.26. Chen *et al.* [2008a] (**neutralization**, **variant cross-recognition or cross-neutralization**)

No. 908
MAb ID 3F9
HXB2 Location Env
Author Location Env
Epitope
Subtype C
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* C clade 97CN54 *HIV component:* Other
Species (Isotype) mouse (IgG1)
References Chen *et al.* 2008a
Keywords neutralization, variant cross-recognition or cross-neutralization

- 3F9: Mice were immunized with a construct of the outer domain (OD) of gp120 of subtype C fused with Fc, and MAbs specific for the CN54 OD were derived by exhaustive screening of the mice sera. The OD-specific 3F9 MAb cross-competed with three other newly identified OD-specific MAbs: 4E1, 1G12, 1H8, but did not cross-compete with 4D3 (bridging sheet) or the V3-specific 2B7 and 4E5. 3F9 showed no neutralization of the three isolates tested, CN54, MN, and 93MW965.26. Chen *et al.* [2008a] (**neutralization**, **variant cross-recognition or cross-neutralization**)

No. 909
MAb ID 3H6
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen
Species (Isotype) mouse
References Pinter *et al.* 1995

- 3H6 database comment: There is another MAb with this ID that recognizes Rev.
- 3H6: Generated in response to virus grown in protein-free medium. Pinter *et al.* [1995]

No. 910
MAb ID 4.11C
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 adjacent to CD4BS
References Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure

- 4.11C: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 4.11C has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 911
MAb ID 4.6H
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 adjacent to CD4BS
References Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure

- 4.6H: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 4.6H has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 912
MAb ID 4.8E
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 CCR5BS
References Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure

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- 4.8E: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 4.8E has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 913
MAb ID 40D3/C11
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References He *et al.* 2002

- 40D3/C11: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—40D3/C11 bound to most R5 and X4 B clade viruses, as well as one of two E clade viruses. He *et al.* [2002]

No. 914
MAb ID 412d (412D)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 CD4i, gp120 CCR5BS
References Lam *et al.* 2008; Phogat *et al.* 2007; Lin & Nara 2007; Huang *et al.* 2007a; Dorfman *et al.* 2006; Xiang *et al.* 2005; Mc Cann *et al.* 2005; Huang *et al.* 2005a; Choe *et al.* 2003
Keywords antibody binding site definition and exposure, co-receptor, neutralization, review, structure

- 412d: Docking of a functional 14-residue CCR5 N-terminus peptide to the crystal structure of gp120-CD4 in complex with sulfated MAb 412d showed that the peptide binds to the base of the V3 loop in a manner similar to that of 412d. To improve peptide stability, sulfo-tyrosine isosteres were incorporated into the peptide, and its solubility was improved by incorporation of an orthogonally functionalized azido tris (ethylenoxy) L-alanine residue. 412d was able to compete and inhibit peptide binding to gp120-CD4. The peptide was used to develop screening assays for small molecule inhibitors of HIV-1 gp120 and CCR5 interactions. Lam *et al.* [2008] (**antibody binding site definition and exposure**, **co-receptor**, **structure**)
- 412d: Nuclear magnetic resonance and x-ray crystallography used to analyze the structure of the CCR5 N terminus and 412d in complex with gp120 and CD4 revealed surprisingly different conformations of tyrosine-sulfated regions of CCR5 and 412d. However, a critical sulfotyrosine on CCR5 (residue 14) and on 412d (residue 100c) induced similar structural rearrangements in gp120. Futrhermore, the gp120 residues that line the sulfotyrosine binding pocket were highly conserved. The structural analyses indicate that engagement of the CCR5 N terminus by gp120 requires formation of a conserved pocket for sulfotyrosine binding, and converts the flexible V3 stem into a rigid β-hairpin. Huang *et al.* [2007a] (**antibody binding site definition and exposure**, **structure**)
- 412d: 412d structure, sulfation, and binding are reviewed in detail. Lin & Nara [2007] (**review**)
- 412D: This review provides information on the HIV-1 glycoprotein properties that make it challenging to target with neutralizing Abs. 412D neutralization properties and binding to HIV-1 envelope, and current strategies to develop versions of the Env spike with functional trimer properties for elicitation of broadly neutralizing Abs, are discussed. In addition, approaches to target cellular molecules, such as CD4, CCR5, CXCR4, and MHC molecules, with therapeutic Abs are reviewed. Phogat *et al.* [2007] (**review**)
- 412d: The CDR3 regions of CD4i Abs (E51, 412d, 17b, C12 and 47e) were cloned onto human IgG1 and tested for their ability to inhibit CCR5 binding. Only E51 successfully immunoprecipitated gp120. Dorfman *et al.* [2006] (**co-receptor**)
- 412d: The structure of the V3 region in the context of gp120 core complexed to the CD4 receptor and to the 412d Ab was attempted to be determined by X-ray resolution, but only the structure for V3 complexed with CD4 and X5 Ab was solved. Huang *et al.* [2005a] (**structure**)
- 412d: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **co-receptor**, **neutralization**, **review**)
- 412d: Binding of 412d to gp120 requires the gp120 β19 strand and the base of the V3 loop, indicating that the epitope for this Ab includes these two regions. The major determinants of 412d preference for CCR5-using HIV-1 strains were determined to be amino acid residues 325 and 326 in the base of the V3 loop. The close mimicry of the CCR5 N terminus by 412d was emphasized by showing that replacement of the CCR5 N terminus by 412d heavy chain CDR3 loop resulted in

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a functional HIV-1 co-receptor. Xiang *et al.* [2005] (**antibody binding site definition and exposure**, **co-receptor**)

- 412d: 412d was obtained from an HIV-1 infected individual with a potent ELISA response to the gp120. It was shown that this MAb heavy chain is sulfate-modified. The sulfates of 412d were present exlusively on tyrosines of its heavy chain CDR3 and they contributed to the binding of this MAb to the gp120 of at least three primary HIV isolates. Binding efficiency of 412d to ADA gp120 was doubled in the presence of CD4, showing that this MAb is a CD4-induced. Association of 412d with ADA gp120-CD4-Ig complex was partially inhibited by a sulfated peptide with a sequence corresponding to the CCR5 amino terminus, indicating that 412d binds a CD4-enhanced epitope overlapping the binding domain of CCR5 amino terminus. Neutralization assays showed that 412d neutralizes primary R5 and R5X4 isolates more efficiently, and X4 isolates less efficiently, than CD4i Abs 17b and 48d. Furthermore, 412d scFv was more than 10 times as potent as full-length 412d at neutralizing ADA. scFv 412d was shown to efficiently bind to gp120 of three R5 isolates but not to the HXBc2 X4 isolate. Choe *et al.* [2003] (**antibody binding site definition and exposure**, **co-receptor**, **neutralization**)

No. 915
MAb ID 47e
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 CD4i, gp120 CCR5BS
References Lin & Nara 2007; Dorfman *et al.* 2006; Mc Cann *et al.* 2005; Choe *et al.* 2003
Keywords antibody binding site definition and exposure, co-receptor, neutralization, review

- 47e: 47e structure, sulfation, and binding are reviewed in detail. Lin & Nara [2007] (**review**)
- 47e: The CDR3 regions of CD4i Abs (E51, 412d, 17b, C12 and 47e) were cloned onto human IgG1 and tested for their ability to inhibit CCR5 binding. Only E51 successfully immunoprecipitated gp120. Dorfman *et al.* [2006] (**co-receptor**)
- 47e: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **co-receptor**, **neutralization**, **review**)
- 47e: 47e was obtained from an HIV-1 infected individual with a potent ELISA response to the gp120. It was shown that this MAb heavy chain is sulfate-modified and that the sulfation is dependent upon a single tyrosine in its heavy chain CDR3.The sulfate on 47e was shown to substantially contribute to this MAb's ability to bind ADA, but not YU2, envelope glycoprotein. Binding efficiency of 47e to ADA gp120 was doubled in the presence of CD4, showing that this MAb is a CD4-induced. Association of 47e with ADA gp120-CD4-Ig complex was partially inhibited by a sulfated peptide with a sequence corresponding to the CCR5 amino terminus, indicating that 47e binds a CD4-enhanced epitope overlapping the binding domain of CCR5 amino terminus. Choe *et al.* [2003] (**antibody binding site definition and exposure**, **co-receptor**)

No. 916
MAb ID 49B11/A1
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References He *et al.* 2002

- 49B11/A1: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—49B11/A1 bound to most R5 and X4 B clade viruses, as well as one of two E clade viruses. He *et al.* [2002]

No. 917
MAb ID 4D3
HXB2 Location Env
Author Location gp120 (425–455)
Epitope
Subtype C
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* C clade 97CN54 *HIV component:* Other
Species (Isotype) mouse (IgG2a)
References Chen *et al.* 2008a
Keywords antibody binding site definition and exposure, neutralization, variant cross-recognition or cross-neutralization

- 4D3: Mice were immunized with a construct of the outer domain (OD) of gp120 of subtype C fused with Fc, and MAbs specific for the CN54 OD were derived by exhaustive screening of the mice sera. The OD-specific 4D3 MAb was mapped to a 30-residue sequence (425-455) representing the C-terminal %beta;-strand of the gp120 bridging sheet. 4D3 showed no neutralization of the three isolates tested, CN54,

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MN, and 93MW965.26. Chen *et al.* [2008a] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**)

No. 918
MAb ID 4E1
HXB2 Location Env
Author Location Env
Epitope
Subtype C
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* C clade 97CN54 *HIV component:* Other
Species (Isotype) mouse (IgG1)
References Chen *et al.* 2008a
Keywords neutralization, variant cross-recognition or cross-neutralization

- 4E1: Mice were immunized with a construct of the outer domain (OD) of gp120 of subtype C fused with Fc, and MAbs specific for the CN54 OD were derived by exhaustive screening of the mice sera. The OD-specific 4E1 MAb cross-competed with three other newly identified OD-specific MAbs: 3F9, 1G12, and 1H8, but it did not cross-compete with 4D3 (bridging sheet) or the V3-specific 2B7 and 4E5. 4E1 showed weak neutralization of the three isolates tested, CN54, MN, and 93MW965.26. Chen *et al.* [2008a] (**neutralization**, **variant cross-recognition or cross-neutralization**)

No. 919
MAb ID 4E5
HXB2 Location Env
Author Location gp120
Epitope
Subtype C
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* C clade 97CN54 *HIV component:* Other
Species (Isotype) mouse (IgG1)
Ab Type gp120 V3
References Chen *et al.* 2008a
Keywords antibody binding site definition and exposure, neutralization, variant cross-recognition or cross-neutralization

- 4E5: Mice were immunized with a construct of the outer domain (OD) of gp120 of subtype C fused with Fc, and MAbs specific for the CN54 OD were derived by exhaustive screening of the mice sera. 4E5 was shown to be V3-specific, its specificity mapped to the centre of the loop, including the GPG crown. 4E5 effectively neutralized 93MW965.26 isolate, but neutralized the MN isolate only marginally. The neutralization of the CN54 isolate by 4E5 was equivocal. Chen *et al.* [2008a] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**)

No. 920
MAb ID 52G5/B9
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References He *et al.* 2002

- 52G5/B9: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—52G5/B9 bound to most R5 and X4 B clade viruses, as well as one of two E clade viruses. He *et al.* [2002]

No. 921
MAb ID 55E4/H1
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References He *et al.* 2002

- 55E4/H1: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—55E4/H1 bound to most R5 and X4 B clade viruses, as well as one of two E clade viruses. He *et al.* [2002]

No. 922
MAb ID 56C4/C8
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing no

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Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References He *et al.* 2002

- 56C4/C8: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—56C4/C8 bound to some R5 and X4 B clade viruses, as well as one of two E clade viruses. He *et al.* [2002]

No. 923
MAb ID 570-D
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) (IgG1λ)
Ab Type gp120 CD4BS
References Holl *et al.* 2006a
Keywords dendritic cells, neutralization

- 570-D: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)

No. 924
MAb ID 57B6/F1
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References He *et al.* 2002

- 57B6/F1: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—57B6/F1 bound some R5 and X4 B clade viruses, and no E clade viruses. He *et al.* [2002]

No. 925
MAb ID 57H5/D7
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References He *et al.* 2002

- 57H5/D7: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—57H5/D7 bound to most R5 and X4 B clade viruses, as well as one of two E clade viruses. He *et al.* [2002]

No. 926
MAb ID 5E
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 CD4BS
References Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure

- 5E: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 5E has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 927
MAb ID 63G4/E2
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B

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Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References He *et al.* 2002

- 63G4/E2: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—63G4/E2 bound to three R5 and three X4 B clade viruses, as well as two E clade viruses. He *et al.* [2002]

No. 928
MAb ID 65B12/C5
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References He *et al.* 2002

- 65B12/C5: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—65B12/C5 bound some R5 and X4 B clade viruses, and no E clade viruses. He *et al.* [2002]

No. 929
MAb ID 694/98D
HXB2 Location Env
Author Location Env (LAI)
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Ling *et al.* 2004
Keywords antibody binding site definition and exposure

- 694-98D: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of the V3 MAb 694-98D to its epitope was decreased by both thrombin and trypsin. Ling *et al.* [2004] (**antibody binding site definition and exposure**)

No. 930
MAb ID 6D8
HXB2 Location Env
Author Location gp120 (21–85)
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Phil Berman
References Callahan *et al.* 1991

- 6D8: Polyanionic polysaccharides were proposed to inhibit viral functions such as binding and syncytia formation through interations mediated through the local high positive charge density in the V3 loop. The binding of this N-term binding antibody is increased by dextransulfate, in contrast to anti-V3 antibodies that are inhibited. Callahan *et al.* [1991]

No. 931
MAb ID 6E10
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen
Species (Isotype)
Research Contact Phil Berman
References Callahan *et al.* 1991; Berman *et al.* 1991

- Isolation of antibody. Berman *et al.* [1991]
- 6E10: Polyanionic polysaccharides were proposed to inhibit viral functions such as binding and syncytia formation through interations mediated through the local high positive charge density in the V3 loop. The binding of this antibody is not inhibited by dextransulfate, in contrast to anti-V3 antibodies. Callahan *et al.* [1991]

No. 932
MAb ID 7-1054
HXB2 Location Env
Author Location gp36 (HIV-2)
Epitope
Neutralizing no
Immunogen
Species (Isotype) mouse
References Scheffel *et al.* 1999

- Binds HIV-2 gp36, used as a control in a study of group O MAbs. Scheffel *et al.* [1999]

No. 933
MAb ID 8.2A
HXB2 Location Env

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Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 C1-C4
References Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure

- 8.2A: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 8.2A has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 934
MAb ID 85G11/D8
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* deglycosylated gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References He *et al.* 2002

- 85G11/D8: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—three of the MAbs were conformation dependent, but did not block sCD4 binding and were part of the same competition group—these MAbs were all raised against a deglycosylated form of gp120—they could not neutralize autologous SF162 and bound some R5 and X4 B clade viruses, and no E clade viruses. He *et al.* [2002]

No. 935
MAb ID 87E4/A8
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* deglycosylated gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Tuen *et al.* 2005; He *et al.* 2002
Keywords antibody interactions, binding affinity

- 87E4/A8: This Ab was included as a negative control. It did not bind to gp120IIIb and it had no effect on the rate of gp120 fragmentation by lysosomal enzyme digestion. Tuen *et al.* [2005] (**antibody interactions**, **binding affinity**)
- 87E4/A8: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—three of the MAbs were conformation dependent, but did not block sCD4 binding and were part of the same competition group—these MAbs were all raised against a deglycosylated form of gp120—they could not neutralize autologous SF162 and bound some R5 and X4 B clade viruses, and no E clade viruses. He *et al.* [2002]

No. 936
MAb ID 8K8
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* mimotopes *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (Isotype) rabbit
Ab Type gp41 NHR (N-heptad repeat), gp41 five-helix bundle (one CHR peptide of six helix bundle is missing)
Research Contact Michael B. Zwick, The Acripps Research Institute, La Jolla, CA, USA, zwick@scripps.edu
References Nelson *et al.* 2008; Gustchina *et al.* 2008
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, binding affinity, neutralization

- 8K8: The neutralization activity of 8K8 is additive with that of N36Mut(e,g) peptide, which is a class 3 inhibitor that disrupts trimerization of the N-heptad repeat (N-HR) in the prehairpin intermediate by sequestering the N-HR into N-HR/N36Mut(e,g) heterodimers. The IC50 for 8K8 alone was estimated to 400 nM, while the IC50 for 8K8 and N36Mut(e,g) in combination was 0.9 nM. Gustchina *et al.* [2008] (**neutralization**)
- 8K8: scFv 8K8 was derived from a rabbit Fab phage display library prepared using the bone marrow RNA extracted from N35ccg-N13 immunized rabbits. The library was screened with N35ccg-N13 peptide, which is a soluble homotrimer corresponding to the HIV-1 gp41 N-heptad repeat (NHR) region. 8K8 bound to N35ccg-N13 but not to recombinant r-gp41 (HXB2) nor to 6-Helix, indicating that 8K8 has a strong preference for gp41 NHRtrimers unoccupied by peptide corresponding to the C-heptad repeat (CHR). In contrast, an IgG engineered form of 8K8 showed weak reactivity with r-gp41 and 6-Helix. 8K8 did not recognize soluble forms of Envs used in typical binding assays, which indicates that the 8K8 epitope is occluded in these Envs. Competition experiments showed that Fab DN9, 8K8, and D5 bind to overlapping but

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distinct epitopes on the NHR coiled-coil mimetics, where the epitopes of DN9 and 8K8 are more closely related to each other than to D5. Immobilized IgG 8K8 did not capture infectious whole HIV-1 virions in presence or absence of sCD4, indicating that 8K8 epitope is restricted on the NHR trimer on the virion surface. 8K8 has a short CDR H3 (7 residues), and its epitope was suggested to be located in a relatively restricted region of NHR near to the hydrophobic pocket. H564 residue in the NHR region was found critical for 8K8 recognition. In neutralization assays, 8K8 showed modest but relatively broad neutralization, including HIV-1 isolates from both subtypes B and C. HIV-1 JR-FL was resistant to neutralization by 8K8. Neutralization potencies of scFv 8K8 and IgG 8K8 were comparable. Neutralization potency of 8K8 was 1 or 2 orders of magnitude less than that of 4E10. Unlike non-neutralizing Abs in this study, whose heavy chain variable regions were encoded by usually expressed VH1a1 and VH1a2 genes, 8K8 was encoded by a rarely expressed VH gene. Nelson *et al.* [2008] (**antibody binding site definition and exposure**, **antibody generation**, **neutralization**, **binding affinity**, **antibody sequence variable domain**)

No. 937
MAb ID 97B1/E8
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* deglycosylated gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References He *et al.* 2002

- 97B1/E8: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120. Three of the MAbs were conformation dependent, but did not block sCD4 binding and were part of the same competition group. These MAbs were all raised against a deglycosylated form of gp120. They could not neutralize autologous SF162 and bound some R5 and X4 B clade viruses, and no E clade viruses. He *et al.* [2002]

No. 938
MAb ID A12
HXB2 Location Env
Author Location Env
Epitope
Neutralizing P
Immunogen vaccine
Vector/Type: protein *Strain:* Other *HIV component:* gp120
Species (Isotype) llama
Ab Type gp120 CD4BS
Research Contact Robin A Weiss, University Colledge London, London, UK, r.weiss@ucl.ac.uk
References Forsman *et al.* 2008
Keywords antibody binding site definition and exposure, antibody generation, binding affinity, kinetics, neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- A12: A12 is a neutralizing VHH (nanobody) Ab devoid of light chains. It was isolated from sera from llamas, who produce immunoglobulins devoid of light chains, immunized with gp120 of HIV-1 CRF07_BC primary isolate CN54, following panning of phage libraries expressing VHH repertoire and a competitive elution with soluble CD4. It was hypothesized that the small size of the VHH, in combination with their protruding CDR3 loops, and their preference for cleft recognition and binding into active sites, may allow for recognition of conserved motifs on gp120 that are occluded from conventional Abs. A12 was able to neutralize HIV-1 primary isolates of subtypes B, C and CRF07_BC, but not subtypes A, D, and A/G. Compared to MAb b12, which neutralized 54% of viruses tested, A12 neutralized 42% of the viruses, but it neutralized a different spectrum of the viruses than b12. A12 showed high affinity binding to IIIB gp120, and inhibited binding of sCD4 to IIIB gp120 and 92UG037 gp140 in a dose-dependent manner. A12 was found to compete with b12 for binding to gp120, and also with MAbs 654-D and GP68, indicating that its epitope overlaps the CD4bs. There was some inhibition observed of A12-gp120 binding by 2G12, 17b, and 447-52D, while 4E10 did not inhibit A12-gp120 binding. A12 was also able to inhibit binding of the other two VHH Abs isolated in this study, D7 and C8, indicating that their epitopes overlap. Forsman *et al.* [2008] (**antibody binding site definition and exposure**, **antibody generation**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **kinetics**, **binding affinity**, **subtype comparisons**)

No. 939
MAb ID A9
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: chimeric GM-CSF *Strain:* B clade IIIB *HIV component:* gp120 *Adjuvant:* GM-CSF
Species (Isotype) mouse (IgG1)
References del Real *et al.* 1999
Keywords antibody generation, antibody sequence variable domain, autoimmunity

- A9: Murine antibody response to the chimeric construction granulocyte-macrophage colony stimulating factor GM-CSF/gp120 was tested, MAbs from normal mice were gp120 specific, MAbs from nude mice bound gp120 but were polyreactive, and from reconstituted mice were half way between – the anti-gp120 response used a high frequency of VH81X, VHQ52, and VH7183 genes, a family used during fetal life and associated with autoimmunity – A9 was a gp120 from a

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BALBc reconstructed nude mouse and had VH gene 7183-2. del Real *et al.* [1999] (**antibody generation**, **autoimmunity**, **antibody sequence variable domain**)

No. 940
MAb ID ADP421 polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype A
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) rabbit
References Jeffs *et al.* 2004
Keywords subtype comparisons, vaccine antigen design

- ADP421: A set of oligomeric envelope proteins were made from six primary isolates for potenial use as vaccine antigens: 92/UG/037 (clade A), HAN2/2 (clade B), 92/BR25/025 (clade C), 92/UG/021 (clade D), 93/BR/029 (clade F) and MVP5180 (clade O). This was one of a panel of MAbs used to explore folding and exposure of well characterized epitopes. The clade C isolate BR25 is apparently misfolded, as conformation-dependent antibodies did not bind to it. ADP421 is a polyclonal rabbit sera raised against CHO-derived IIIB gp120. ADP421 bound to antigens from all clades A-F, as well as group O. Polyclonal sera raised in rabbits against these antigens cross-bound the other antigens, but none of the sera had neutralizing activity. Jeffs *et al.* [2004] (**vaccine antigen design**, **subtype comparisons**)

No. 941
MAb ID AG10H9
HXB2 Location Env
Author Location gp41 (717–751)
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact BabCO
References Ohagen *et al.* 2003
Keywords brain/CSF, variant cross-recognition or cross-neutralization

- AG10H9: Env genes derived from uncultured brain biopsy samples from four HIV-1 infected patients with late-stage AIDS were compared to env genes from PBMC samples. Brain isolates did not differ in the total number or positions of N-glycosylation sites, patterns of coreceptor usage, or ability to be recognized by gp160 and gp41 MAbs. AG10H9 recognized most variants gp41 and gp160 from 3/4 individuals by WB, but not the 4th. Ohagen *et al.* [2003] (**brain/CSF**, **variant cross-recognition or cross-neutralization**)

No. 942
MAb ID AH48
HXB2 Location Env
Author Location gp120 (V3)
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Crooks *et al.* 2008; Sheppard *et al.* 2007b; Zwick *et al.* 2003
Keywords antibody binding site definition and exposure, antibody generation, antibody interactions, binding affinity, neutralization, variant cross-recognition or cross-neutralization

- AH48: The study compared Ab neutralization against the JR-FL primary isolate and trimer binding affinities judged by native PAGE. There was direct quantitative relationship between monovalent Fab-trimer binding and neutralization, implying that neutralization begins as each trimer is occupied by one Ab. In BN-PAGE, neutralizing Fabs and sCD4 were able to shift JR-FL trimers, In contrast, most non-neutralizing Fabs, AH48 in particular, bound to monomer, but their epitopes were conformationally occluded on trimers, confirming the exclusive relationship of trimer binding and neutralization. Crooks *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- AH48: This Ab was shown not to react with C clade gp140 (97CN54). Sheppard *et al.* [2007b] (**variant cross-recognition or cross-neutralization**)
- AH-48: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. AH48 is a novel anti-V3 Fab first used in this study. Zwick *et al.* [2003] (**antibody generation**, **antibody interactions**)

No. 943
MAb ID B4
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: chimeric GM-CSF *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgM)
References del Real *et al.* 1999
Keywords antibody generation, antibody sequence variable domain, autoimmunity

- B4: Murine antibody response to the chimeric construction granulocyte-macrophage colony stimulating factor GM-CSF/gp120 was tested, MAbs from normal mice were gp120 specific, MAbs from nude mice bound gp120 but were polyreactive, and from reconstituted mice were half way between – the anti-gp120 response used a high frequency of VH81X, VHQ52, and VH7183 genes, a family used during fetal life and associated with autoimmunity – B4 was an anti-gp120 from a BALBc reconstructed nude mouse and had VH gene

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J606. del Real *et al.* [1999] (**antibody generation**, **autoimmunity**, **antibody sequence variable domain**)

No. 944
MAb ID B5
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: chimeric GM-CSF *Strain:* B clade IIIB *HIV component:* gp120 *Adjuvant:* GM-CSF
Species (Isotype) mouse (IgG1)
References del Real *et al.* 1999
Keywords antibody generation, antibody sequence variable domain, autoimmunity

- B5: Murine antibody response to the chimeric construction granulocyte-macrophage colony stimulating factor GM-CSF/gp120 was tested, MAbs from normal mice were gp120 specific, MAbs from nude mice bound gp120 but were polyreactive, and from reconstituted mice were half way between – the anti-gp120 response used a high frequency of VH81X, VHQ52, and VH7183 genes, a family used during fetal life and associated with autoimmunity – B5 was a gp120 specific MAb from a BALBc mouse and had VH gene J558. del Real *et al.* [1999] (**antibody generation**, **autoimmunity**, **antibody sequence variable domain**)

No. 945
MAb ID B6
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: chimeric GM-CSF *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgM)
References del Real *et al.* 1999
Keywords antibody generation, antibody sequence variable domain, autoimmunity

- B6: Murine antibody response to the chimeric construction granulocyte-macrophage colony stimulating factor GM-CSF/gp120 was tested, MAbs from normal mice were gp120 specific, MAbs from nude mice bound gp120 but were polyreactive, and from reconstituted mice were half way between – the anti-gp120 response used a high frequency of VH81X, VHQ52, and VH7183 genes, a family used during fetal life and associated with autoimmunity – B6 was a gp120 from a BALBc reconstructed nude mouse and had VH gene J558. del Real *et al.* [1999] (**antibody generation**, **autoimmunity**, **antibody sequence variable domain**)

No. 946
MAb ID B97-11C5
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Julia L. Hurwitz, St. Jude Children's research Hospital, julia.hurwitz@stjude.org
References Slobod *et al.* 2005
Keywords variant cross-recognition or cross-neutralization

- B97-11C5: A binding analysis of this Ab to four different Env proteins showed that B97-11C5 bound to one out of four Envs. Slobod *et al.* [2005] (**variant cross-recognition or cross-neutralization**)

No. 947
MAb ID BAT267
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
References Fung *et al.* 1987

No. 948
MAb ID BAT401
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
References Fung *et al.* 1987

No. 949
MAb ID BAT509
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade IIIB *HIV component:* HIV-1
Species (Isotype) mouse (IgG1)
References Fung *et al.* 1987

No. 950
MAb ID C02-17
HXB2 Location Env
Author Location gp120 (JR-FL)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4i
References Bowley *et al.* 2007

Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- C02-17: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. C02-17 was identified only by yeast display, and is a CD4i antibody. Bowley *et al.* [2007] (**antibody binding site definition and exposure**, **antibody generation**, **binding affinity**, **antibody sequence variable domain**, **assay standardization/improvement**)

No. 951
MAb ID C02-19
HXB2 Location Env
Author Location gp120 (JR-FL)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4i
References Bowley *et al.* 2007
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- C02-19: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. C02-19 was identified using only yeast display, and is a CD4i antibody; C02-19 and D02-33 have the same VH sequence. Bowley *et al.* [2007] (**antibody binding site definition and exposure**, **antibody generation**, **binding affinity**, **antibody sequence variable domain**, **assay standardization/improvement**)

No. 952
MAb ID C02-34
HXB2 Location Env
Author Location gp120 (JR-FL)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 V3
References Bowley *et al.* 2007
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- C02-34: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. C02-34 was identified only by yeast display, and it binds to V3. Bowley *et al.* [2007] (**antibody binding site definition and exposure**, **antibody generation**, **binding affinity**, **antibody sequence variable domain**, **assay standardization/improvement**)

No. 953
MAb ID C02-41
HXB2 Location Env
Author Location gp120 (JR-FL)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4BS
References Bowley *et al.* 2007
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- C02-41: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. C02-41 was identified using both methods, and binds to the CD4BS. Bowley *et al.* [2007] (**antibody binding site definition and exposure**, **antibody generation**, **binding affinity**, **antibody sequence variable domain**, **assay standardization/improvement**)

No. 954
MAb ID C02-53
HXB2 Location Env
Author Location gp120 (JR-FL)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4i
References Bowley *et al.* 2007
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- C02-53: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. C02-53 was identified only by yeast display, and is a CD4i antibody; C02-53 and D02-7 have the same VH sequence. Bowley *et al.* [2007] (**antibody binding site definition and exposure**, **antibody generation**, **binding affinity**, **antibody sequence variable domain**, **assay standardization/improvement**)

No. 955
MAb ID C02-7
HXB2 Location Env
Author Location gp120 (JR-FL)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4i
References Bowley *et al.* 2007
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- C02-7: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. C02-7 was identified only by yeast display, and is a CD4i antibody. Bowley *et al.* [2007] (**antibody binding site definition and exposure**, **antibody generation**, **binding affinity**, **antibody sequence variable domain**, **assay standardization/improvement**)

No. 956
MAb ID C18-2
HXB2 Location Env
Author Location gp120 (JR-FL)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4BS
References Bowley *et al.* 2007
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- C18-2: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. C18-2 was identified only by yeast display, and it binds to the CD4 binding site. Bowley *et al.* [2007] (**antibody binding site definition and exposure**, **antibody generation**, **binding affinity**, **antibody sequence variable domain**, **assay standardization/improvement**)

No. 957
MAb ID C31
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
References Boyer *et al.* 1991

- C31: Broadly-reactive group specific MAb – high yield cultivation of human MAb. Boyer *et al.* [1991]

No. 958
MAb ID C8
HXB2 Location Env
Author Location Env
Epitope
Neutralizing P
Immunogen vaccine
Vector/Type: protein *Strain:* Other *HIV component:* gp120
Species (Isotype) llama
Ab Type gp120 CD4BS
Research Contact Robin A Weiss, University Colledge London, London, UK, r.weiss@ucl.ac.uk
References Forsman *et al.* 2008
Keywords antibody binding site definition and exposure, antibody generation, binding affinity, kinetics, neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- C8: C8 is a neutralizing VHH (nanobody) Ab devoid of light chains. It was isolated from sera from llamas, who produce immunoglobulins devoid of light chains, immunized with gp120 of HIV-1 CRF07_BC primary isolate CN54, following panning of phage libraries expressing VHH repertoire and a competitive elution with soluble CD4. It was hypothesized that the small size of the VHH, in combination with their protruding CDR3 loops, and their preference for cleft recognition and binding into active sites, may allow for recognition of conserved motifs on gp120 that are occluded from conventional Abs. C8 was able to neutralize HIV-1 primary isolates of subtypes B, C and CRF07_BC, but not subtypes A, D, and A/G. Compared to MAb b12, which neutralized 54% of viruses tested, C8 neutralized 35% of the viruses, but it neutralized a different spectrum of the viruses than b12. C8 showed high affinity binding to IIIB gp120, with a fast off-rate, and inhibited binding of sCD4 to IIIB gp120 and 92UG037 gp140 in a dose-dependent manner. C8 was found to compete with b12 for binding to gp120, and also with MAbs 654-D and GP68, indicating that its epitope overlaps the CD4bs. There was some inhibition observed of C8-gp120 binding by 2G12, 17b, and 447-52D, while 4E10 did not inhibit C8-gp120 binding. C8 was also able to inhibit binding of the other two VHH Abs isolated in this study, A12 and D7, indicating that their epitopes overlap. Forsman *et al.* [2008] (**antibody binding site definition and exposure**, **antibody generation**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **kinetics**, **binding affinity**, **subtype comparisons**)

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No. 959
MAb ID CD4-IgG2
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 CD4BS
References Tasca *et al.* 2008; Pugach *et al.* 2008; Dey *et al.* 2008; Gray *et al.* 2007b; Dunfee *et al.* 2007; Srivastava *et al.* 2005; Herrera *et al.* 2005; Beddows *et al.* 2005b; Pantophlet *et al.* 2003a
Keywords antibody binding site definition and exposure, binding affinity, co-receptor, neutralization, review

- CD4-IgG2: Five amino acids in the gp41 N-terminal region that promote gp140 trimerization (I535, Q543, S553, K567 and R588) were considered. Their influence on the function and antigenic properties of JR-FL Env expressed on the surfaces of pseudoviruses and Env-transfected cells was studied. Various non-neutralizing antibodies bind less strongly to the Env mutant, but neutralizing antibody binding is unaffected. There was no difference in CD4-IgG2 binding to wild type and mutant JR-FL, and CD4-IgG2 inhibited infection of the two pseudoviruses with comparable potencies. Dey *et al.* [2008] (**binding affinity**)
- CD4-IgG2: In order to assess whether small molecule CCR5 inhibitor resistant viruses were more sensitive to neutralization by NAbs, two escape mutant viruses, CC101.19 and D1/85.16, were tested for their sensitivity to neutralization by CD4-IgG2, compared to the sensitivity of CC1/85 parental isolate and the CCcon.19 control isolate. The CC101.19 escape mutant has 4 sequence changes in V3 while the D1/85.16 has no sequence changes in V3 and relies on other sequence changes for its resistance. Both escape mutant viruses were unchanged in their sensitivity to neutralization by CD4-IgG2 compared to parental and control viruses. Binding of CD4-IgG2 to each of the gp120 proteins was comparable. Pugach *et al.* [2008] (**co-receptor**, **neutralization**, **binding affinity**)
- CD4-IgG2: The neutralization profile of early R5, intermediate R5X4, and late X4 viruses from a rhesus macaque infected with SHIV-SF162P3N was assessed. The parental R5 virus was neutralized by by CD4-IgG2 but with the 40-fold lower potency than the R5X4 intermediate and the late X4 virus, which were neutralized with equal potency. The enhanced neutralization susceptibility of the dual-tropic and the X4 viruses to CD4-IgG2 suggests adoption of an increasingly open conformation of the Env gp120 over time. Tasca *et al.* [2008] (**co-receptor**, **neutralization**)
- CD4-IgG2: A D386N change in the V4 region, which results in restoration of N-glycosylation at this site, resulted in a 2-fold increase in resistance to neutralization of a mutant virus by CD4-IgG2 compared to wildtype. There was no association between increased sensitivity to CD4-IgG2 neutralization and enhanced macrophage tropism. Dunfee *et al.* [2007] (**neutralization**)
- CD4-IgG2: Deletion of glycosylation site in position 386 (N386Q) in two different subtype C envelope clones resulted in a decrease in sensitivity of corresponding viruses to neutralization by CD4-IgG2. Gray *et al.* [2007b] (**neutralization**)
- CD4-IgG2: The major infectivity and neutralization differences between a PBMC-derived HIV-1 W61D strain and its T-cell line adapted counterpart were conferred by the interactions of three Env amino acid substitutions, E440G, D457G and H564N. Chimeric Env-pseudotyped virus Ch5, containing all three of the mutations, was less neutralization sensitive to CD4-IgG2 than Ch2, which did not contain any of these mutations. Any Env-pseudotyped viruses containing D457G mutation were markedly resistant to neutralization by CD4-IgG2, while viruses containing E440G and H564N were neutralization sensitive. Also, binding of CD4-IgG2 to any gp120 that contained D457G mutation was severely disrupted. Beddows *et al.* [2005b] (**neutralization**, **binding affinity**)
- CD4-IgG2: Furin co-transfection did not have an effect on the reactivity of Δ140ct HXBc2 and 3.2P pseudoviruses with CD4-IgG2. Herrera *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)
- CD4-IgG2: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **review**)
- CD4-IgG2: This is a recombinant Ab-like fusion protein in which the heavy- and light-chain variable domains of human IgG2 have been replaced with the D1D2 domains of human CD4. Affinity of this Ab to gp120 did not increase in any of the gp120-mutants studied. 29 mutations in the gp120 resulted in decrease (20-50%) in CD4-IgG2 binding affinity, indicating loss of certain functional features required to maintain CD4BS. Some gp120-mutations increased and some decreased its neutralization by this Ab, however, neutralization and binding affinity did not correlate. Pantophlet *et al.* [2003a] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)

No. 960
MAb ID CM51
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Lin & Nara 2007; Mc Cann *et al.* 2005; Choe *et al.* 2003
Keywords antibody binding site definition and exposure, co-receptor, neutralization, review

- CM51:CM51 structure, sulfation, and binding are reviewed in detail. Lin & Nara [2007] (**review**)
- CM51: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses

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elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **co-receptor**, **neutralization**, **review**)

- CM51: CM51 was obtained from an HIV-1 infected individual with a potent ELISA response to the gp120. It was shown that this MAb heavy chain is sulfate-modified. Choe *et al.* [2003] (**antibody binding site definition and exposure**)

No. 961
MAb ID CO11
HXB2 Location Env
Author Location gp120 (V3)
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 V3
Research Contact James Robinson, Tulane University, New Orleans, LA, USA
References Patel *et al.* 2008; Pantophlet *et al.* 2008; Robinson *et al.* 2005; Haynes *et al.* 2005a; Pantophlet *et al.* 2004; Grundner *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, assay development, binding affinity, HAART, ART, neutralization, structure, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- CO11: CO11 neutralized two of the 15 subtype B isolates tested, 93TH305 and 92BR020c. Binding affinity of MAb CO11 to gp120 was strongly reduced upon substitutions of His308, Pro313 (500-fold), or Arg315 to Ala. The dependence on Pro313 suggests that a precise conformation of the V3 β hairpin turn may be critical for binding of CO11. Thus, CO11 may need to interact with V3 from an angle, which does not permit access to V3 on many different primary viruses. CO11 inability to neutralize 6 of the 15 viruses tested could not be explained by substitution of important contact residues. The fine specificity of CO11 was mapped onto V3 in the structural context of gp120. This showed that the residues important for CO11 binding form a somewhat disjointed pattern, and that CO11 likely also contacts neighboring residues. Pantophlet *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **structure**)
- CO11: To examine sequence and conformational differences between subtypes B and C, several experiments were preformed with 11 MAbs regarding binding and neutralization. Both binding and neutralization studies revealed that the 11 MAbs could be divided in three different groups, and that the most differences between the subtypes were located in the stem and turn regions of V3. CO11 belonged to the group 3 MAbs, which are able to bind subtype B but not subtype C gp120 and V3 peptide. CO11 was able to bind subtype B V3 in the subtype C Env backbone chimera, but not the reverse, indicating that CO11 binds to a structure created by the subtype B V3 sequence that is not impacted by the gp120 backbone. For both subtypes B and C, CO11 required H13 and R18 residues in order to bind, indicating that these residues likely define key aspects of the Ab epitope. CO11 was not able to neutralize JR-FL or SF162 isolates, but a chimeric SF162 variant with a JR-FL-like V3 sequence was hypersensitive to neutralization by this Ab. Patel *et al.* [2008] (**neutralization**, **binding affinity**, **subtype comparisons**)
- CO11: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. CO11 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)
- CO11: A reverse capture assay was developed to asses what kind of human MAbs were produced in EBV B-cell transformation assays performed on PBMC sampled at different timepoints from three HIV-1 infected patients on HAART. The reverse capture assay was validated by the solid phase MAbs that could not capture biotin-MAbs of the same or overlapping specificity when reacted with patient virus envelope glycoproteins preincubated with or without sCD4. Reverse capture assay showed that the produced Abs from the patients were able to block binding of biotin-labeled CO11, however the blocking was low, indicating presence of relatively few V3-binding Abs. Robinson *et al.* [2005] (**antibody generation**, **assay development**, **HAART, ART**)
- CO11: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only 3 additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including CO11. Pantophlet *et al.* [2004] (**vaccine antigen design**)

No. 962
MAb ID D02-1
HXB2 Location Env
Author Location gp120 (JR-FL)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4i
References Bowley *et al.* 2007
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

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- D02-1: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. D02-1 was identified only using yeast display, and is a CD4i antibody with an affinity increase of 2-5 fold when sCD4 is present. Bowley *et al.* [2007] (**antibody binding site definition and exposure**, **antibody generation**, **binding affinity**, **antibody sequence variable domain**, **assay standardization/improvement**)

No. 963
MAb ID D02-20
HXB2 Location Env
Author Location gp120 (JR-FL)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4BS
References Bowley *et al.* 2007
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- D02-20: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. D02-20 was identified using both methods, and binds to the CD4BS. Bowley *et al.* [2007] (**antibody binding site definition and exposure**, **antibody generation**, **binding affinity**, **antibody sequence variable domain**, **assay standardization/improvement**)

No. 964
MAb ID D02-24
HXB2 Location Env
Author Location gp120 (JR-FL)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4i
References Bowley *et al.* 2007
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- D02-24: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. D02-24 was identified only by yeast display, and is a CD4i antibody. Bowley *et al.* [2007] (**antibody binding site definition and exposure**, **antibody generation**, **binding affinity**, **antibody sequence variable domain**, **assay standardization/improvement**)

No. 965
MAb ID D02-3
HXB2 Location Env
Author Location gp120 (JR-FL)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Bowley *et al.* 2007
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- D02-3: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. D02-3 was identified only by yeast display, and its binding site is unknown. Bowley *et al.* [2007] (**antibody binding site definition and exposure**, **antibody generation**, **binding affinity**, **antibody sequence variable domain**, **assay standardization/improvement**)

No. 966
MAb ID D02-33
HXB2 Location Env
Author Location gp120 (JR-FL)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4i
References Bowley *et al.* 2007
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- D02-33: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. D02-33 was identified using only yeast display, and is a CD4i antibody; C02-19 and D02-33 have the same VH sequence. Bowley *et al.* [2007] (**antibody binding site definition and exposure**, **antibody**

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generation, **binding affinity**, **antibody sequence variable domain**, **assay standardization/improvement**)

No. 967
MAb ID D02-34
HXB2 Location Env
Author Location gp120 (JR-FL)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4i
References Bowley *et al.* 2007
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- D02-34: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. D02-34 was identified only by yeast display, and is a CD4i antibody. Bowley *et al.* [2007] (**antibody binding site definition and exposure**, **antibody generation**, **binding affinity**, **antibody sequence variable domain**, **assay standardization/improvement**)

No. 968
MAb ID D02-6
HXB2 Location Env
Author Location gp120 (JR-FL)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4BS
References Bowley *et al.* 2007
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- D02-6: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. D02-6 was identified using both methods, and binds to the CD4BS. Bowley *et al.* [2007] (**antibody binding site definition and exposure**, **antibody generation**, **binding affinity**, **antibody sequence variable domain**, **assay standardization/improvement**)

No. 969
MAb ID D02-7
HXB2 Location Env
Author Location gp120 (JR-FL)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4i
References Bowley *et al.* 2007
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- D02-7: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. D02-7 was identified only by yeast display, and is a CD4i antibody; C02-53 and D02-7 have the same VH sequence. Bowley *et al.* [2007] (**antibody binding site definition and exposure**, **antibody generation**, **binding affinity**, **antibody sequence variable domain**, **assay standardization/improvement**)

No. 970
MAb ID D1
HXB2 Location Env
Author Location gp41 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB
HIV component: oligomeric gp140
Species (Isotype) mouse (IgG)
References Otteken *et al.* 1996

- D1: MAbs D1, D16, had T37 bind to oligomeric gp160 equally well – pulse label experiments of MAb binding to non-cleavable gp160 revealed that these MAbs bound with a delay, epitopes forming with a half-life of 30 min. Otteken *et al.* [1996]

No. 971
MAb ID D10
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Patricia Earl
References Wright *et al.* 2008; Huang *et al.* 2005b
Keywords isotype switch, mucosal immunity, neutralization

- D10: Several IgG MAbs were isotype switched to IgA and tested for their abilities to generate immune complexes with HIV-1 and be excreted from polarized epithelial cells from the basolateral to the apical surface via polymeric Ig receptor (pIgR) binding. IgA D10 showed robust excretion abilities which corresponded to increased binding of D10 to HIV, and,

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as immune complex with the virus, to pIgR. The excretion of the D10-HIV complex was IgA Ab concentration dependent, as well as time dependent, depending on on the duration of basolateral exposure of the immune complexes. Immune complexes with D10 plus D47 showed synergistic abilities, as the binding and excretion increased significantly with both Abs present than with only one of the Abs. D10 excreted infectious virus, correlating with it being a non-neutralizing Ab. These results show that IgA Abs have potential to excrete HIV from mucosal lamina propria thus decreasing the viral burden and access to susceptible cells. Wright *et al.* [2008] (**isotype switch**, **mucosal immunity**)

- D10: By isotype switching, IgG and IgA variants of D10 were produced. Both D10 IgA and IgG showed no significant neutralization of virus in conventional neutralization assays nor did they show any capability of intracellular neutralization of HIV-1. D10 IgA was, however, efficiently transported into the cells, but showed no colonization with HIV protein. D10 IgA did not significantly inhibit production of virus. Huang *et al.* [2005b] (**isotype switch**, **neutralization**, **mucosal immunity**)

No. 972
MAb ID D12
HXB2 Location Env
Author Location gp41 (IIIB)
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Research Contact Patricia Earl and Christopher Broder, NIH
References Yang *et al.* 2000; LaBranche *et al.* 1999; Otteken *et al.* 1996; Earl *et al.* 1997; Richardson *et al.* 1996; Broder *et al.* 1994; Earl *et al.* 1994
Keywords antibody binding site definition and exposure, antibody generation, antibody interactions, vaccine antigen design

- D12: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) – gp41 MAbs T4, D12, T3, and D50 bound less efficiently to gp140-GNC4 than did pooled sera, but T4 and D12 recognized the gp140-GNC4 timer equivalently to gp140(-), and T3 and D50 recognized the trimer at greater levels than gp140(-). Yang *et al.* [2000] (**vaccine antigen design**)
- D12: D12 was used in WB of HIV-1 transmembrane proteins in a study which showed that determinants of HIV-1 CD4 independence map outside regions required for coreceptor specificity – IIIBx, a CD4-independent variant of IIIB, has a truncated gp41. LaBranche *et al.* [1999]
- D12: MAbs D10 and D12 are very easily blocked by human sera from HIV+ individuals. Earl *et al.* [1997]
- D12: MAbs D4, D10, D11, D12, and D41 all bind only to complete oligomer – pulse label experiments of MAb binding to noncleavable gp160 revealed that these MAbs bound with a delay, epitopes forming with a half life of 30 min. Otteken *et al.* [1996] (**antibody binding site definition and exposure**)
- D12: This antibody was blocked more strongly by human sera than other anti-gp41 MAbs (D20, D43, D61, and T4) in a oligomeric ELISA assay. Richardson *et al.* [1996] (**antibody interactions**)
- D12: One of 18 MAbs (e. g. D4 and D40) that bind to a conformation-dependent epitope in gp41 that bind preferentially, but not exclusively, to oligomers – neutralizes IIIB and SF2. Broder *et al.* [1994] (**antibody binding site definition and exposure**)
- D12: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994] (**antibody generation**)

No. 973
MAb ID D16
HXB2 Location Env
Author Location gp41 (IIIB)
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: protein *HIV component:* dimeric Env
Species (Isotype) mouse (IgG)
Research Contact Patricia Earl and Christopher Broder, NIH
References Earl *et al.* 1997; Weissenhorn *et al.* 1996; Earl *et al.* 1994

- D16: One of eleven MAbs (D16, D17, D31, D36, D37, D40, D44, D55, D59, T37, and T45) that are conformation dependent and that can block the binding of the MAb D50 that binds to the linear peptide gp41(642-665) – reactive with 9/10 HIV-1 strains all except HIV-1 ADA, which has the change E659D and E662A that may result in the loss of binding (ELLE to DLLA). Earl *et al.* [1997]
- D16: Precipitates both oligomeric gp140 and soluble monomeric gp41(21-166)that lacks the fusion peptide and membrane anchor, along with MAbs D16, D38, D40, D41, and D54. Weissenhorn *et al.* [1996]
- D16: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 974
MAb ID D17
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen
Species (Isotype) mouse
Ab Type gp41 cluster II
References Zhang *et al.* 2008

- D17: D17 did not compete with the newly defined neutralizing mAb m44 for binding to gp41. Zhang *et al.* [2008]

No. 975
MAb ID D4
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing

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Immunogen vaccine
Vector/Type: chimeric GM-CSF *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgG1)
References del Real *et al.* 1999
Keywords antibody generation, antibody sequence variable domain, autoimmunity

- D4: Murine antibody response to the chimeric construction granulocyte-macrophage colony stimulating factor GM-CSF/gp120 was tested, MAbs from normal mice were gp120 specific, MAbs from nude mice bound gp120 but were polyreactive, and from reconstituted mice were half way between – the anti-gp120 response used a high frequency of VH81X, VHQ52, and VH7183 genes, a family used during fetal life and associated with autoimmunity – D4 was a gp120 from a BALBc reconstructed nude mouse and had VH gene J558. del Real *et al.* [1999] (**antibody generation**, **autoimmunity**, **antibody sequence variable domain**)

No. 976
MAb ID D40
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen
Species (Isotype) mouse
Ab Type gp41 cluster II
References Zhang *et al.* 2008

- D40: D40 did not compete with the newly defined neutralizing mAb m44 for binding to gp41. Zhang *et al.* [2008]

No. 977
MAb ID D43
HXB2 Location Env
Author Location gp41 (HXB2)
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* dimeric Env
Species (Isotype) mouse (IgG)
Research Contact Patricia Earl and Christopher Broder, NIH
References Earl *et al.* 1997; Richardson *et al.* 1996; Earl *et al.* 1994

- D43: Partially conformation dependent – doesn't bind to short peptides, but does bind to the region spanning 641-683 – binding can be blocked by MAbs T3, D38 and D45 – MAbs in this competition group reacted with 9/10 HIV-1 strains, not binding to JRFL. Earl *et al.* [1997]
- D43: This is a linear gp41 epitope, mapping in the region 635-678 – human sera blocked binding in oligomeric ELISA assay to a similar extent for gp41 MAbs D20, D43, D61, and T4. Richardson *et al.* [1996]
- D43: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 978
MAb ID D5
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing L, P
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgG1)
Ab Type gp41 NHR (N-heptad repeat), gp41six-helix bundle, gp41 five-helix bundle (one CHR peptide of six helix bundle is missing)
References Nelson *et al.* 2008; Miller *et al.* 2005
Keywords antibody binding site definition and exposure, binding affinity, neutralization, structure, variant cross-recognition or cross-neutralization

- D5: IgG D5 bound to recombinant r-gp41 (HXB2) and to to 6-Helix. D5 did not recognize soluble forms of Envs used in typical binding assays, which indicates that the D5 epitope is occluded in these Envs. Competition experiments showed that Fab DN9, 8K8, and D5 bind to overlapping but distinct epitopes on the NHR coiled-coil mimetics, where the epitopes of DN9 and 8K8 are more closely related to each other than to D5. Immobilized D5 did not capture infectious whole HIV-1 virions in presence or absence of sCD4, indicating that D5 epitope is restricted on the NHR trimer on the virion surface. In neutralization assays, D5 showed modest but relatively broad neutralization, including HIV-1 isolates from both subtypes B and C. Neutralization potency of D5 was 1 or 2 orders of magnitude less than that of 4E10. NHR mutant residues L568A and K574A induced resistance to neutralization by D5. Nelson *et al.* [2008] (**neutralization**, **binding affinity**)
- D5: A human scFv designated D5 was selected from phage libraries using gp41-based peptides. When convertrd to IgG1 it retained antiviral activity. D5-IgG1 neutralized laboratory and primary isolates of HIV-1, including isolates from subtypes B, C, F and CRFs AE and BF. The gp41 interaction surface of D5-IgG was a conformational epitope overlapping the HR1 hydrophobic pocket. The epitope was shown to be highly conserved in HIV-1. Mutation of key pocket residues of gp41 conferred resistance to neutralization by D5. Miller *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**, **structure**)

No. 979
MAb ID D7
HXB2 Location Env
Author Location Env
Epitope
Neutralizing P
Immunogen vaccine
Vector/Type: protein *Strain:* Other *HIV component:* gp120
Species (Isotype) llama
Ab Type gp120 CD4BS
Research Contact Robin A Weiss, University Colledge London, London, UK, r.weiss@ucl.ac.uk
References Forsman *et al.* 2008

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Keywords antibody binding site definition and exposure, antibody generation, binding affinity, kinetics, neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- D7: D7 is a neutralizing VHH (nanobody) Ab devoid of light chains. It was isolated from sera from llamas, who produce immunoglobulins devoid of light chains, immunized with gp120 of HIV-1 CRF07_BC primary isolate CN54, following panning of phage libraries expressing VHH repertoire and a competitive elution with soluble CD4. It was hypothesized that the small size of the VHH, in combination with their protruding CDR3 loops, and their preference for cleft recognition and binding into active sites, may allow for recognition of conserved motifs on gp120 that are occluded from conventional Abs. D7 was able to neutralize HIV-1 primary isolates of subtypes B, C and CRF07_BC, but not subtypes A, D, and A/G. Compared to MAb b12, which neutralized 54% of viruses tested, D7 neutralized 31% of the viruses, but it neutralized a different spectrum of the viruses than b12. D7 showed high affinity binding to IIIB gp120, and inhibited binding of sCD4 to IIIB gp120 and 92UG037 gp140 in a dose-dependent manner. D7 was found to compete with b12 for binding to gp120, and also with MAbs 654-D and GP68, indicating that its epitope overlaps the CD4bs. There was some inhibition observed of D7-gp120 binding by 2G12, 17b, and 447-52D, while 4E10 did not inhibit D7-gp120 binding. D7 was also able to inhibit binding of the other two VHH Abs isolated in this study, A12 and C8, indicating that their epitopes overlap. Forsman *et al.* [2008] (**antibody binding site definition and exposure**, **antibody generation**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **kinetics**, **binding affinity**, **subtype comparisons**)

No. 980
MAb ID DN9
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp41 NHR (N-heptad repeat), gp41 five-helix bundle (one CHR peptide of six helix bundle is missing)
Research Contact Michael B. Zwick, The Acripps Research Institute, La Jolla, CA, USA, zwick@scripps.edu
References Nelson *et al.* 2008
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, binding affinity, neutralization

- DN9: Fab DN9 was derived from a human Fab phage display library prepared using the bone marrow RNA extracted from an HIV-1 positive individual. The library was screened with N35ccg-N13 peptide, which is a soluble homotrimer corresponding to the HIV-1 gp41 NHR region. DN9 bound to N35ccg-N13 but not to recombinant r-gp41 (HXB2) nor to 6-Helix, indicating that DN9 has a strong preference for NHR trimers unoccupied by peptide corresponding to the C-heptad repeat (CHR). Confirming this, DN9 did not recognize soluble forms of Envs used in typical binding assays, which also indicates that the DN9 epitope is occluded in these Envs. Competition experiments showed that Fab DN9, mAb 8K8, and D5 bind to overlapping but distinct epitopes on the NHR coiled-coil mimetics, where the epitopes of DN9 and 8K8 are more closely related to each other than to D5. DN9 epitope was found distinct from the non-neutralizing Abs in this study, as DN9 does not bind to gp41, gp140, or gp160 as the non-neutralizing Ab did. DN9 has a long CDR H3 (20 residues), and its epitope was suggested to be located in a relatively restricted region of NHR near to the hydrophobic pocket. In neutralization assays, DN9 showed modest but relatively broad neutralization, including HIV-1 isolates from both subtypes B and C. Nelson *et al.* [2008] (**antibody binding site definition and exposure**, **antibody generation**, **neutralization**, **binding affinity**, **antibody sequence variable domain**)

No. 981
MAb ID E047
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 CCR5BS
References Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure

- E047: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. E047 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 982
MAb ID E2E
HXB2 Location Env
Author Location gp140 (WHO-15_28)
Epitope
Subtype D
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* gp140 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) mouse
References Billington *et al.* 2007
Keywords antibody generation

- 2E2: The T30 antibody was used to partially purify a D subtype rgp140 that forms a stable trimer and may be suitable for structural studies. The partially purifed protein was used to immunize mice, and one of the MAbs obtained from the immunized mice, 2E2, was used for further immunoaffintiy purification the protein. Billington *et al.* [2007] (**antibody generation**)

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No. 983
MAb ID ED10
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 CCR5BS
References Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure

- ED10: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. ED10 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 984
MAb ID ED47
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 CD4i
References DeVico *et al.* 2007
Keywords neutralization

- ED47: Macaques were immunized with either CD4, gp120, cross-linked gp120-human CD4 complex (gp120-CD4 XL), and with single chain complex containing gp120 rhesus macaque CD4 domains 1 and 2 (rhFLSC). Sera from the rhFLSC immunized animals showed highest competition titers, being able to block gp120-CD4 complex interactions with ED47 more efficiently than sera from animals immunized with the three other proteins. Competition titers of ED47 correlated with the absence of detectable tissue viremia. DeVico *et al.* [2007] (**neutralization**)

No. 985
MAb ID EH21
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 C1-C4
References Visciano *et al.* 2008b; Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure

- EH21: A significantly higher level of anti-V3 Abs (694/98D and 447-52D) and anti-C1 mAb (EH21) bound to gp120 complexed with anti-CD4bs mAbs than to gp120 alone or in complex with other non-CD4bs Abs, indicating that binding of anti-CD4bs Abs to gp120 increases exposure of specific V3 and C1 mAb epitopes. Visciano *et al.* [2008b] (**antibody binding site definition and exposure**)
- EH21: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. EH21 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 986
MAb ID F1
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 CD4BS
References Haynes *et al.* 2005a; Fujii *et al.* 1993

- F1: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. F1 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a]
- F1 database note: There is a Nef (Fujii1993) and a CD4BS (Haynes2005) MAb that are called F1. Fujii *et al.* [1993]; Haynes *et al.* [2005a]

No. 987
MAb ID F223
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG3λ)
References Cavacini *et al.* 1999

- F223: binds to HIV-1 gp120 and to uninfected lymphocytes binding to a 159-kd auto-antigen expressed on most B cells and a small fraction of T and NK cells – the antibody enhances HIV-1 infection in a complement-dependent manner – F223 light chains have a strong homology with VLgamma2, the heavy chain to the germline gene VH3-H.11 – N-linked carbohydrates are key for recognition of both gp120 and the autoantigen – MAb 3D6 also uses VH3 and has autoreactivity. Cavacini *et al.* [1999]

No. 988
MAb ID F285
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
References Wisnewski *et al.* 1996; Wisnewski *et al.* 1995

- F285: F285 is V H1 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996]

No. 989
MAb ID F2A3
HXB2 Location Env
Author Location
Epitope
Subtype B
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 V3
Research Contact James Robinson, Tulane University, New Orleans, LA, USA
References Pantophlet *et al.* 2008; Bowley *et al.* 2007; Liao *et al.* 2006; Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure, binding affinity, neutralization, structure, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- F2A3: F2A3 neutralized two of the 15 subtype B isolates tested, 93TH305 and 92BR020c. Binding affinity of MAb F2A3 to gp120 was strongly reduced upon substitutions of His308, or K305 to Ala, suggesting that the F2A3 epitope overlaps mostly with the N-terminal flank of the V3 region. Binding of F2A3 was substantially enhanced by substitutions I309A, F317A, Y318A, and D325A, indicating that their interaction with neighboring residues likely affects how well F2A3 epitope is presented. F2A3 inability to neutralize 5 of the 15 viruses tested could not be explained by substitution of important contact residues. The fine specificity of F2A3 was mapped onto V3 in the structural context of gp120. This showed that the residues important for F2A3 binding form a nearly linear arrangement on the V3 structure, and that the residues that increased Ab binding when changed to Ala are crowded around the linear arrangement, suggesting an important role of the adjacent residues for contact residue positioning. Pantophlet *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **structure**)
- F2A3: Yeast display was compared to phage display and shown to select all the scFv identified by phage display and additional novel antibodies. F2A3 was used in competition assays to determine the binding region of the MAbs selected from the yeast displayed antibody library. Bowley *et al.* [2007]
- F2A3: The gp140δCFI protein of CON-S M group consensus protein and gp140CFI and gp140CF proteins of CON6 and WT viruses from HIV-1 subtypes A, B and C were expressed in recombinant vaccinia viruses and tested as immunogens in guinea pigs. F2A3 was shown to bind specifically only to CON6 and subtype A gp140CFIs. No specific binding was observed for the CON-S nor for the rest of the recombinant proteins and the two subtype B gp120 proteins. Liao *et al.* [2006] (**antibody binding site definition and exposure**, **vaccine antigen design**, **subtype comparisons**)
- F2A3: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. F2A3 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 990
MAb ID F3.9F
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 V3
References Patel *et al.* 2008; Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure, binding affinity, neutralization, subtype comparisons

- F3.9F: To examine sequence and conformational differences between subtypes B and C, several experiments were preformed with 11 MAbs regarding binding and neutralization. Both binding and neutralization studies revealed that the 11 MAbs could be divided in three different groups, and that the most differences between the subtypes were located in the stem and turn regions of V3. F3.9F belonged to the group 1 MAbs, which are able to bind both subtype B and C gp120 proteins and peptides. F3.9F was also able to bind both subtype C V3 in the subtype B Env backbone chimera, and reverse, indicating that F3.9F binds to V3 in a way that is not affected by the gp120 backbone. For subtype B, changes in the position 13 (H13R) and/or position 18 (R18Q) showed no difference of F3.9F binding compared to wildtype. For subtype C, H13 residue enhanced binding of F3.9F, but the R18 mutation reduced binding, indicating that R18 affects the conformation of V3 subtype C. Although F3.9F bound to JR-FL V3, this isolate was resistant to neutralization by F3.9F. F3.9F was able to neutralize SF-162, and a chimeric SF162 variant with a JR-FL-like V3 sequence was hypersensitive to neutralization by this Ab. Patel *et al.* [2008] (**neutralization**, **binding affinity**, **subtype comparisons**)
- F3.9F: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. F3.9F has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 991
MAb ID F39F
HXB2 Location Env
Author Location gp120 (V3)
Epitope

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Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 V3
Research Contact James Robinson, Tulane Medical School, New Orleans, LA, USA
References Gao *et al.* 2005a
Keywords antibody binding site definition and exposure

- F39F: Monomeric gp120 and trimeric gp140CF proteins synthesized from an artificial group M consensus Env gene (CON6) bound well to F39F, indicating correct exposure of the F39F epitope. Gao *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 992
MAb ID F424
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Ferrantelli *et al.* 2004a
Keywords variant cross-recognition or cross-neutralization

- F424: Nabs against HIV-1 M group isolates were tested for their ability to neutralize 6 randomly selected HIV-1 O group strains. F424 is noted to be a MAb derived from a subtype B infected individual, that binds to an undefined epitope in gp120 and can neutralize some M group viruses, but it was not particularly effective at neutralization of the O group viruses tested. Ferrantelli *et al.* [2004a] (**variant cross-recognition or cross-neutralization**)

No. 993
MAb ID F425 B4e8 (F425-B4e8, F425, F425b)
HXB2 Location Env
Author Location gp120 (V3)
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 V3
Research Contact L. Cavacini
References Pugach *et al.* 2008; Patel *et al.* 2008; Keele *et al.* 2008; Dey *et al.* 2008; Binley *et al.* 2008; Holl *et al.* 2006a; Pantophlet *et al.* 2007; McKnight & Aasa-Chapman 2007; Dhillon *et al.* 2007; Xiang *et al.* 2005; Selvarajah *et al.* 2005; Mc Cann *et al.* 2005; Kalia *et al.* 2005; Pantophlet *et al.* 2004; Cavacini *et al.* 2003
Keywords acute/early infection, antibody binding site definition and exposure, binding affinity, co-receptor, dendritic cells, neutralization, optimal epitope, review, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- F425: 24 broadly neutralizing plasmas from HIV-1 subtype B an C infected individuals were investigated using a series of mapping methods to identify viral epitopes targeted by NAbs. V3 Ab activity was measured by three assays where F425 was used as a control. Binley *et al.* [2008] (**neutralization**)
- F425-B4e8: Five amino acids in the gp41 N-terminal region that promote gp140 trimerization (I535, Q543, S553, K567 and R588) were considered. Their influence on the function and antigenic properties of JR-FL Env expressed on the surfaces of pseudoviruses and Env-transfected cells was studied. Various non-neutralizing antibodies bind less strongly to the Env mutant, but neutralizing antibody binding is unaffected. F425-B4e8 captured significantly fewer mutant pseudovirions than wild type, but F425-B4e8 inhibited infection of the two pseudoviruses with comparable potencies. Dey *et al.* [2008] (**binding affinity**)
- F425-B4e8: A mathematical model was developed and used to derive transmitted or founder Env sequences from individuals with acute HIV-1 subtype B infection. All but three of the transmitted or early founder Envs were resistant to neutralization by F425-B4e8, indicating that the coreceptor binding surfaces on transmitted/founder Envs are conformationally masked. sCD4 could trigger a conformational change in gp120 of these Envs and render the virus susceptible to neutralization by F425-B4e8. Keele *et al.* [2008] (**neutralization**, **acute/early infection**)
- F425 B4e8: To examine sequence and conformational differences between subtypes B and C, several experiments were preformed with 11 MAbs regarding binding and neutralization. Both binding and neutralization studies revealed that the 11 MAbs could be divided in three different groups, and that the most differences between the subtypes were located in the stem and turn regions of V3. F425 B4e8 belonged to the group 1 MAbs, which are able to bind both subtype B and C gp120 proteins and peptides. F425 B4e8 was able to bind both subtype C V3 in the subtype B Env backbone chimera, and reverse, indicating that F425 B4e8 binds to V3 in a way that is not affected by the gp120 backbone. For subtype B, changes in the position 13 (H13R) and/or position 18 (R18Q) showed no difference of F425 B4e8 binding compared to wildtype. For subtype C, H13 residue enhanced binding of F425 B4e8, but the R18 mutation reduced binding, indicating that R18 affects the conformation of V3 subtype C. F425 B4e8 did not neutralize JR-FL isolate, but did neutralize SF162. A chimeric SF162 variant with a JR-FL-like V3 sequence was hypersensitive to neutralization by F425 B4a1, suggesting an important role of one or more of the three V3 amino acids that differ between these two isolates in defining the epitope and/or structure of the protein. Patel *et al.* [2008] (**neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)
- F425: In order to assess whether small molecule CCR5 inhibitor resistant viruses were more sensitive to neutralization by NAbs, two escape mutant viruses, CC101.19 and D1/85.16, were tested for their sensitivity to neutralization by F425, compared to the sensitivity of CC1/85 parental isolate and the CCcon.19 control isolate. The CC101.19 escape mutant has 4 sequence changes in V3 while the D1/85.16 has no sequence changes in V3 and relies on other sequence changes

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for its resistance. None of the control or resistant viruses were sensitive for neutralization by F425, although F425 bound strongly to gp120 from CC1/85 and CC101.19. These results indicate that V3-dependent and -independent changes responsible for CCR5 inhibitor resistance do not necessarily alter the exposure of V3 to some of the V3 Abs. Pugach *et al.* [2008] (**antibody binding site definition and exposure**, **co-receptor**, **neutralization**, **binding affinity**)

- F425 B4e8: Peptides containing the V3 epitope for F425 B4e8 did not inhibit neutralization by broadly neutralizing sera from two clade B and one clade A infected asymptomatic individuals. Dhillon *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**)
- F425-B4e8: This review summarizes data on possible vaccine targets for elicitation of neutralizing Abs and discusses whether it is more practical to design a clade-specific than a clade-generic HIV-1 vaccine. Development of a neutralizing Ab response in HIV-1 infected individuals is reviewed, including data that show no apparent division of different HIV-1 subtypes into clade-related neutralization groups. Also, a summary of the neutralizing activity of mAb F425-B4e8 in different HIV-1 clades is provided. McKnight & Aasa-Chapman [2007] (**variant cross-recognition or cross-neutralization**, **review**)
- F425 B4e8: The neutralization breadth of F425 B4e8 was assessed using a panel of 40 primary HIV-1 isolates. The Ab neutralized 8/16 clade B, 1/11 clade C and 2/6 clade D viruses, and its neutralization activity was comparable to mAb 447-52D. In contrast to previous reports, it is suggested here that F425 B4e8 interacts primarily with the crown/tip of V3, based on the scanning mutagenesis analyses of the V3 region, in particular with Ile309, Arg315, and Phe317. Pantophlet *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **optimal epitope**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- F425 B4e8: This Ab was shown to inhibit HIV-1 BaL replication in both macrophages and PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication by this Ab for macrophages and iDCs can occur by two distinct mechanisms, neutralization of infectivity involving only the Fab part of the IgG, and, an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**dendritic cells**)
- F425b4e8: Point mutations in the highly conserved structural motif LLP-2 within the intracytoplasmic tail of gp41 resulted in conformational alternations of both gp41 and gp120. The alternations did not affect virus CD4 binding, coreceptor binding site exposure, or infectivity of the virus, but did result in increased relative neutralization resistance of the LLP-2 mutant virus to F425b4e8, compared with wildtype virus. The increased neutralization resistance of LLP-2 virus was associated with decreased F425b4e8 binding to its epitope. Kalia *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- F425: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**neutralization**, **variant cross-recognition or cross-neutralization**, **review**)
- F425 B4e8: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. V3 MAbs (447-52D, 19b, F245-B4e8 and 39F) bound to the GDMR antigen, but either did not bind or had diminished binding to mCHO. Selvarajah *et al.* [2005] (**vaccine antigen design**, **vaccine-specific epitope characteristics**)
- F425b: This Ab recognized gp120 glycoproteins from CCR5-using MN, ADA and YU2 strains and from the dual-tropic 89.6 strain, but it did not recognize the gp120 from the CXCR4-using HXBc2. gp120 from HXBc2 containing the V3 loop of YU2 strain was efficiently recognized by F425b, indicating the role of the V3 loop in recognition of CCR5 strains by this Ab. Changing the residues 325 and 326 at the base of the V3 loop from the amino acids predominant in the CXCR4-using strains to amino acids predominant in the CCR5-using strains did not result in binding of F425b. Xiang *et al.* [2005] (**antibody binding site definition and exposure**, **co-receptor**)
- F425 B4e8: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including F425 B4e8. This MAb bound to the initial construct, but introduction of glycosylation sites at positions 320 and 325 inhibited binding. Pantophlet *et al.* [2004]

No.	994
MAb ID	F425B4a1
HXB2 Location	Env
Author Location	gp120 (V3)
Epitope	
Neutralizing	
Immunogen	
Species (Isotype)	(IgG1λ)
Ab Type	gp120 V3
References	Patel *et al.* 2008; Holl *et al.* 2006a
Keywords	binding affinity, dendritic cells, neutralization, subtype comparisons

- F425 B4a1: To examine sequence and conformational differences between subtypes B and C, several experiments were preformed with 11 MAbs regarding binding and neutralization. Both binding and neutralization studies revealed that the 11 MAbs could be divided in three different groups, and that the most differences between the subtypes were located in the stem and turn regions of V3. F425 B4a1 belonged to the group 1 MAbs, which are able to bind both subtype B and C gp120 proteins and peptides. F425 B4a1 was able to bind both subtype C V3 in the subtype B Env backbone chimera, and reverse, indicating that F425 B4a1 binds to V3 in a way that is not affected by the gp120 backbone. For subtype B, changes in the position 13 (H13R) and/or position 18 (R18Q) showed no difference of F425 B4a1 binding compared to wildtype. For subtype C, H13 residue enhanced binding of F425 B4a1, but the R18 mutation reduced binding, indicating that R18 affects the conformation of V3 subtype C. F425 B4a1 did not neutralize JR-FL isolate, but did neutralize SF162. A chimeric SF162 variant with a JR-FL-like V3 sequence was hypersensitive to neutralization by F425 B4a1, suggesting an important role of one or more of the three V3 amino acids that differ between these two isolates in defining the epitope and/or structure of the protein. Patel *et al.* [2008] (**neutralization**, **binding affinity**, **subtype comparisons**)

- F425B4a1: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication occurs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)

No. 995
MAb ID F530
HXB2 Location Env
Author Location gp120 (V3)
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V3
Research Contact Cavacini L
References Pantophlet *et al.* 2008
Keywords antibody binding site definition and exposure, binding affinity, neutralization, structure, variant cross-recognition or cross-neutralization

- F530: F530 neutralized 5 of the 15 subtype B isolates tested. Binding affinity of MAb F530 to gp120 was diminished by similar substitutions as for MAbs CO11, F2A3, LA21 and LE11. However, the binding affinity of F530 was not diminished by the His308 to Ala change. F530 inability to neutralize 6 of the 15 viruses tested could not be explained by substitution of important contact residues. The fine specificity of F530 was mapped onto V3 in the structural context of gp120. The map was similar to the maps of MAbs CO11, F2A3, LA21 and LE311, however, the ability of F530 to bind V3 without requiring the presence of Arg315 suggests that F350 interacts mostly with the N-terminal flank of the V3 loop. Pantophlet *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **structure**)

No. 996
MAb ID F7
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: chimeric GM-CSF *Strain:* B clade IIIB *HIV component:* gp120 *Adjuvant:* GM-CSF
Species (Isotype) mouse (IgG1)
References del Real *et al.* 1999
Keywords antibody generation, antibody sequence variable domain, autoimmunity

- F7: Murine antibody response to the chimeric construction granulocyte-macrophage colony stimulating factor GM-CSF/gp120 was tested, MAbs from normal mice were gp120 specific, MAbs from nude mice bound gp120 but were polyreactive, and from reconstituted mice were half way between – the anti-gp120 response used a high frequency of VH81X, VHQ52, and VH7183 genes, a family used during fetal life and associated with autoimmunity – F7 was a gp120 specific MAb from a BALBc mouse and had VH gene 7183(81X), previously found expressed only in fetal liver. del Real *et al.* [1999] (**antibody generation**, **autoimmunity**, **antibody sequence variable domain**)

No. 997
MAb ID Fab 3663
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human
Ab Type gp41six-helix bundle
References Gustchina *et al.* 2008; Gustchina *et al.* 2007
Keywords antibody binding site definition and exposure, binding affinity, kinetics, neutralization, optimal epitope

- Fab 3663: Bivalent Fab 3663 (bF-3663) does not neutralize HXB2 on its own, but it reduces the neutralization IC50 of N36Mut(e,g) peptide, which is a class 3 inhibitor that disrupts trimerization of the N-heptad repeat (N-HR) in the prehairpin intermediate by sequestering the N-HR into N-HR/N36Mut(e,g) heterodimers. Gustchina *et al.* [2008] (**neutralization**, **kinetics**)
- Fab 3663: Fab 3663 was selected from a human phage library by panning against a chimeric construct that exposes coiled-coil of gp41 N helices. The epitope for the Fab 3663 consists of: W571, K574 and Q575 with a likely contribution from Q567, and is located in the shallow groove on the N helices, exposed between two C helices in the fusiogenic six-helix bundle conformation of gp41. Fab 3663 had no neutralizing activity. Gustchina *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **optimal epitope**, **binding affinity**)

No. 998
MAb ID Fab 3670

HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human
Ab Type gp41six-helix bundle
References Gustchina *et al.* 2008; Gustchina *et al.* 2007
Keywords antibody binding site definition and exposure, binding affinity, kinetics, neutralization, optimal epitope

- Fab 3670: Bivalent Fab 3670 (bF-3670) does not neutralize HXB2 on its own, but it reduces the neutralization IC50 of N36Mut(e,g) peptide, which is a class 3 inhibitor that disrupts trimerization of the N-heptad repeat (N-HR) in the prehairpin intermediate by sequestering the N-HR into N-HR/N36Mut(e,g) heterodimers. Gustchina *et al.* [2008] (**neutralization**, **kinetics**)
- Fab 3670: Fab 3670 was selected from a human phage library by panning against a chimeric construct that exposes coiled-coil of gp41 N helices. The epitope for the Fab 3670 consists of: W571, K574 and Q575 with a likely contribution from Q567, and is located in the shallow groove on the N helices, exposed between two C helices in the fusiogenic six-helix bundle conformation of gp41. Fab 3670 had no neutralizing activity. Gustchina *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **optimal epitope**, **binding affinity**)

No. 999
MAb ID Fab 3674
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human
Ab Type gp41six-helix bundle
References Gustchina *et al.* 2008; Gustchina *et al.* 2007
Keywords antibody binding site definition and exposure, binding affinity, kinetics, neutralization, optimal epitope, variant cross-recognition or cross-neutralization

- Fab 3674: The IC50 for bivalent Fab 3675 (bF-3674) in a standard neutralization assay is 88nM and is only minimally affected in the postattachment neutralization assay. The neutralization half-life for bF-3674 is 20.6 minutes and is increased 30% to 27.7 minutes in the presence of N36Mut(e,g) peptide, which is a class 3 inhibitor that prolongates temporal window of neutralization by disrupting trimerization of the N-heptad repeat (N-HR) in the prehairpin intermediate by sequestering the N-HR into N-HR/N36Mut(e,g) heterodimers. Both HXB2 and HIV-1 primary isolates of subtypes B and C were neutralized synergistically by bF-3674 and N36Mut(e,g). HXB2 was also neutralized synergistically by bF-3674 and CD4. Gustchina *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**, **kinetics**)
- Fab 3674: Fab 3674 was selected from a human phage library by panning against a chimeric construct that exposes coiled-coil of gp41 N helices. The epitope for the Fab 3674 comprises of: E560, H564, W571, K574 and Q575, and is located in the shallow groove on the N helices, exposed between two C helices in the fusiogenic six-helix bundle conformation of gp41. Fab 3674 had broadly neutralizing activity against several subtype B isolates, and also subtypes A and C, as its epitope is conserved among these subtypes. A fusion inhibitor (C34) and Fab 3674 were shown to have additive and synergistic actions on the fusion inhibition of HIV-1. Gustchina *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **optimal epitope**, **variant cross-recognition or cross-neutralization**, **binding affinity**)

No. 1000
MAb ID Fab A12
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
References Binley *et al.* 1996

- Fab A12: Uncharacterized epitope – variable regions sequenced. Binley *et al.* [1996]

No. 1001
MAb ID Fab A2
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
References Binley *et al.* 1996

- Fab A2: Uncharacterized epitope – variable regions sequenced. Binley *et al.* [1996]

No. 1002
MAb ID Fab L9
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
References Binley *et al.* 1996

- Fab L9: Uncharacterized epitope – variable regions sequenced. Binley *et al.* [1996]

No. 1003
MAb ID G12
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing

B Cell

Immunogen vaccine
Vector/Type: chimeric GM-CSF *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgM)
References del Real *et al.* 1999
Keywords antibody generation, antibody sequence variable domain, autoimmunity

- G12: Murine antibody response to the chimeric construction granulocyte-macrophage colony stimulating factor GM-CSF/gp120 was tested, MAbs from normal mice were gp120 specific, MAbs from nude mice bound gp120 but were polyreactive, and from reconstituted mice were half way between – the anti-gp120 response used a high frequency of VH81X, VHQ52, and VH7183 genes, a family used during fetal life and associated with autoimmunity – G12 was a gp120 from a BALBc reconstructed nude mouse and had VH gene 7183-6. del Real *et al.* [1999] (**antibody generation**, **autoimmunity**, **antibody sequence variable domain**)

No. 1004
MAb ID G2
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: chimeric GM-CSF *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgM)
References del Real *et al.* 1999
Keywords antibody generation, antibody sequence variable domain, autoimmunity

- G2: Murine antibody response to the chimeric construction granulocyte-macrophage colony stimulating factor GM-CSF/gp120 was tested, MAbs from normal mice were gp120 specific, MAbs from nude mice bound gp120 but were polyreactive, and from reconstituted mice were half way between – the anti-gp120 response used a high frequency of VH81X, VHQ52, and VH7183 genes, a family used during fetal life and associated with autoimmunity – G2 was a gp120 from a BALBc reconstructed nude mouse and had VH gene Q52. del Real *et al.* [1999] (**antibody generation**, **autoimmunity**, **antibody sequence variable domain**)

No. 1005
MAb ID G34
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 V2
References Srivastava *et al.* 2008
Keywords binding affinity, subtype comparisons

- G34: Trimeric envelope glycoproteins with a partial deletion of the V2 loop derived from subtype B SF162 and subtype C TV1 were compared. G34 did not recognize either B or C trimers, since it is a V2 loop specific Ab. Subtype C trimer had many biophysical, biochemical, and immunological characteristics similar to subtype B trimer, except for a difference in the three binding sites for CD4, which showed cooperativity of CD4 binding in subtype C but not in subtype B. Srivastava *et al.* [2008] (**binding affinity**, **subtype comparisons**)

No. 1006
MAb ID H2
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen
Species (Isotype) human (IgMκ)
Research Contact BioInvent, Lund, Sweden, commercial
References Muller *et al.* 1991

- H2: Anti-idiotypic MAbs (10B3 and 2All) against MAb H2 were generated by immunization of BALBc mice with H2 – they also react with seropositive sera. Muller *et al.* [1991]

No. 1007
MAb ID H211
HXB2 Location Env
Author Location gp120 (V3)
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 V3
Research Contact James Robinson
References Patel *et al.* 2008
Keywords antibody binding site definition and exposure, binding affinity, neutralization, subtype comparisons

- H211: To examine sequence and conformational differences between subtypes B and C, several experiments were preformed with 11 MAbs regarding binding and neutralization. Both binding and neutralization studies revealed that the 11 MAbs could be divided in three different groups, and that the most differences between the subtypes were located in the stem and turn regions of V3. H211 belonged to the group 2 MAbs, which are able to bind subtype B but not subtype C gp120, and are able to bind both V3 peptides. For subtype B, H211 required an R18 residue in order to bind, but the binding was not significantly affected by the H13R change. For subtype C, Q18R mutation did not restore binding to gp120, but the R13H-Q18R double mutation did. Peptide binding was affected only by the R13H mutation, indicating that the poor binding of Q18R gp120 mutant has a structural basis. H211 was not able to neutralize JR-FL isolate, but neutralized SF162. A chimeric SF162 variant with a JR-FL-like V3 sequence was hypersensitive to neutralization by this Ab. Patel *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**, **subtype comparisons**)

No. 1008
MAb ID H8
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope

B Cell

Neutralizing
Immunogen vaccine
Vector/Type: chimeric GM-CSF *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgM)
References del Real *et al.* 1999
Keywords antibody generation, antibody sequence variable domain, autoimmunity

- H8: Murine antibody response to the chimeric construction granulocyte-macrophage colony stimulating factor GM-CSF/gp120 was tested, MAbs from normal mice were gp120 specific, MAbs from nude mice bound gp120 but were polyreactive, and from reconstituted mice were half way between – the anti-gp120 response used a high frequency of VH81X, VHQ52, and VH7183 genes, a family used during fetal life and associated with autoimmunity – H8 was a gp120 from a BALBc reconstructed nude mouse and had VH gene Q52. del Real *et al.* [1999] (**antibody generation**, **autoimmunity**, **antibody sequence variable domain**)

No. 1009
MAb ID HBW4
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
References Wisnewski *et al.* 1996; Wisnewski *et al.* 1995; Moran *et al.* 1993

- HBW4: HBW4 is V H2 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996]
- HBW4: Heavy (V HII) and light (V lambdaII) chain sequenced. Moran *et al.* [1993]

No. 1010
MAb ID IVI-4G6 (4G6)
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen vaccine
Species (Isotype) mouse (IgG2b)
Research Contact K. Miyakoshi (Feji-Rebio Co, Tokyo, Japan)
References Okada *et al.* 2005; Yin *et al.* 2001
Keywords antibody interactions

- 4G6: Hybridoma cell lines from trans-chromosome knock-out mice immunized with HIV-1 infected cells produced two human mAbs, 9F11 and 2G9, that reacted with HIV-1 infected cells. 2G9 induced apoptosis of HIV-1 infected cells and 9F11 was able to induce complement-mediated cytolysis. None of the mAbs are thought to bind directly to HIV-1. Unlike 2G9, 4G6 did not react with OM10.1 cells maintained in a latently infected state in the presence of AZT, but it did react when the virus replication was activated in the absence of AZT and in the presence of TNF-α. Okada *et al.* [2005] (**antibody interactions**)
- IVI-4G6: A bi-specific Ab (BFA) was made by combining Fab fragments of gp41-specific MAb IVI-4G6 and CD3-specific Mab UCHT1 – the BFA suppressed HIV-1 propagation culture and eliminated latently infected cells. Yin *et al.* [2001]

No. 1011
MAb ID IgA6/30λ
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing yes
Immunogen HIV-1 exposed seronegative
Species (Isotype) human
References Berry *et al.* 2003
Keywords antibody generation, antibody sequence variable domain, genital and mucosal immunity, HIV exposed persistently seronegative (HEPS)

- A panel of anti-gp120 single-chain variable fragment (scFv) Ab was isolated from cervical B lymphocytes of unexposed uninfected Kenyan prostitutes. These Abs recognize gp120 in ELISA and using flow cytometry. IgG1b12 does not inhibit binding of the new clones to HIV, so the epitopes are distinct. Sequencing of the V genes of the scFv clones show they are unique. Berry *et al.* [2003] (**antibody generation**, **genital and mucosal immunity**, **HIV exposed persistently seronegative (HEPS)**, **antibody sequence variable domain**)

No. 1012
MAb ID IgA6/5k
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing yes
Immunogen HIV-1 exposed seronegative
Species (Isotype) human
References Berry *et al.* 2003
Keywords antibody generation, antibody sequence variable domain, genital and mucosal immunity, HIV exposed persistently seronegative (HEPS)

- A panel of anti-gp120 single-chain variable fragment (scFv) Ab was isolated from cervical B lymphocytes of unexposed uninfected Kenyan prostitutes. These Abs recognize gp120 in ELISA and using flow cytometry. IgG1b12 does not inhibit binding of the new clones to HIV, so the epitopes are distinct. Sequencing of the V genes of the scFv clones show they are unique. Berry *et al.* [2003] (**antibody generation**, **genital and mucosal immunity**, **HIV exposed persistently seronegative (HEPS)**, **antibody sequence variable domain**)

No. 1013
MAb ID IgA6/L4
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing yes
Immunogen HIV-1 exposed seronegative
Species (Isotype) human
References Berry *et al.* 2003

B Cell

Keywords antibody generation, antibody sequence variable domain, genital and mucosal immunity, HIV exposed persistently seronegative (HEPS)

- A panel of anti-gp120 single-chain variable fragment (scFv) Ab was isolated from cervical B lymphocytes of unexposed uninfected Kenyan prostitutes. These Abs recognize gp120 in ELISA and using flow cytometry. IgG1b12 does not inhibit binding of the new clones to HIV, so the epitopes are distinct. IgA6/4L is neutralizing. Sequencing of the V genes of the scFv clones show they are unique. Berry *et al.* [2003] (**antibody generation**, **genital and mucosal immunity**, **HIV exposed persistently seronegative (HEPS)**, **antibody sequence variable domain**)

No. 1014
MAb ID K14
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing no
Immunogen
Species (Isotype) human (IgG1)
References Schutten *et al.* 1997; Schutten *et al.* 1996; Schutten *et al.* 1995b; Schutten *et al.* 1995a; Teeuwsen *et al.* 1990

- K14: In a study of NSI and SI virus neutralization, K14 did not influence viral entry. Schutten *et al.* [1997]
- K14: Reduced affinity for both SI and NSI viruses relative to MAb MN215, failed to neutralize SI strain. Schutten *et al.* [1995b]
- K14: Did not bind to peptides spanning gp41, but it does not react with Env deletion mutant 643-692 – does not react with HIV-2– competition experiments showed this was an immunodominant conserved epitope in HIV-1 positive sera from Europe and Africa. Teeuwsen *et al.* [1990]

No. 1015
MAb ID KU32
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen
Species (Isotype) human
References Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure

- KU32: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. KU32 was noted to have some polyspecific autoreactivity in the text, but it was not clear how this was manifested from the results. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 1016
MAb ID LA15
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 CCR5BS
References Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure

- LA15: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. LA15 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 1017
MAb ID LA21
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 V3
References Pantophlet *et al.* 2008; Sheppard *et al.* 2007b; Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure, binding affinity, neutralization, structure, variant cross-recognition or cross-neutralization

- LA21: LA21 neutralized two of the 15 subtype B isolates tested. Binding affinity of MAb LA21 to gp120 was strongly reduced upon substitutions of His308, or Pro313 (250-fold), to Ala. The dependence on Pro313 suggests that a precise conformation of the V3 β hairpin turn may be critical for binding of LA21. Thus, LA21 may need to interact with V3 from an angle, which does not permit access to V3 on many different primary viruses. LA21 inability to neutralize 6 of the 15 viruses tested could not be explained by substitution of important contact residues. The fine specificity of LA21 was mapped onto V3 in the structural context of gp120. This showed that the residues important for LA21 binding form a somewhat disjointed pattern, and that LA21 likely also contacts neighboring residues. Pantophlet *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **structure**)
- LA21: This Ab was shown not to react with clade C gp140 (97CN54). Sheppard *et al.* [2007b] (**variant cross-recognition or cross-neutralization**)
- LA21: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. LA21 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

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No. 1018
MAb ID LA28
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 CCR5BS
References Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure

- LA28: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. LA28 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 1019
MAb ID LE311
HXB2 Location Env
Author Location gp120 (V3)
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact James Robinson, Tulane University, New Orleans, LA, USA
References Vaine *et al.* 2008; Pantophlet *et al.* 2008; Crooks *et al.* 2007; Derby *et al.* 2006; Crooks *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation, assay standardization/improvement, binding affinity, neutralization, structure, vaccine antigen design, variant cross-recognition or cross-neutralization

- LE311: LE311 neutralized three of the 15 subtype B isolates tested. Binding affinity of MAb LE311 to gp120 was strongly reduced upon substitutions of His308, Pro313, or K305 to Ala, suggesting that the LE311 epitope overlaps mostly with the N-terminal flank of the V3 region and that a precise conformation of the V3 β hairpin turn may be critical for Ab binding. Thus, LE311 may need to interact with V3 from an angle, which does not permit access to V3 on many different primary viruses.LE311 inability to neutralize 6 of the 15 viruses tested could not be explained by substitution of important contact residues. The fine specificity of LE311 was mapped onto V3 in the structural context of gp120. This showed that the residues important for LE311 binding form a nearly linear arrangement on the V3 structure. Pantophlet *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **structure**)
- LE311: Sera from both gp120 DNA prime-protein boost immunized rabbits and from protein-only immunized rabbits competed for binding to LE311, indicating elicitation of LE311-like Abs by both immunization regimens. Competitive virus capture assay revealed higher titers of LE311-like Abs in animals immunized with DNA prime-protein boost than in protein-only immunized animals. Vaine *et al.* [2008] (**vaccine antigen design**)
- LE311: Guinea pigs were immunized with gp120 protein, or with three types of VLPs containing disulfide-shackled functional trimers (SOS-VLP), uncleaved nonfunctional Env (UNC-VLP), naked VLP bearing no Env. LE311 was used in a capture assay showing that most of the SOS-VLP and UNC-VLP sera contained high titers of anti-V3 Abs. gp120 sera showed only moderate titers of V3 competing Abs. Crooks *et al.* [2007] (**neutralization**)
- LE311: Macaques were immunized with SF162gp140, ΔV2gp140, ΔV2ΔV3gp140 and ΔV3gp140 constructs and their antibody responses were compared to the broadly reactive NAb responses in a macaque infected with SHIV SF162P4, and with pooled sera from humans infected with heterologous HIV-1 isolates (HIVIG). LE311-like Abs were present in low titers in sera from gp140 immunized animals and in higher titers in the SHIV-infected animal. LE311 captured JRFL more efficiently when the virus was pre-incubated with sCD4. Derby *et al.* [2006] (**antibody generation**, **neutralization**)
- LE311: LE311 was investigated in differnt neutralization formats, including the standard format that measures activity over the entire infection period and several formats that emphasize various stages of infection. LE311 dramatically neutralized in the post-CD4 format but did not have any activity in the standard format. LE311 did not have any activity in the post-CD4/CCR5 format. This suggests that the post-CD4, pre-CCR5 phase of infection is a narrow window of opportunity for neutralization of JR-FL by LE311 Ab. Addition of a disulfide bridge linking gp120 and gp41 resulted in detectable activity of LE311 in the standard format. Visualization of Env-Ab binding was conducted by BN-PAGE band shifts. Crooks *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **assay standardization/improvement**)

No. 1020
MAb ID LF17
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 CCR5BS
References Srivastava *et al.* 2008; Haynes *et al.* 2005a
Keywords antibody binding site definition and exposure, binding affinity, subtype comparisons

- LF17: Trimeric envelope glycoproteins with a partial deletion of the V2 loop derived from subtype B SF162 and subtype C TV1 were compared. The magnitude of LF17 binding to subtype C trimer was lower than to subtype B trimer, either in the presence or absence of CD4. However, the fold increase in binding of LF17 in presence of CD4 was similar for both subtypes, indicating similar structural rearrangements. Subtype C trimer had many biophysical, biochemical, and immunological characteristics similar to subtype B trimer, except for a difference in the three binding sites for CD4, which showed

B Cell

cooperativity of CD4 binding in subtype C but not in subtype B. Srivastava *et al.* [2008] (**binding affinity**, **subtype comparisons**)

- LF17: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. LF17 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 1021
MAb ID M2
HXB2 Location Env
Author Location
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Species (Isotype)
Ab Type gp120 V4
References Ren *et al.* 2005
Keywords antibody binding site definition and exposure, neutralization

- M2: This antibody is specific for a peptide flag inserted into the V4 loop of YU-2, a neutralization resistant variant with a short V4 loop. IgG1b12 and 2F5 could neutralize both the WT YU-2 and the modified variant. The high diversity of V4 suggests it does not play a direct role in receptor binding or viral entry, yet M2, specific for the peptide insert tag, can neutralize the modified virus, demonstrating that neutralizing activity doesn't have to block funtionality of the virus. Ren *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**)

No. 1022
MAb ID M25
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: purified HIV-1
Species (Isotype) mouse (IgGκ)
References Watkins *et al.* 1996; di Marzo Veronese *et al.* 1985

- M25: heavy and light chains cloned and sequenced – binding requires heavy and light chain in combination, in contrast to M77. Watkins *et al.* [1996]

No. 1023
MAb ID MAG 6B
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse
Research Contact C. Y. Kang, IDEC Inc
References Kang *et al.* 1994

- MAG 6B: Amino acid substitutions that reduce binding 10 fold: 256 S/Y, 257 T/R or G or A, 262 N/T, 368 D/R or T, 370 E/R or Q, 381 E/P, 384 Y/E, 421 K/L, 475 M/S, 477 D/V. Kang *et al.* [1994]

No. 1024
MAb ID MO28
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing no
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgM)
References Ohlin *et al.* 1989

- MO28: This antibody was raised by *in vitro* stimulation with a recombinant Env penv9 – the discontinuous epitope involves hydrophobic regions 632-646, 677-681 and 687-691, proximal to and spanning the transmembrane region – this specificity is unusual in HIV-1 positive sera. Ohlin *et al.* [1989]

No. 1025
MAb ID MO30
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing no
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgM)
References Ohlin *et al.* 1989

- MO30: This antibody was raised by *in vitro* stimulation with a recombinant Env penv9 – the discontinuous epitope involves hydrophobic regions 632-646, 677-681 and 687-691, proximal to and spanning the transmembrane region – this specificity is unusual in HIV-1 positive sera. Ohlin *et al.* [1989]

No. 1026
MAb ID MO43
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing no
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgM)
References Ohlin *et al.* 1989

- MO43: This antibody was raised by *in vitro* stimulation with a recombinant Env penv9 – the discontinuous epitope of MO43 involves hydrophobic regions 632-646, 677-681 and 687-691, proximal to and spanning the transmembrane region – this specificity is unusual in HIV-1 positive sera. Ohlin *et al.* [1989]

No. 1027
MAb ID Md1
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing

B Cell

Immunogen
Species (Isotype)
Research Contact Myers R.
References Vincent *et al.* 2008
Keywords antibody binding site definition and exposure

- Md1: Md1 reacted with maltose-binding proteins MBP30 and MBP32, containing both HR1 and HR2 domains of gp41, but did not react with MBP37 and MBP44, containing only the HR2 domain, nor with MBP-HR1, containing only the HR1 domain. In addition, Md1 bound to MBP44/N36 and MBP-HR1/C34 complexes reaching a plateau at a concentration of $\sim$ 1 µg/ml. In ELISA, Md1 reacted with the complex formed between MBP-HR1 and H44 (His-targeted protein) and C34, but failed to recognize the mixture of MBP-HR1 and T20, MBP3 and C34, and MBP3 and H44. In addition, Md1 recognized the peptide complex N36/C34 but not the peptides individually. Vincent *et al.* [2008] (**antibody binding site definition and exposure**)

No. 1028
MAb ID N03B11
HXB2 Location Env
Author Location
Epitope
Subtype C
Neutralizing
Immunogen vaccine
Vector/Type: HIV-1 immunogen *Strain:* C clade 97CN54 *HIV component:* gp140 *Adjuvant:* CpG immunostimulatory sequence (ISS)
Species (Isotype) humanized mouse (IgM)
References Sheppard *et al.* 2007b
Keywords antibody binding site definition and exposure, antibody generation, binding affinity, kinetics, neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- N03B11: This novel Env-specific IgM Ab was isolated from hybridoma derived from splenocytes from humanized mice immunized with a clade C Env vaccine. N03B11 was shown to bind to Env of two geographically distant clade C isolates but not to Env from other clades. It was shown to bind conformational epitope within the immunodominant region of gp41 ectodomain. This Ab showed no effect on infectivity. Sheppard *et al.* [2007b] (**antibody binding site definition and exposure**, **antibody generation**, **neutralization**, **variant cross-recognition or cross-neutralization**, **kinetics**, **binding affinity**, **subtype comparisons**)

No. 1029
MAb ID N2
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp41 NHR (N-heptad repeat), gp41six-helix bundle, gp41 five-helix bundle (one CHR peptide of six helix bundle is missing)
References Nelson *et al.* 2008
Keywords antibody generation, antibody sequence variable domain, binding affinity, neutralization

- N2: Fab N2 was derived from a human Fab phage display library prepared using the bone marrow RNA extracted from an HIV-1 positive individual. The library was screened with N35ccg-N13 peptide, which is a soluble homotrimer corresponding to the HIV-1 gp41 NHR region. N2 bound to N35ccg-N13 and to recombinant r-gp41 (HXB2). N2 did not neutralize HXB2. As other human-derived Abs in this study, N2 has a long CDR H3 (19 residues), and it was shown to bind to Envs used in typical epitope binding assays, unlike the neutralizing Abs in this study. While N2 had no observable reactivity with a peptide corresponding to the C-heptad repeat of gp41 (C34), low nanomolar concentrations of C34 were sufficient to induce recognition of IZN36 (another mimetic peptide) by N2. The neutralizing Abs in this study were, however, able to recognize IZN36 without C34. Nelson *et al.* [2008] (**antibody generation**, **neutralization**, **binding affinity**, **antibody sequence variable domain**)

No. 1030
MAb ID N2-4
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Research Contact Evan Hersh and Yoh-Ichi Matsumoto
References Robinson *et al.* 1990b

- N2-4: NIH AIDS Research and Reference Reagent Program: 528.
- N2-4: No enhancing activity for HIV-1 IIIB. Robinson *et al.* [1990b]

No. 1031
MAb ID N3C5
HXB2 Location Env
Author Location
Epitope
Subtype C
Neutralizing
Immunogen vaccine
Vector/Type: HIV-1 immunogen *Strain:* C clade 97CN54 *HIV component:* gp140 *Adjuvant:* CpG immunostimulatory sequence (ISS)
Species (Isotype) humanized mouse (IgM)
References Sheppard *et al.* 2007b
Keywords antibody binding site definition and exposure, antibody generation, binding affinity, kinetics, neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

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- N3C5: This novel Env-specific IgM Ab was isolated from hybridoma derived from splenocytes from humanized mice immunized with a clade C Env vaccine. N3C5 was shown to bind to both homologous gp140 and heterologous gp140 from clades C and A with high affinity, but not to clade B. It was shown to bind conformational epitope within the immunodominant region of gp41 ectodomain. This Ab weakly neutralized the autologous isolate. Sheppard *et al.* [2007b] (**antibody binding site definition and exposure**, **antibody generation**, **neutralization**, **variant cross-recognition or cross-neutralization**, **kinetics**, **binding affinity**, **subtype comparisons**)

No. 1032
MAb ID N70-2.3a
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
Research Contact James Robinson, Tulane University, LA
References Takeda *et al.* 1992; Robinson *et al.* 1990a

- N70-2.3a: Fc receptor mediated enhancement of HIV-1 infection – binds a conformational site in the carboxyl half of gp120, distinct from 1.5e. Takeda *et al.* [1992]
- N70-2.3a: Broad reactivity. Robinson *et al.* [1990a]

No. 1033
MAb ID P43110
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Advanced Biosciences (Kensington, MD)
References VanCott *et al.* 1995; di Marzo Veronese *et al.* 1992

- P43110: Does not recognized denatured form of the gp120 protein. VanCott *et al.* [1995]

No. 1034
MAb ID P5-3
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Research Contact Evan Hersh and Yoh-Ichi Matsumoto
References Pincus *et al.* 1991; Robinson *et al.* 1990b

- P5-3: NIH AIDS Research and Reference Reagent Program: 378.
- P5-3: Poor immunotoxin activity when coupled to RAC – isotype specified as: IgG3lambda. Pincus *et al.* [1991]
- P5-3: No enhancing activity for HIV-1 IIIB. Robinson *et al.* [1990b]

No. 1035
MAb ID PA-1 (PA1)
HXB2 Location Env
Author Location gp120 (V3)
Epitope
Neutralizing No
Immunogen
Species (Isotype) mouse
Ab Type gp120 V3
Research Contact Dr, William Olson, Progenics Pharmaceuticals
References Dey *et al.* 2008; Crooks *et al.* 2007; Beddows *et al.* 2007; Dey *et al.* 2007a; Moore *et al.* 2006; Beddows *et al.* 2005a
Keywords antibody binding site definition and exposure, binding affinity, neutralization, vaccine antigen design

- PA1: Five amino acids in the gp41 N-terminal region that promote gp140 trimerization (I535, Q543, S553, K567 and R588) were considered. Their influence on the function and antigenic properties of JR-FL Env expressed on the surfaces of pseudoviruses and Env-transfected cells was studied. Various non-neutralizing antibodies bind less strongly to the Env mutant, but neutralizing antibody binding is unaffected. PA1 captured significantly fewer mutant pseudovirions than wild type, and PA1 failed to inhibit infection by either pseudovirus. Dey *et al.* [2008] (**binding affinity**)
- PA1: Sera from rabbits immunized with either monomeric gp120, trimeric cleavage-defective gp140 or disulfide-stabilized soluble trimeric gp140 were incubated with bead-immobilized gp120 and cyclic V3 previously shown to be able to deplete this Ab from test serum. The neutralizing activity of the sera was only slightly reduced, indicating that only a minor fraction of Abs in the sera was directed towards the V3 region. Beddows *et al.* [2007] (**neutralization**, **vaccine antigen design**)
- PA1: PA1 was used for probing in Western blot and SDS-PAGE assays of VLP particles containing disulfide-shackled functional Env trimers (SOS-VLPs). Crooks *et al.* [2007]
- PA-1: SOSIP Env proteins are modified by the introduction of a disulfide bond between gp120 and gp41 (SOS), and an I559P (IP) substitution in gp41, and form trimers. The KNH1144 subtype A virus formed more stable trimers than did the prototype subtype B SOSIP Env, JRFL. The stability of gp140 trimers was increased for JR-FL and Ba-L SOSIP proteins by substituting the five amino acid residues in the N-terminal region of gp41 with corresponding residues from KNH1144 virus. b12, 2G12, 2F5, 4E10 and CD4-IgG2 all bound similarly to the WT and to the stabilized JRFL SOSIP timers, suggesting that the trimer-stabilizing substitutions do not impair the overall antigenic structure of gp140 trimers. 17b binding was induced similarly by CD4 for the WT and stabilized forms. Non-neutralizing MAbs PA-1 (V3) and b6 (CD4BS) bound less efficiently to the stabilized trimer. Dey *et al.* [2007a] (**vaccine antigen design**)
- PA1: Western blots were probed with PA1 and B12 to analyze Envs derived from VLPs. Moore *et al.* [2006]
- PA1: This Ab was used in an Ab depletion assay to test whether neutralizing Abs in sera from rabbits immunized with a soluble, cleaved trimeric gp140 (SOSIP gp140) recognized

B Cell

gp120 or its V3 region. Unlike gp120 beads, V3-peptide beads did not remove any of the PA1 from the test-sera, indicating that only a minor fraction of the total anti-gp120 Abs were directed to V3. Beddows *et al.* [2005a] (**antibody binding site definition and exposure**)

No. 1036
MAb ID R21
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* mimotopes *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (Isotype) rabbit
Ab Type gp41 NHR (N-heptad repeat), gp41six-helix bundle, gp41 five-helix bundle (one CHR peptide of six helix bundle is missing)
Research Contact Michael B. Zwick, The Acripps Research Institute, La Jolla, CA, USA, zwick@scripps.edu
References Nelson *et al.* 2008
Keywords antibody generation, antibody sequence variable domain, neutralization

- R21: R21 was derived from a rabbit Fab phage display library prepared using the bone marrow RNA extracted from N35ccg-N13 immunized rabbits. The library was screened with N35ccg-N13 peptide, which is a soluble homotrimer corresponding to the HIV-1 gp41 NHR region. The CDR H3 region of 1R21 was 14 residues in length. R21 did not neutralize HIV-1 HXB2. Unlike neutralizing Abs in this study, whose heavy chain variable regions were encoded by a rarely expressed VH gene, the non-neutralizing Ab R21 was encoded by the usually expressed VH1a2. While R21 had no observable reactivity with a peptide corresponding to the C-heptad repeat of gp41 (C34), low nanomolar concentrations of C34 were sufficient to induce recognition of IZN36 (another mimetic peptide) by R21. The neutralizing Abs in this study were, however, able to recognize IZN36 without C34. Nelson *et al.* [2008] (**antibody generation**, **neutralization**, **antibody sequence variable domain**)

No. 1037
MAb ID R3
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* mimotopes *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (Isotype) rabbit
Ab Type gp41 NHR (N-heptad repeat), gp41 five-helix bundle (one CHR peptide of six helix bundle is missing)
References Nelson *et al.* 2008
Keywords antibody generation, antibody sequence variable domain

- R3: R3 was derived from a phage libraries from pooled output phages derived from rabbit and human Fab phage display libraries, prepared using the bone marrow RNA extracted from N35ccg-N13 immunized rabbits and from HIV-1 infected individuals, followed by four rounds against N35ccg-N1 in the presence of excess of recombinant r-gp41. N35ccg-N13 peptide is a soluble homotrimer corresponding to the HIV-1 gp41 NHR region. R3 CDR H3 sequence had significant sequence homology to mAb 8K8, but their light chains were unrelated. R3 was found to have similar binding properties as 8K8, and was found to neutralize HXB2 and a few primary isolates with potency similar to 8K8. Unlike non-neutralizing Abs in this study, whose heavy chain variable regions were encoded by usually expressed VH1a1 and VH1a2 genes, R3 heavy chain variable region was encoded by a rarely expressed VH gene. Nelson *et al.* [2008] (**antibody generation**, **antibody sequence variable domain**)

No. 1038
MAb ID R7
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* mimotopes *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (Isotype) rabbit
Ab Type gp41 NHR (N-heptad repeat), gp41 five-helix bundle (one CHR peptide of six helix bundle is missing)
References Nelson *et al.* 2008
Keywords antibody generation, antibody sequence variable domain

- R7: R7 was derived from a phage libraries from pooled output phages derived from rabbit and human Fab phage display libraries, prepared using the bone marrow RNA extracted from N35ccg-N13 immunized rabbits and from HIV-1 infected individuals, followed by four rounds against N35ccg-N1 in the presence of excess of recombinant r-gp41. N35ccg-N13 peptide is a soluble homotrimer corresponding to the HIV-1 gp41 NHR region. R7 CDR H3 sequence had significant sequence homology to mAb 8K8, but their light chains were unrelated. R7 was found to have similar binding properties as 8K8, and was found to neutralize HXB2 and a few primary isolates with potency similar to 8K8. Unlike non-neutralizing Abs in this study, whose heavy chain variable regions were encoded by usually expressed VH1a1 and VH1a2 genes, R7 heavy chain variable region was encoded by a rarely expressed VH gene. Nelson *et al.* [2008] (**antibody generation**, **antibody sequence variable domain**)

No. 1039
MAb ID Sb1
HXB2 Location Env
Author Location gp120 (JR-FL)
Epitope

B Cell

Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4i
References Lin & Nara 2007; Bowley *et al.* 2007; Choe *et al.* 2003
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity, co-receptor, review

- Sb1: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. Sb1 was identified using both methods, and is a CD4i antibody. Bowley *et al.* [2007] (**antibody binding site definition and exposure**, **antibody generation**, **binding affinity**, **antibody sequence variable domain**, **assay standardization/improvement**)
- Sb1: Tyrosine sulfation of Sb1 and other Abs, and its effect on Ab binding and neutralization, is reviewed. Lin & Nara [2007] (**review**)
- Sb1: Sb1 was obtained from an HIV-1 infected individual with a potent and broadly neutralizing activity of his serum. It was shown that scFv Sb1 was sulfate-modified and it is implied that the sulfates are localized exclusively within the heavy chain CDR3 region of this MAb. Binding efficiency of scFv Sb1 to ADA gp120 was doubled in the presence of CD4, showing that this MAb is CD4-induced. Association of scFv Sb1 with ADA gp120-CD4-Ig complex was partially inhibited by a sulfated peptide with a sequence corresponding to the CCR5 amino terminus, indicating that Sb1 binds a CD4-enhanced epitope overlapping the binding domain of CCR5 amino terminus. scFv Sb1 was shown to efficiently bind to gp120 of three R5 isolates but not to the HXBc2 X4 isolate. Choe *et al.* [2003] (**antibody binding site definition and exposure**, **co-receptor**)

No. 1040
MAb ID T15G1 (TG15)
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing no
Immunogen
Species (Isotype)
References Lee *et al.* 2006; Binley *et al.* 1999
Keywords antibody binding site definition and exposure, dendritic cells, neutralization, subtype comparisons

- TG15: Unlike the nonneutralizing TG15 MAb, the membrane bound scFv derived from this MAb was shown to have broad neutralizing activity to subtype A, C and D HIV-1 primary isolates. In addition to inhibition of cell-free viruses, the cell surface expressed scFv significantly blocked transfer of captured HIV-1 from DCs to target CD4 T-cells. Lee *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**, **dendritic cells**, **subtype comparisons**)
- T15G1: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999]

No. 1041
MAb ID T20
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Dey *et al.* 2008; Sugiura *et al.* 1999; Otteken *et al.* 1996; Earl *et al.* 1994
Keywords binding affinity

- T20: Five amino acids in the gp41 N-terminal region that promote gp140 trimerization (I535, Q543, S553, K567 and R588) were considered. Their influence on the function and antigenic properties of JR-FL Env expressed on the surfaces of pseudoviruses and Env-transfected cells was studied. Various non-neutralizing antibodies bind less strongly to the Env mutant, but neutralizing antibody binding is unaffected. The IC50 for T20 against the wild type was 2-fold greater than against the mutant. Dey *et al.* [2008] (**binding affinity**)
- T20: A comparison of 25 gp120 specific, conformation dependent MAbs was done – T20 is part of a group of MAbs labeled AII – all AII MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, and could only partially blocked CD4 binding. Sugiura *et al.* [1999]
- T20: Pulse label experiments of 4 MAbs (D20, D27, T20, and T22) binding to noncleavable gp140 revealed that these anti-CD4BS MAbs bound with a delay, and that the epitope formed with a t 1/2 of about 10 minutes. Otteken *et al.* [1996]
- T20: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1042
MAb ID T27

B Cell

HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1994

- T27: A comparison of 25 gp120 specific, conformation dependent MAbs was done – T27 is part of a group of MAbs labeled AII – all AII MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, and could only partially blocked CD4 binding. Sugiura *et al.* [1999]
- T27: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1043
MAb ID T3
HXB2 Location Env
Author Location gp41 (HXB2)
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: tetrameric Env *HIV component:* Env
Species (Isotype) mouse (IgG)
References Zhang *et al.* 2008; Yang *et al.* 2000; Zwick *et al.* 2001b; Earl *et al.* 1997; Earl *et al.* 1994
Keywords binding affinity

- T3: T3 competed with the newly defined neutralizing mAb m44 for binding to gp41. T3 bound strongly to both 5HB and 6HB regions. Zhang *et al.* [2008] (**binding affinity**)
- T3: T3 partially competes with MAb Z13, but not MAb 4E10, both of which bind to gp41 proximally to the 2F5 epitope and have a broad neutralizing potential. Zwick *et al.* [2001b]
- T3: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) – gp41 MAbs T4, D12, T3, and D50 bound less efficiently to gp140-GNC4 than did pooled sera, but T4 and D12 recognized the gp140-GNC4 timer equivalently to gp140(-), and T3 and D50 recognized the trimer at greater levels than gp140(-). Yang *et al.* [2000]
- T3: Partially conformation dependent – doesn't bind to short peptides, but does bind to the region spanning 641-683 – binding can be blocked by MAbs D43, D38 and D45 – MAbs in this competition group reacted with 9/10 HIV-1 strains, not binding to JRFL. Earl *et al.* [1997]
- T3: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1044
MAb ID T30
HXB2 Location Env
Author Location gp41 (580–640)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: tetrameric Env *HIV component:* Env
Species (Isotype) mouse
Research Contact C. Broder
References Zhang *et al.* 2008; Billington *et al.* 2007; Ohagen *et al.* 2003; Earl *et al.* 1997; Earl *et al.* 1994
Keywords antibody binding site definition and exposure, antibody generation, brain/CSF, escape

- T30: T30 did not compete with the newly defined neutralizing mAb m44 for binding to gp41. Zhang *et al.* [2008]
- T30: Binds to ILAVERY...NNYTS, and binding involves the N-linked carbohydrate at N616. The T30 antibody was used to partially purify a D subtype rgp140 that forms a stable trimer and may be suitable for structural studies. The partially purifed protein was used to immunize mice, and one of the MAbs, 2E2, was used to then further purify the protein. Billington *et al.* [2007]
- T30: Env genes derived from uncultured brain biopsy samples from four HIV-1 infected patients with late-stage AIDS were compared to env genes from PBMC samples. Brain isolates did not differ in the total number or positions of N-glycosylation sites, patterns of coreceptor usage, or ability to be recognized by gp160 and gp41 MAbs. T30 recognized most variants (10/13) gp41 by WB, and all of the gp160s. Ohagen *et al.* [2003] (**brain/CSF**, **escape**)
- T30: Binds in the region 580 to 640, but does not bind to peptides spanning this region – binding depends on N-linked glycosylation of Asn 616 – no other antibody tested inhibited binding, but binding could be inhibited by sera from HIV+ individuals. Earl *et al.* [1997] (**antibody binding site definition and exposure**)
- T30: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994] (**antibody generation**)

No. 1045
MAb ID T33
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype)
Research Contact Patricia Earl
References Wright *et al.* 2008
Keywords isotype switch, mucosal immunity

- T33: Several IgG MAbs were isotype switched to IgA and tested for their abilities to generate immune complexes with HIV-1 and be excreted from polarized epithelial cells from the basolateral to the apical surface via polymeric Ig receptor (pIgR) binding. Unlike IgA D10, D47, D19, and D25, IgA T33 was not able to excrete HIV. T33 bound weakly to HIV but the produced immune complex failed to associate with pIgR. These results show that some IgA Abs have potential to excrete HIV from mucosal lamina propria thus decreasing the viral burden and access to susceptible cells. Wright *et al.* [2008] (**isotype switch**, **mucosal immunity**)

No. 1046
MAb ID T4
HXB2 Location Env
Author Location gp41 (IIIB)
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
References Srivastava *et al.* 2002; Yang *et al.* 2000; Stamatatos *et al.* 2000; Binley *et al.* 1999; Earl *et al.* 1997; Otteken *et al.* 1996; Weissenhorn *et al.* 1996; Richardson *et al.* 1996; Broder *et al.* 1994; Earl *et al.* 1994
Keywords antibody binding site definition and exposure, antibody generation, antibody interactions, vaccine antigen design

- T4: Oligomeric gp140 (o-gp140) derived from R5 primary isolate US4 was characterized for use as a vaccine reagent – antigen capture ELISA was used to compare the antigenicity of gp120 and o-gp140 using a panel of well characterized MAbs – T4 recognized o-gp140. Srivastava *et al.* [2002] (**antibody binding site definition and exposure**)
- T4: Soluble gp140 derived from SF162, a neutralization-resistant primary isolate, and SF162AV2 a neutralization-susceptible isolate with 30 amino acids deleted from the V2 loop, were generated with or without the gp120-gp41 cleavage site intact – all forms are recognized by oligomer-specific MAb T4 and show enhanced binding of CD4i MAb 17b when sCD4 is bound – the fused forms are less efficiently recognized than the cleaved forms by polyclonal neutralizing sera from HIV-infected patients – the V3 loop is more exposed on the fused form. Stamatatos *et al.* [2000] (**vaccine antigen design**)
- T4: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) – gp41 MAbs T4, D12, T3, and D50 bound less efficiently to gp140-GNC4 than did pooled sera, but T4 and D12 recognized the gp140-GNC4 timer equivalently to gp140(-), and T3 and D50 recognized the trimer at greater levels than gp140(-). Yang *et al.* [2000] (**vaccine antigen design**)
- T4: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999] (**vaccine antigen design**)
- T4: This antibody, along with 7 others (M10, D41, D54, T6, T9, T10 and T35), can block the linear murine MAb D61, and the human MAb 246-D, which both bind to the immunodominant region near the two Cys in gp41 – most of these antibodies are oligomer dependent – all of the MAbs are reactive with ten different HIV-1 strains – members of this competition group are blocked by sera from HIV-1 + individuals. Earl *et al.* [1997] (**antibody interactions**)
- T4: MAbs T4 and T6 bind only to oligomer, and pulse chase experiments indicate that the epitope is very slow to form, requiring one to two hours. Otteken *et al.* [1996] (**antibody binding site definition and exposure**)
- T4: Does not bind to soluble monomeric gp41(21-166) that lacks the fusion peptide and membrane anchor, only to the oligomer gp140, as does T6. Weissenhorn *et al.* [1996] (**antibody binding site definition and exposure**)
- T4: one of five MAbs (T4, T6, T9, T10 and T35) in a competition group that bind to a conformation-dependent epitope in gp41 and is oligomer specific – neutralizes IIIB and SF2. Broder *et al.* [1994] (**antibody binding site definition and exposure**)
- T4: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994] (**antibody generation**)

No. 1047
MAb ID T8
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype) mouse
Ab Type gp120 C1
Research Contact P.Earl, NIH
References Wang *et al.* 2007a; Gao *et al.* 2005a
Keywords antibody binding site definition and exposure, binding affinity, vaccine antigen design

- T8: Chimeric VLPs, containing chimeric Con-S ΔCFI Env proteins with heterologous signal peptide (SP), transmembrane (TM), and cytoplasmic tail (CT) sequences, were all shown to bind to T8, indicating correct Env glycoprotein conformation and conserved epitope exposure on the VLPs. Wang *et al.* [2007a] (**antibody binding site definition and exposure**, **binding affinity**)
- T8: Monomeric gp120 and trimeric gp140CF proteins synthesized from an artificial group M consensus Env gene (CON6) bound with high affinity to T8, indicating correct exposure of the T8 epitope. T8 could not induce conformational changes of gp120 and gp140CF required for binding of MAb 17b. Gao *et al.* [2005a] (**antibody binding site definition and exposure**, **vaccine antigen design**, **binding affinity**)

No. 1048
MAb ID V3-G2-10

B Cell

HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade NL43 *HIV component:* V3
Species (Isotype) mouse
Ab Type gp120 V3
References Sakaguchi *et al.* 2005
Keywords antibody generation, binding affinity, neutralization

- V3-G2-10: This exceptionally high affinity mAb was generated by immunization of transgenic mice over-expressing germinal center-associated DNA primase (GANP). The Ab showed neutralizing activity. Sakaguchi *et al.* [2005] (**antibody generation**, **neutralization**, **binding affinity**)

No. 1049
MAb ID V3-G2-25
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade NL43 *HIV component:* V3
Species (Isotype) mouse
Ab Type gp120 V3
References Sakaguchi *et al.* 2005
Keywords antibody generation, binding affinity, neutralization

- V3-G2-25: This exceptionally high affinity mAb was generated by immunization of transgenic mice over-expressing germinal center-associated DNA primase (GANP). The Ab showed neutralizing activity. Sakaguchi *et al.* [2005] (**antibody generation**, **neutralization**, **binding affinity**)

No. 1050
MAb ID V3-W1-2
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade NL43 *HIV component:* V3
Species (Isotype) mouse
Ab Type gp120 V3
References Sakaguchi *et al.* 2005
Keywords antibody generation, binding affinity, neutralization

- V3-W1-2: This exceptionally high affinity mAb was generated by immunization of transgenic mice over-expressing germinal center-associated DNA primase (GANP). The Ab showed neutralizing activity. Sakaguchi *et al.* [2005] (**antibody generation**, **neutralization**, **binding affinity**)

No. 1051
MAb ID V3-W1-8
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade NL43 *HIV component:* V3
Species (Isotype) mouse
Ab Type gp120 V3
References Sakaguchi *et al.* 2005
Keywords antibody generation, binding affinity, neutralization

- V3-W1-8: This exceptionally high affinity mAb was generated by immunization of transgenic mice over-expressing germinal center-associated DNA primase (GANP). The Ab showed neutralizing activity. Sakaguchi *et al.* [2005] (**antibody generation**, **neutralization**, **binding affinity**)

No. 1052
MAb ID WR102
HXB2 Location Env
Author Location gp41
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: liposome, protein *Strain:* B clade IIIB, B clade MN *HIV component:* gp140 *Adjuvant:* lipid A
Species (Isotype) mouse (IgM)
References Karasavvas *et al.* 2008
Keywords kinetics, vaccine antigen design

- WR102: WR102 was generated by immunization of mice with liposomes containing both Chol and gp140. WR102 exhibited dual specificity where it bound to both pure Chol and to pure gp140. WR102 bound to gp41 but not to gp120. Chol and gp140 each independently contributed with binding energy to WR102. The results indicate that Abs with both lipid and protein specificity can be induced by active immunization. Karasavvas *et al.* [2008] (**vaccine antigen design**, **kinetics**)

No. 1053
MAb ID WR204
HXB2 Location Env
Author Location gp41
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide in liposome *Strain:* B clade IIIB, B clade MN *HIV component:* mimotopes *Adjuvant:* lipid A
Species (Isotype) mouse (IgMκ)
References Karasavvas *et al.* 2008
Keywords vaccine antigen design

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- WR204: WR204 was generated by immunization of mice with liposomes containing both GalCer and a mper48 peptide. WR204 exhibited dual specificity where it bound to both pure GalCerl and to pure peptide. WR204 exhibited broad lipid binding, where it also bound to Chol, DMPC, DMPG and gp41, but it did not bind to gp120 or PA. The results indicate that Abs with both lipid and protein specificity can be induced by active immunization. Karasavvas *et al.* [2008] (**vaccine antigen design**)

No. 1054
MAb ID m14
HXB2 Location Env
Author Location Env
Epitope
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
Research Contact D. S. Dimitrov
References Zhang *et al.* 2008; Chen *et al.* 2008b; Kramer *et al.* 2007; Zhang *et al.* 2006a; Zhou *et al.* 2007; Zhang & Dimitrov 2007; Choudhry *et al.* 2007; Mc Cann *et al.* 2005
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, binding affinity, neutralization, review, structure, variant cross-recognition or cross-neutralization

- m14: A newly identified domain Ab m36 did not compete for binding to gp120Bal-CD4 with m14, however, it competed with m14 for binding to gp140GXC-44 in the absence of CD4, indicating that m36 epitope is localized close to the CD4 binding site. Chen *et al.* [2008b] (**binding affinity**)
- m14: m14 did not compete with the newly detected mAb m44 for binding to gp41. Zhang *et al.* [2008]
- m14: m18 and m14 have sequences and binding activity similar to two other broadly neturalizing MAbs, m22 and m24, that were identified by screening a phage-displayed antibody library with a gp140 from the donor R2, who had high levels of broadly neutralizing antibodies. All 4 MAbs competed with IgG1b12 and sCD4. Choudhry *et al.* [2007] (**antibody generation**, **neutralization**, **antibody sequence variable domain**)
- m14: This review summarizes m14 Ab epitope, properties and neutralization activity. Kramer *et al.* [2007] (**review**)
- m14: Novel approaches based on sequential (SAP) and competitive (CAP) antigen panning methodiologies, and use of antigens with increased exposure of conserved epitopes, for enhanced identification of broadly cross-reactive neutralizing Abs are reviewed. Abs identified by these methods are described. Zhang & Dimitrov [2007] (**review**)
- m14: This Ab was used to determine the degree to which fixation of gp120 in its CD4-bound conformation restricts antigenic recognition. m14 was not able to bind well to the stabilized gp120. Zhou *et al.* [2007] (**binding affinity**)
- m14: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**, **review**, **structure**)

No. 1055
MAb ID m16 (scFv m16)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing P
Immunogen in vitro stimulation or selection
Species (Isotype) human
Ab Type gp120 CD4i
References Chen *et al.* 2008b; Zhang & Dimitrov 2007; Kramer *et al.* 2007; Choudhry *et al.* 2006; Mc Cann *et al.* 2005; Zhang *et al.* 2004b
Keywords antibody binding site definition and exposure, autologous responses, binding affinity, co-receptor, enhancing activity, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- m16: A newly identified domain Ab m36 competed for binding to gp120Bal-CD4 with m16, indicating m36 is a CD4i Ab. Chen *et al.* [2008b] (**binding affinity**)
- m16: This review summarizes m16 Ab epitope, properties and neutralization activity. Kramer *et al.* [2007] (**review**)
- m16: Novel approaches based on sequential (SAP) and competitive (CAP) antigen panning methodiologies, and use of antigens with increased exposure of conserved epitopes, for enhanced identification of broadly cross-reactive neutralizing Abs are reviewed. Abs identified by these methods are described. Zhang & Dimitrov [2007]
- m16: Neutralization of HIV-1 primary isolates of clade B by different formats of m16 was determined in cells expressing high or low surface concentrations of CD4 and CCR5 receptors. CD4 cell surface concentration had no effect on the inhibitory activity of this Ab while the CCR5 surface concentration had a significant effect decreasing the 50% inhibitory concentration of m16 in cell lines with low CCR5. Choudhry *et al.* [2006] (**co-receptor**, **neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- m16: 2F5: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **review**)

B Cell

- m16: This antibody was selected by sequential antigen panning (SAP) of a human phage display library against recombinant soluble HIV-1 envelope glycoproteins (Envs) (gp140s) and their complexes with soluble CD4. m16 inhibited cell fusion mediated by the Envs of 9 HIV-1 isolates from clades A, B, E and G with potency comparable to that Fab X5. Zhang *et al.* [2004b] (**autologous responses**, **enhancing activity**, **neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1056
MAb ID m18 (M18, FAb M18)
HXB2 Location Env
Author Location Env
Epitope
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
Research Contact D. S. Dimitrov
References Prabakaran *et al.* 2006; Zhou *et al.* 2007; Zhang & Dimitrov 2007; Lin & Nara 2007; Kramer *et al.* 2007; Choudhry *et al.* 2007; McCaffrey *et al.* 2004; Zhang *et al.* 2003
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, binding affinity, mimics, neutralization, review, structure, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- m18: m18 and m14 have sequences and binding activity similar to two other broadly neturalizing MAbs, m22 and m24, that were identified by screening a phage-displayed antibody library with a gp140 from the donor R2, who had high levels of broadly neutralizing antibodies. All 4 MAbs competed with IgG1b12 and sCD4. Choudhry *et al.* [2007] (**antibody generation**, **neutralization**, **antibody sequence variable domain**)
- m18: This review summarizes m18 Ab epitope, properties and neutralization activity. Kramer *et al.* [2007] (**review**)
- m18: m18 structure and binding are reviewed in detail. Lin & Nara [2007] (**review**, **structure**)
- m18: Novel approaches based on sequential (SAP) and competitive (CAP) antigen panning methodiologies, and use of antigens with increased exposure of conserved epitopes, for enhanced identification of broadly cross-reactive neutralizing Abs are reviewed. Abs identified by these methods are described. Zhang & Dimitrov [2007] (**review**)
- m18: This Ab was used to determine the degree to which fixation of gp120 in its CD4-bound conformation restricts antigenic recognition. m18 was not able to bind well to the stabilized gp120. Zhou *et al.* [2007] (**antibody binding site definition and exposure**, **binding affinity**)
- m18: The high resolution crystal structure of Fab m18 was determined and compared to the structure of b12 and F105. Unique conformations of H2 and H3 regions were observed. H2 is highly bulged while H3 shows striking similarity to the CD4 domain D1 that dominates binding of CD4 to gp120. Docking simulations of the m18-gp120 show significant resemblance of the interactions observed in the gp12-CD4 complex, suggesting that m18 mimics some structural features of CD4. Prabakaran *et al.* [2006] (**antibody binding site definition and exposure**, **mimics**, **structure**)
- m18: Called M18. Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The loss of the glycan within the V3 loop (GM299 V3) or adjacent to V3 in C2 (GM292 C2), left SF162 susceptible to neturalization by FAb M18, and the glycan mutants in C3 (GM329 C3), C4 (GM438 C4), or V5 (GM454 V5) became resistant to M18 neutralization. The M18 epitope is unknown. V3 glycans tended to sheild V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans sheilded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- m18: m18 was selected from a human Fab phage display library by a new method called sequential antigen panning (SAP), using a series of antigens to screen the library to pick broadly cross-reactive isolates. The epitope of m18 is independent of CD4 binding. The phage display library was constructed using the combined bone marrow of three long term non-progressors with potent NAb activity in their sera. m18 bound to gp140s from primary isolates from clades A-F with nM affinities. The ability to block cell mediated fusion by m18 was compared to Fabs X5 and b12 for a clade A, CRF01 EA, G, and 6 clade B isolates, and the inhibitory activity of m18 was slightly lower but comparable to neutralizing Fabs b12 and X5. It also showed broad cross-neutralization; 11/15 pseudotyped Envs from primary isolates from clades A-F were inhibited in an IC50 assay at concentration less than or equal to 100 ug/ml; X5 was also tested and somewhat more potent, generally requiring lower concentrations and inhibiting 13/15 primary isolates. Zhang *et al.* [2003] (**antibody generation**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1057
MAb ID m22
HXB2 Location Env
Author Location Env
Epitope
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
Research Contact D. S. Dimitrov
References Zhang & Dimitrov 2007; Choudhry *et al.* 2007
Keywords antibody generation, antibody sequence variable domain, neutralization

- m22: m18 and m14 have sequences and binding activity similar to two other broadly neturalizing MAbs, m22 and m24, that were identified by screening a phage-displayed antibody library with a gp140 from the donor R2, who had high levels of broadly neutralizing antibodies. All 4 MAbs competed with IgG1b12 and sCD4. Choudhry *et al.* [2007] (**antibody generation**, **neutralization**, **antibody sequence variable domain**)

No. 1058
MAb ID m24
HXB2 Location Env
Author Location Env
Epitope
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
Research Contact D. S. Dimitrov
References Zhang & Dimitrov 2007; Choudhry *et al.* 2007
Keywords antibody generation, antibody sequence variable domain, neutralization, review

- m24: m18 and m14 have sequences and binding activity similar to two other broadly neturalizing MAbs, m22 and m24, that were identified by screening a phage-displayed antibody library with a gp140 from the donor R2, who had high levels of broadly neutralizing antibodies. All 4 MAbs competed with IgG1b12 and sCD4. Choudhry *et al.* [2007] (**antibody generation**, **neutralization**, **antibody sequence variable domain**)
- m24: Novel approaches based on sequential (SAP) and competitive (CAP) antigen panning methodiologies, and use of antigens with increased exposure of conserved epitopes, for enhanced identification of broadly cross-reactive neutralizing Abs are reviewed. Abs identified by these methods are described. Zhang & Dimitrov [2007] (**review**)

No. 1059
MAb ID m36
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human
Ab Type gp120 CD4i
Research Contact Dimiter S Dimitrov, National Institutes of Health, Fredrick, MD. dimitrov@ncifcrf.gov
References Chen *et al.* 2008b
Keywords antibody binding site definition and exposure, binding affinity, neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- m36: An HIV-1 neutralizing domain Ab (dAb), m36, was identified from a human antibody variable domain library by panning against Envs from different isolates. The VH m36 bound to gp120-CD4 complexes better than to gp120 alone, and competed with CD4i Abs, indicating its epitope is induced by CD4. m36 neutralized HIV-1 isolates from clades A, B and C with a potency twofold higher than that of the broadly-neutralizing MAb m9. m36 neutralized clade D isolate with lower potency than m9, and did not neutralize clade E HIV-1 isolate. Large-size fusion proteins of m36 exhibited diminished neutralizing activity, suggesting that m36 epitope is sterically restricted. Preincubation of the fusion proteins with sCD4 restored their neutralizing activity. Chen *et al.* [2008b] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)

No. 1060
MAb ID m43
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Zhang & Dimitrov 2007
Keywords review

- m43: Novel approaches based on sequential (SAP) and competitive (CAP) antigen panning methodiologies, and use of antigens with increased exposure of conserved epitopes, for enhanced identification of broadly cross-reactive neutralizing Abs are reviewed. Abs identified by these methods are described. Zhang & Dimitrov [2007] (**review**)

No. 1061
MAb ID m44
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type C-HR
References Zhang *et al.* 2008
Keywords antibody binding site definition and exposure, antibody generation, neutralization, variant cross-recognition or cross-neutralization

- m44: The highly neutralizing Ab m44 was isolated by phage library panning, derived from three HIV-1 infected long term nonprogressors with sera with broadest and most potent neutralization. The phage library was panned with uncleaved Env ectodomains and the derived m44 mAb was shown to neutralize primary isolates from different clades with potency significantly higher than that of 4E10 or Z13. m44 neutralized clade C SHIV more potently than 2F5 and b12. The neutralization potency of m44 was significantly higher in PBMC than in TZM-bl cell-line based assay. Site-directed alanine-scanning mutagenesis revealed that the epitope for m44 is conserved, conformational, and is located at the C-HR and a stretch of residues at the C-terminal portion of the loop. m44 did not bind to human self-antigens. Zhang *et al.* [2008] (**antibody binding site definition and exposure**, **antibody generation**, **neutralization**, **variant cross-recognition or cross-neutralization**)

No. 1062
MAb ID m46
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing P
Immunogen HIV-1 infection

B Cell

Species (Isotype) human
Research Contact D. S. Dimitrov
References Zhang *et al.* 2008; Zhang & Dimitrov 2007; Kramer *et al.* 2007; Choudhry *et al.* 2007
Keywords antibody generation, antibody sequence variable domain, assay standardization/improvement, neutralization, review, subtype comparisons

- m46: m46 did not compete with the newly detected mAb m44 for binding to gp41. A fusion protein of gp41 constructed for alanine-scanning mutagenesis bound to m46, indicating that its antigenic structure was intact. Zhang *et al.* [2008]
- m46: m46 was identified by screening a phage-displayed antibody library with a gp140 from the donor R2, who had high levels of broadly neutralizing antibodies. m46 binds to a conformational epitope on gp41 and did not compete with 2F5, 4E10 or Z13. It bound to a 5 helix bundle, but not to N-heptad repeat coil-coils or a 6-helix bundle. It is broadly neutralizing, to levels comparable to T20, when tested using PBMC with low CCR5 levels, but less potently when the neutralization assay was performed in a cell line with high CCR5 levels. Isolates from different clades had differing degrees of neutralization sensitivity. Choudhry *et al.* [2007] (**antibody generation**, **neutralization**, **subtype comparisons**, **antibody sequence variable domain**, **assay standardization/improvement**)
- m46: This review summarizes m46 Ab epitope, properties and neutralization activity. Kramer *et al.* [2007] (**review**)
- m46: Novel approaches based on sequential (SAP) and competitive (CAP) antigen panning methodiologies, and use of antigens with increased exposure of conserved epitopes, for enhanced identification of broadly cross-reactive neutralizing Abs are reviewed. Abs identified by these methods are described. Zhang & Dimitrov [2007] (**review**)

No. 1063
MAb ID m47
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Polonis *et al.* 2008; Zhang & Dimitrov 2007
Keywords assay standardization/improvement, neutralization, review

- m47: This minireview summarizes data on differences in neutralizing activities of MAbs and pooled human sera using a traditional primary cell neutralization assay and the more standardized TZM-bl reporter cell line assay. Also, suggestions are made on how to improve and standardize neutralization assays for comparable use in different laboratories. m47 neutralization was tested against a panel of 60 HIV-1 primary isolates (10 each from clades A-D, CRF01_AE and CRF02_AG) in the two assays. 16 viruses from the PBMC assay and only 1 virus from the TZM-assay were neutralized by this Ab. Thus, m47 showed better neutralization in the PBMC system. In total, however, the assay discordances were shown to be bi-directional and not attributable to assay sensitivity. Polonis *et al.* [2008] (**neutralization**, **review**, **assay standardization/improvement**)
- m47: Novel approaches based on sequential (SAP) and competitive (CAP) antigen panning methodiologies, and use of antigens with increased exposure of conserved epitopes, for enhanced identification of broadly cross-reactive neutralizing Abs are reviewed. Abs identified by these methods are described. Zhang & Dimitrov [2007] (**review**)

No. 1064
MAb ID m48
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
References Zhang *et al.* 2008; Kramer *et al.* 2007; Zhang *et al.* 2006a; Zhang & Dimitrov 2007
Keywords antibody binding site definition and exposure, antibody generation, binding affinity, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- m48: m48 did not compete with the newly detected mAb m44 for binding to gp41. A fusion protein of gp41 constructed for alanine-scanning mutagenesis bound to m48, indicating that its antigenic structure was intact. Zhang *et al.* [2008]
- m48: This review summarizes m48 Ab epitope, properties and neutralization activity. Kramer *et al.* [2007] (**review**)
- m48: Novel approaches based on sequential (SAP) and competitive (CAP) antigen panning methodiologies, and use of antigens with increased exposure of conserved epitopes, for enhanced identification of broadly cross-reactive neutralizing Abs are reviewed. Abs identified by these methods are described. Zhang & Dimitrov [2007] (**review**)
- m48: A novel gp-41 specific human monoclonal Ab, m48, was derived using competitive antigen panning (CAP). This Ab was derived from an immune library derived from long-term nonprogressors with high titers of broadly cross-reactive neutralizing Abs. m48 was shown to recognize a conformational epitope on gp-41 dependant on disulfide bonds. In PBMC assays, m48 was able to neutralize a panel of HIV-1 isoaltes from different clades more potently than other broadly cross-reactive neutralizing Abs. Zhang *et al.* [2006a] (**antibody binding site definition and exposure**, **antibody generation**, **neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)

No. 1065
MAb ID m6
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 CD4i
References Kramer *et al.* 2007
Keywords review

- m6: This review summarizes m6 Ab epitope, properties and neutralization activity. Kramer *et al.* [2007] (**review**)

B Cell

No. 1066
MAb ID m9 (scFv m9)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing P
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgG)
Ab Type gp120 adjacent to CD4BS
Research Contact Zhang2004
References Polonis *et al.* 2008; Chen *et al.* 2008b; Zhang & Dimitrov 2007; Kramer *et al.* 2007; Choudhry *et al.* 2006; Huang *et al.* 2005a; Zhang *et al.* 2004a
Keywords antibody generation, assay standardization/improvement, co-receptor, enhancing activity, neutralization, review, structure, subtype comparisons, variant cross-recognition or cross-neutralization

- m9: A newly identified domain Ab m36 exhibited twofold higher neutralization potency than m9 against HIV-1 isolates from clades A, B and C. m9 neutralized a clade D HIV-1 isolate more potently than m36. Chen *et al.* [2008b] (**neutralization**, **variant cross-recognition or cross-neutralization**)
- m9: This minireview summarizes data on differences in neutralizing activities of MAbs and pooled human sera using a traditional primary cell neutralization assay and the more standardized TZM-bl reporter cell line assay. Also, suggestions are made on how to improve and standardize neutralization assays for comparable use in different laboratories. m9 neutralization was tested against a panel of 60 HIV-1 primary isolates (10 each from clades A-D, CRF01_AE and CRF02_AG) in the two assays. 7 viruses from the PBMC assay and 13 viruses from the TZM-assay were not neutralized by this Ab. Thus, m9 showed better neutralization in the PBMC system. In total, however, the assay discordances were shown to be bi-directional and not attributable to assay sensitivity. Polonis *et al.* [2008] (**neutralization**, **review**, **assay standardization/improvement**)
- m9: This review summarizes m9 Ab epitope, properties and neutralization activity. The effect of differential CCR5 cell surface expression on m9 neutralization activity is discussed. Kramer *et al.* [2007] (**co-receptor**, **neutralization**, **review**)
- m9: Novel approaches based on sequential (SAP) and competitive (CAP) antigen panning methodiologies, and use of antigens with increased exposure of conserved epitopes, for enhanced identification of broadly cross-reactive neutralizing Abs are reviewed. Abs identified by these methods are described. Zhang & Dimitrov [2007] (**review**)
- m9: Neutralization of HIV-1 primary isolates from different clades (A, B, C, D and E) by m9 was determined in cells expressing high or low surface concentrations of CD4 and CCR5 receptors. CD4 cell surface concentration had no effect on the inhibitory activity of this Ab while the CCR5 surface concentration had a significant effect decreasing the 50% inhibitory concentration of m9 in cell lines with low CCR5. Choudhry *et al.* [2006] (**co-receptor**, **neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- m9: The structure of the V3 region in the context of gp120 core complexed to the CD4 receptor and to the m9 Ab was attempted to be determined by X-ray resolution, but only the structure for V3 complexed with CD4 and X5 Ab was solved. Huang *et al.* [2005a] (**structure**)
- m9: This antibody was selected by subjecting a random mutagenesis library of the scFv X5 to sequential rounds of selection on non-homologous HIV-1 envelope glycoproteins dubbed sequential antigen panning (SAP). scFv m9 has higher neutralization activity and is able to inhibit a broader range of HIV-1 primary isolates compared to scFv X5. Zhang *et al.* [2004a] (**antibody generation**, **enhancing activity**, **neutralization**)

No. 1067
MAb ID multiple Fabs
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Burton *et al.* 1991

- A panel of anti-gp120 Fabs was generated by antigen selection from a random combinatorial library prepared from bone marrow from an asymptomatic individual. Burton *et al.* [1991]

No. 1068
MAb ID multiple MAbs
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* gp120
Species (Isotype) mouse
References Denisova *et al.* 1996

- When gp120 was used as an immunogen, in contrast to gp120 bound to an anti-V3 MAb, few MAbs were generated and all bound better to the native than to the denatured protein – MAbs generated were: G1B12, G2F7, G9G8, G12F12, G1B8, G11F11, G9E8, G1B11, G1B6, G6F2, G2E7. Denisova *et al.* [1996]

No. 1069
MAb ID multiple MAbs
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: gp120-CD4 complex *HIV component:* gp120
Species (Isotype) mouse
References Denisova *et al.* 1996

B Cell

- When gp120-CD4 was used as an immunogen, in contrast to gp120 bound to an anti-V3 MAb, few MAbs were generated and all bound better to the native than to the denatured protein – MAbs generated were: CG43, CG41, CG49, CG53, CG42, CG4, CG46, CG40, CG52, CG51, CG48, CG50, CG125, CG124, CG121. Denisova *et al.* [1996]

No. 1070
MAb ID multiple MAbs
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein-Ab complex *HIV component:* gp120-Mab complex
Species (Isotype) mouse
References Denisova *et al.* 1996

- When anti-V3 MAb M77 was bound to gp120 and used as an immunogen, it stimulated many MAbs to linear epitopes, as well as an array of MAbs to discontinuous epitope – 10 of 36 MAbs were mapped to linear epitopes and are mentioned elsewhere in this database, the others are: GV5H1, GV4D5, GV4G10, GV1A8, GV10H5, GV8E11, GV2H4, GV6E6, GV1F7, GV1G9, GV4G5, GV6B12, GV1E8, GV2B7, GV1B11, GV6H5, GV6G2, GV6B5, GV1E10, GV5E3, GV5B9, GV5F4, GV6G4, GV1A12, GV5C11, GV6B6, GV3C10. Denisova *et al.* [1996]

No. 1071
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing L P
Immunogen HIV-1 infection
Species (Isotype) human (IgG3)
References Scharf *et al.* 2001

- IgG3: HIVIG was separated into immunoglobulin classes and IgG3 neutralization of HIV strains X4, R5 and X4R5 strains was superior to IgG1 and IgG2, and IgG3 was also a more potent inhibitor of viral fusion – the IgG3 advantage was lost when only Fabs were considered, indicating the IgG3 neutralization efficacy is enhanced due to a longer hinge region of the heavy chain in comparison to IgG1 and IgG2. Scharf *et al.* [2001]

No. 1072
MAb ID polyclonal
HXB2 Location Env
Author Location gp140 (IIIB)
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp120, gp140 *Adjuvant:* MPL-SE adjuvant, QS21
Species (Isotype) rabbit (IgG)
References Earl *et al.* 2001

- Immunization of rabbits with oligomeric gp140 induced production of higher levels of cross-reactive neutralizing Abs than immunization with gp120 – immunization of Rhesus macaques with gp140 yielded strong NAb against IIIB, modest against other lab-adapted strains, and no NAb activity against primary isolates – most neutralizing activity could not be blocked by a V3 peptide – 3/4 vaccinated macaques showed no viral replication upon intravenous challenge with SHIV-HXB2. Earl *et al.* [2001]

No. 1073
MAb ID polyclonal
HXB2 Location Env
Author Location gp160 (IIIB)
Epitope
Neutralizing
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade NL43 *HIV component:* gp160 *Adjuvant:* aluminum hydroxide
Species (Isotype) human
References Cox *et al.* 1999

- 60 asymptomatic HIV-1 infected patients were vaccinated with rec gp160 in alum, produced in a baculovirus expression vector in insect cells (VaxSyn), 64 received placebo, and all were followed in a 5 year longitudinal study – a mean of 78% of vaccinated and 82% of those receiving placebo had demonstrable ADCC at the different time intervals in the study, and the vaccine did not enhance ADCC production – patients with rapid and slow disease progression showed similar ADCC levels. Cox *et al.* [1999]

No. 1074
MAb ID polyclonal
HXB2 Location Env
Author Location gp160 (89.6)
Epitope
Neutralizing yes
Immunogen vaccine
Vector/Type: modified vaccinia Ankara (MVA) *Strain:* B clade 89.6 *HIV component:* Env, Gag-Pol *Adjuvant:* IL-2/Ig
Species (Isotype) macaque
References Barouch *et al.* 2001b

- Four rhesus macaques were vaccinated with a modified vaccinia Ankara (MVA) vaccine that elicited strong CTL responses as well as antibody responses. The animals were infected when challenged with pathogenic SHIV-89.6P, but had potent CTL responses, secondary NAb responses upon challenge, partial preservation of CD4+ T-cell counts, lower viral loads, and no evidence of disease or mortality by day 168 after challenge—monkeys that got a sham vaccine had high viral load, progressed to disease, and 2/4 were dead by day 168. Barouch *et al.* [2001b]

No. 1075
MAb ID polyclonal
HXB2 Location Env
Author Location gp160
Epitope

Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human
References Ahmad *et al.* 2001

- High CD4+ T-cell count and low viral load was correlated with high ADCC anti-HIV-1 Env Ab titers in a study of 46 HIV-1 infected individuals from all disease stages. Ahmad *et al.* [2001]

No. 1076
MAb ID polyclonal
HXB2 Location Env
Author Location gp160
Epitope
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Beirnaert *et al.* 2001

- Neutralizing antibodies are thought to inhibit HIV entry by blocking either binding or fusion – six broadly cross-neutralizing sera that can neutralize group M and O viruses inhibit the binding to PBMCs – the nine primary isolates tested in this study represented very diverse subtypes and recombinant forms, and different co-receptor usage. Beirnaert *et al.* [2001]

No. 1077
MAb ID polyclonal
HXB2 Location Env
Author Location gp160
Epitope
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Beirnaert *et al.* 2000

- Sera from 66 HIV individuals from diverse geographic locations could neutralize primary isolates to different extents: broad cross-neutralizing isolates could neutralize 14 primary isolates from HIV-1 group M clades A-H and three O isolates, limited cross-neutralizing sera neutralized some isolates, and non-neutralizing sera—6/7 broadly neutralizing sera were from African women, despite only 14/66 study subjects being women—ability to neutralize three key isolates, MN lab (envB/gagB, X4 coreceptor), VI525 (envG/gagH, envA/gagA, R5X4) and CA9 (Group O, R5) was predictive of being able to neutralize an additional set of 14 primary isolates. Beirnaert *et al.* [2000]

No. 1078
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (SF2)
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF2 *HIV component:* gp120 *Adjuvant:* MF59, PLG
Species (Isotype) mouse, baboon
References O'Hagan *et al.* 2000

- Microparticles were used as an adjuvant for entrapped HIV-1 gp120 and induced strong serum IgG responses in mice – polylactide co-glycolide polymer (PLG) microparticles in combination with MF-59 had the highest response. O'Hagan *et al.* [2000]

No. 1079
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (SF2, US4)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA, protein *Strain:* B clade SF2, B clade US4 *HIV component:* gp120 *Adjuvant:* aluminum phosphate, MF59, PLG
Species (Isotype) macaque, guinea pig, mouse
References O'Hagan *et al.* 2001

- DNA vaccines of codon-optimized Env and Gag genes driven by CMV promotors and absorbed on to PLG microparticles were more effective than naked DNA at eliciting strong Ab responses (more rapid, higher titer, more stable), comparable to gp120 in MF-59. O'Hagan *et al.* [2001]

No. 1080
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) chimpanzee (IgG)
References Moore & Burton 1999; Shibata *et al.* 1999

- polyclonal: Commentary discussing this finding noting the particularly high neutralization titer and limited breadth of the chimpanzee sera used in this study. Moore & Burton [1999]
- polyclonal: Purified IgG from chimpanzee sera infected with several HIV-1 strains was used for passive administration to macaques which were subsequently challenged with the virulent SHIV bearing the HIV-1 env DH12 – *in vitro* neutralization correlated with protection *in vivo*. Shibata *et al.* [1999]

No. 1081
MAb ID polyclonal
HXB2 Location Env
Author Location gp160 (MN)
Epitope
Neutralizing L P
Immunogen HIV-1 infection
Species (Isotype) human (IgA)
References Moja *et al.* 2000

- 15 samples isolated from parotid saliva were selected for study as they had anti-Env IgA – IgA neutralizing activity was detected that was not directed at either EDELKWA or the V3 loop. Moja *et al.* [2000]

No. 1082
MAb ID polyclonal
HXB2 Location Env
Author Location gp120

B Cell

Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN, B clade SF2 *HIV component:* gp120
Species (Isotype)
References McElrath *et al.* 2000

- After 3 immunizations, 210/241 (87%) HIV-1 uninfected vaccinees in a phase II trial developed NAbs – of 140 patients receiving 4 vaccinations, 53% had persistent neutralizing antibodies to homologous virus, and 34% to heterologous virus, measured at day 728 after initial immunization – immunogens were well tolerated– but IVDUs had a decreased Ab response relative to lower risk groups. McElrath *et al.* [2000]

No. 1083
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* gp120 *Adjuvant:* GM-CSF/gp120 chimera
Species (Isotype) mouse
References Rodríguez *et al.* 1999

- The murine Ab response to a chimeric of granulocyte-macrophage colony stimulating factor GM-CSF/gp120 in vaccinia was not higher titer that the response to a gp120-vaccinia construct, but the breadth of the Ab response was greater – a cellular response of greater intensity was trigged to the GM-CSF/gp120 vaccinia construct, as measured by proliferation and Elispot. Rodríguez *et al.* [1999]

No. 1084
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (YU2)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: stabilized Env trimer *Strain:* B clade HXBc2, B clade YU2 *HIV component:* Env
Species (Isotype) mouse (IgG)
Research Contact Joseph Sodroski, Harvard Medical School
References Yang *et al.* 2001

- Soluble Env trimers were created that were designed to mimic functional Env oligomers – stabilized timers could induce neutralizing antibodies more effectively than gp120, and Abs to the YU2 trimer were cross-reactive within clade B and could neutralize several primary and TCLA reactive strains – the stabilized primers did not neutralize primary isolates outside the B clade, from clades C, D, and E – HXBc2 stabilized trimer antigen elicited strong neutralizing Abs against the homologous isolate HXBc2 TCLA strain, but not against primary isolates. Yang *et al.* [2001]

No. 1085
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (MN)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN *HIV component:* gp120 *Adjuvant:* aluminum hydroxide, QS21
Species (Isotype) human
References Evans *et al.* 2001

- Vaccination with QS21 adjuvant and rsgp120 elicited stronger and more sustained neutralizing antibody responses and lymphocyte proliferation with lower doses of rsgp120 than alum formulations, suggesting QS21 may be a means to reduce the does of soluble protein. Evans *et al.* [2001]

No. 1086
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing yes
Immunogen HIV-1 infection
Species (Isotype) human
References Binley *et al.* 2000

- HAART inhibited the development of anti-gp120 Ab when initiated during primary infection and sometimes in patients treated within 2 years of HIV-1 infection – HAART during primary infection usually did not inhibit the development of weak NAb responses against autologous virus – 3/4 patients intermittently adherent developed high titers of autologous NAbs, largely coincident with brief viremic periods. Binley *et al.* [2000]

No. 1087
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (SIV)
Epitope
Neutralizing yes
Immunogen HIV-1 infection
Species (Isotype) macaque
References Reitter *et al.* 1998

- This study concerned an SIV mutated strain that lacked 4th, 5th and 6th sites for N-linked glycosylation – monkeys infected with the mutant viruses had increased neutralizing activity in their sera relative to monkeys infected with the parental strain. Reitter *et al.* [1998]

No. 1088
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing yes
Immunogen HIV-1 infection
Species (Isotype) human
References Kim *et al.* 2001

B Cell

• After HAART reduction of viral load to <400 for three visits over a 12 month interval, 2/11 patients were found to have increased anti-Env Ab binding titers, and neutralizing Abs titers increased against primary isolates US1, and CM237 – no NAB titer increase was seen to more readily neutralized isolate BZ167 – this suggests that in certain individuals the control of HIV-1 by HAART may augment immune control of HIV. Kim *et al.* [2001]

No. 1089
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing yes
Immunogen HIV-1 exposed seronegative
Species (Isotype) human (IgA)
References Kaul *et al.* 2001b

• Kaul *et al.* provide a concise summary of the findings concerning the presence of Mucosal IgA in highly exposed, uninfected subjects, arguing for a role in protection. Kaul *et al.* [2001b]

No. 1090
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing yes
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF2 *HIV component:* gp120 *Adjuvant:* MF59
Species (Isotype) human
References Nitayaphan *et al.* 2000

• A phase I/II trial was conducted in 52 seronegative Thais immunizing with rgp120 SF2 – the vaccine was safe and 39/40 developed NAb responses to the autologous SF2, while 22/40 were able to cross-neutralize the heterologous strain MN. Nitayaphan *et al.* [2000]

No. 1091
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (SF2)
Epitope
Neutralizing yes
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF2 *HIV component:* gp120, p24 Gag *Adjuvant:* Immune stimulating complexes (ISCOM)
Species (Isotype) macaque
References Heeney *et al.* 1998a

• The immune responses induced in Rhesus monkeys using two different immunization strategies was studied – one vaccine group was completely protected from challenge infection, the other vaccinees and controls became infected – protected animals had high titers of heterologous NAbs, and HIV-1-specific T helper responses – increases in RANTES, MIP 1 alpha and MIP 1 beta produced by circulating CD8+ T cells were also associated with protection. Heeney *et al.* [1998a]

No. 1092
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide, protein *Strain:* B clade SF2, B clade SF33 *HIV component:* gp120 *Adjuvant:* Immune stimulating complexes (ISCOM), MF59
Species (Isotype) macaque
References Verschoor *et al.* 1999

• Attempts were made to broaden immune responses induced in Rhesus monkeys by immunization of animals previously immunized that had resisted homologous challenge, with a second immunization with ISCOM-peptides or a boost with gp120 from SF33 – animals didn't survive a second challenge heterologous challenge virus SHIV(SF33) raising concerns about early antigenic sin. Verschoor *et al.* [1999]

No. 1093
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing yes
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF2, CRF01 CM235 *HIV component:* gp120 *Adjuvant:* MF59
Species (Isotype) baboon
References VanCott *et al.* 1999

• Immunization with rgp120 CM235 (CRF01) induced Abs capable of neutralizing TCLA subtype E (CRF01) and subtype B isolates, while rgp120SF2 induced Abs could only neutralize subtype B TCLA isolates – neither immunogen induced Abs capable of neutralizing primary HIV-1 isolates – both rgp120CM235 and rgp120SF2 induced Abs to regions within C1, V1/V2, V3, and C5, but unique responses were induced by rgp120CM235 to epitopes within C2, and by rgp120SF2 to multiple epitopes within C3, V4, and C4 – CM235 baboon sera bound 3- to 12-fold more strongly than the SF2 baboon sera to all subtype E gp120s while binding to subtype B gp120s (except SF2) were within two to threefold for the SF2 and CM235 baboon sera. VanCott *et al.* [1999]

No. 1094
MAb ID polyclonal
HXB2 Location Env
Author Location gp140 (SF162DeltaV2)
Epitope
Neutralizing yes
Immunogen vaccine
Vector/Type: DNA with CMV promotor *Strain:* B clade SF162 *HIV component:* gp140 *Adjuvant:* MF59
Species (Isotype) macaque, rabbit (IgG)
References Barnett *et al.* 2001

B Cell

- SF162ΔV2 is a virus that has a 30 amino acids deletion in the V2 loop that does not abrogate its infectivity but renders it highly susceptible to neutralization—when incorporated into a codon-optimized DNA vaccine with a CMV promoter and delivered by gene gun, SF162ΔV2 gave higher neutralizing Ab titers against SF162 than did SF162 itself, and Abs that cross-neutralized non-homologous primary isolates were obtained only when SF162ΔV2, but not intact SF162, was used as the immunogen—Control MAbs 2F5 and 2G12 could neutralize all of the following primary isolates: 91US056(R5), 92US714(R5), 92US660(R5), 92HT593(R5X4), and BZ167(R5X4), while after the first protein boost, the sera from two SF162ΔV2 immunized macaques could neutralize 91US056(R5), 92US714(R5), 92US660(R5) and ADA(R5), but not 92HT593(R5X4) or 92US657(R5)—the pattern of cross-recognition shifted after the second boost. Barnett *et al.* [2001]

No. 1095
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Binley *et al.* 1997b

- Retention of anti-Env antibodies and loss of anti-Gag antibodies during progression was studied, and suggested to be the result of the loss of T-cell help and the unique ability of Env to stimulate B cells even in a backdrop of declining CD4 cells, because of the ability of Env to bind to the CD4 molecule. Binley *et al.* [1997b]

No. 1096
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (W61D)
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade W61D *HIV component:* gp120
Species (Isotype) human
References Beddows *et al.* 1999

- rgp120 derived from a R5X4 subtype B virus, HIV-1 W61D, was used to vaccinate healthy volunteers and the resulting sera were compared with HIV-1 positive subjects – vaccinee sera had more potent responses to linear V1/V2 and V3 epitopes than did the sera from HIV-1 + individuals, but could only neutralize homologous or heterologous virus only after adaptation to T-cell lines – neutralization activity was lost after re-adaptation to growth in PBMCs – in contrast, sera from infected individuals could neutralize both PBMC and T-cell line adapted viruses. Beddows *et al.* [1999]

No. 1097
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *HIV component:* Gag, gp120, V3
Species (Isotype) macaque
References Wagner *et al.* 1998b

- A VLP is a non-infectious virus-like particle self-assembled from HIV Pr55 gag – macaques were immunized with VLPs bound to either gp120 or V3+CD4 linear domains – Gag and Env specific CTL were stimulated in each case, and Ab response to gag and gp120 and was elicited, but the gp120 neutralizing response occurred only with whole gp120, not V3+CD4 – despite the CTL and Ab response, immunized macaques were infected by intervenous challenge with SHIV chimeric challenge stock. Wagner *et al.* [1998b]

No. 1098
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA *HIV component:* gp120, gp160
Species (Isotype) mouse
References Shiver *et al.* 1997

- DNA vaccinations of BALBc mice with a gp120 or gp160 DNA vaccine elicited a strong T cell proliferative response with Th1-like secretion of gamma interferon and IL-2, with little or no IL-4, as well as antigen specific gp120 Abs. Shiver *et al.* [1997]

No. 1099
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: DNA *HIV component:* Env, Gag, Pol, Vif *Adjuvant:* B7, IL-12
Species (Isotype) mouse
References Kim *et al.* 1997b

- A gag/pol, vif or CMN160 DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules B7 and IL-12, gave a dramatic increase in both the cytotoxic and proliferative responses in mice – the Ab response was detected by ELISA, but the CMN160 DNA vaccinated mice showed a neutralizing Ab response. Kim *et al.* [1997b]

No. 1100
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing P
Immunogen HIV-1 infection

B Cell

Species (Isotype) human
References Bradney *et al.* 1999

- Sera were taken from long term non-progressors and evidence for viral escape was noted – serum could neutralize earlier autologous isolates, but not contemporary isolates. Bradney *et al.* [1999]

No. 1101
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L P
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade SF2 *HIV component:* Env, Gag
Species (Isotype) human
References Belshe *et al.* 1998

- NAbs were obtained by a HIV-1 gag/env in canary pox vaccination of eight volunteers after boosting with rgp120 against lab strains – 1/8 primary isolates was neutralized, BZ167. Belshe *et al.* [1998]

No. 1102
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* Gag, gp120, Protease *Adjuvant:* MF59
Species (Isotype) human
References Belshe *et al.* 2001; Belshe *et al.* 1998

- A phase 2 trial was conducted in 435 volunteers with vCP201, a canary pox vector carrying gp120 (MN in vCP201, and SF2 in the boost), p55 (LAI) and protease (LAI), either alone or with a gp120 boost – NAbs against MN were obtained in 56% of those who received vCP201 alone, and in 94% of those who got the prime with the gp120 boost. Belshe *et al.* [1998]

No. 1103
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype) human
References Neshat *et al.* 2000

- HIV-1 gp120 appears to be a B cell superantigen that binds to members of the V_{H3} Ig gene family—the gp120 binding site was localized to the Fab portion of the Ab, and discontinuous residues in the V_H region were critical. Neshat *et al.* [2000]

No. 1104
MAb ID polyclonal
HXB2 Location Env
Author Location gp41 (539–684 BH10)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* gp41
Species (Isotype) mouse (IgG)
References Bai *et al.* 2000

- Murine rsgp41 antisera recognized a common epitope on human IFNα (aa 29-35 and aa 123-140) and on human IFNβ (aa 31-37 and aa 125-142), suggesting that elevated levels of Ab to IFNs found in HIV+ individuals may be due to a cross-reactive gp41 response. Bai *et al.* [2000]

No. 1105
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (BH10)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade 89.6, B clade ADA, B clade IIIB *HIV component:* gp120 *Adjuvant:* C3d fusion
Species (Isotype) mouse (IgG)
References Ross *et al.* 2001

- gp120 was fused with murine complement protein C3d in a DNA vaccine to enhance the titers of Ab to Env – fusion to C3d resulted in a more rapid onset of Ab response and avidity maturation, after three immunizations in BALB/c mice with DNA on a gold bead delivered with a gene gun, but not in strong neutralizing Ab response. Ross *et al.* [2001]

No. 1106
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (SF162DeltaV2)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with protein boost *Strain:* B clade SF162 *HIV component:* gp140 *Adjuvant:* MF59
Species (Isotype) macaque
References Cherpelis *et al.* 2001a; Cherpelis *et al.* 2001b

- Two animals were immunized both intradermally and intramuscularly at weeks 0, 4, and 8 with a codon optimized DNA vector expressing the SF162V2 gp140 envelope with an intact gp120-gp41 cleavage site, and both developed lymphoproliferative responses and potent neutralizing Abs – CD8+ T lymphocytes were depleted in the animals and they were challenged with SHIV162P4 – at peak viremia, plasma viral levels in the vaccinated animals were 1 to 4 logs lower than those in the unvaccinated animals. Cherpelis *et al.* [2001b]
- HIV-1 SF162ΔV2 gp140 envelope was used in a DNA-prime plus protein-boost vaccination methodology in Rhesus macaques, the animals were depleted of their CD8+ T lymphocytes, and challenged with pathogenic SHIV(SF162P4)—the vaccinated macaques had lower peak viremia, rapidly cleared

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virus from the periphery, and developed delayed seroconversion to SIV core antigens relative to non-vaccinated controls. Cherpelis *et al.* [2001a]

No. 1107
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
References Sarmati *et al.* 2001

- Some HIV-1 infected patients have increasing CD4 counts despite failing ARV, and CD4 levels are correlated with HIV-1 specific NAbs – no correlation was found between NAbs and viral load in this patients. Sarmati *et al.* [2001]

No. 1108
MAb ID polyclonal
HXB2 Location Env
Author Location gp41 (539–684 BH10)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* gp41
Species (Isotype) mouse (IgG)
References Bai *et al.* 2000

- There is a common epitope in HIV-1 gp41, and IFNalpha and IFNbeta. Bai *et al.* [2000]

No. 1109
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing no
Immunogen
Species (Isotype) human (IgM)
References Llorente *et al.* 1999

- Combinatorial antibody analysis by phage display and flow cytometry demonstrated that gp120 in HIV-1 negative people is recognized by IgM, but not IgG Abs – IgM Fab reactivity is observed throughout the entire sequence of HIV-1 IIIB gp120 and is characterized by low affinity binding and near germline configuration reflecting a lack of maturation of the IgM repertoire – no neutralizing activity was observed in a non-infected individual before isotope switching. Llorente *et al.* [1999]

No. 1110
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (SF2)
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF2 *HIV component:* gp120
Species (Isotype) human (IgM)
References Locher *et al.* 1999

- High risk volunteers were vaccinated with SF2 gp120 – 3 breakthrough cases were studied – SF2 neutralizing Abs were observed, but Ab titers to autologous virus were never high and took 6 months after HIV-1 infection to develop – viral loads were similar to HIV-1 infected individuals who had not been vaccinated. Locher *et al.* [1999]

No. 1111
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (subtype A, B, C, D, CRF01)
Epitope
Subtype A, B, C
Neutralizing yes
Immunogen vaccine
Vector/Type: formaldehyde-fixed whole-cell *HIV component:* gp120
Species (Isotype) mouse (IgG)
References Nunberg 2002; LaCasse *et al.* 1999

- A retraction was printed (Science 296:1025, 2002) noting that an unknown cytotoxic effect of these complex sera accounted for a major fraction of the neutralization reported in LaCasse *et al.* [1999] Nunberg [2002]. LaCasse *et al.* [1999]; Nunberg [2002]
- In this study, immunogens were generated that were thought to capture transient envelope-CD4-coreceptor structures that arise during HIV binding and fusion by formaldehyde-fixation of co-cultures of cells expressing HIV-1 Env and those expressing CD4 and CCR5 receptors – these cells elicited NAbs in CD4- and CCR5-transgenic mice that neutralized 23/24 primary isolates from clades A-E. LaCasse *et al.* [1999]

No. 1112
MAb ID polyclonal
HXB2 Location Env
Author Location (B consensus)
Epitope
Subtype B
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
References Morris *et al.* 2001b

- Ab responses before HAART therapy and after one year of therapy were measured in 8 individuals that were classified HAART successes, and 10 patients who were classified as HAART failures – V3 peptide antibody binding titers to the B-consensus and MN and SF2 variants, and neutralization of HIV-1 MN and four subtype B clinical isolates were tested – subjects with strong anti-V3 and NAb humoral immune responses before starting HAART were more likely to achieve sustained viral suppression to <500 copies RNA/ml on HAART – HIV-specific Ab responses declined after 1 year of successful viral suppression on HAART. Morris *et al.* [2001b]

No. 1113
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope

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Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Pilgrim *et al.* 1997

- Sera from long-term nonprogressors(LTNP) had broader NAbs against heterologous primary isolates and were more likely to neutralize the contemporaneous autologous isolate than were sera from short-term nonprogressors and normal progressors – in 4 individuals followed from acute infection, NAbs were detected against the early autologous isolate by 5-40 weeks, and not detected in an additional 2 cases after 27-45 weeks. Pilgrim *et al.* [1997]

No. 1114
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
References Moog *et al.* 1997

- Autologous and heterologous NAbs were studied in 18 individuals who were sampled early after sero-conversion and followed longitudinally – autologous NAbs were not detected in sera collected at the same time as the viruses were isolated – NAbs detected against the seroconversion autologous strains were not detected one year after seroconversion, and were highly specific to the virus present at the early phase of HIV infection – heterologous neutralization of primary isolates were not detected until after 2 years. Moog *et al.* [1997]

No. 1115
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing yes
Immunogen HIV-1 infection
Species (Isotype) human
References Montefiori *et al.* 2001

- In 7/9 patients in whom HAART was initiated during early seroconversion, NAbs to autologous strains were not found immediately following treatment interuption after 1-3 years, and Env and Gag Abs were low or undetected by ELISA indicating, that early HAART suppresses the normal antibody response to HIV-1, presumably by limiting the concentration of viral antigens needed to drive B-cell maturation – in 3 patients with a viral rebound autologous NAbs rapidly appeared and correlated with spontaneous down-regulation of viremia – prolonged control of viremia after stopping treatment persisted in the absence of detectable NAbs, suggesting that cellular immune responses alone can control viremia under certain circumstances – these results support the notion that virus-specific B-cell priming, combined with CD8+ CTL induction, may be beneficial for HIV-1 vaccines that aim to suppress viremia in the absence of complete protection to prevent disease and reduce the rate of virus transmission. Montefiori *et al.* [2001]

No. 1116
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Scala *et al.* 1999

- Random peptide libraries were screened using sera from HIV-infected subjects to identify mimotopes, peptides that mimic conformational or linear epitopes specifically recognized by Abs from HIV-1 infected individuals – the sera of simian SHIV-infected monkeys also recognized the specific peptides, and mice immunized with the selected peptides elicited HIV-specific Abs that neutralized HIV-1 isolates IIIB and NL4-3. Scala *et al.* [1999]

No. 1117
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *HIV component:* mimotopes
Species (Isotype) mouse (IgG)
References Scala *et al.* 1999

- Random peptide libraries were screened using sera from HIV-infected subjects to identify mimotopes, peptides that mimic conformational or linear epitopes specifically recognized by Abs from HIV-1 infected individuals – the sera of simian SHIV-infected monkeys also recognized the specific peptides, and mice immunized with the selected peptides elicited HIV-specific Abs that neutralized HIV-1 isolates IIIB and NL4-3. Scala *et al.* [1999]

No. 1118
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *HIV component:* Env, Gag *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse (IgG)
References Lebedev *et al.* 2000

- Virus-like particles (VLPs) in the form of spherical particles with yeast dsRNA enveloped in a polysaccharide matrix carrying the protein TBI, that contains fragments of HIV Env and Gag, were used to immunize BALB/c mice and induced specific Abs against HIV-1 as measured by ELISA with TBI. Lebedev *et al.* [2000]

No. 1119
MAb ID polyclonal

HXB2 Location Env
Author Location
Epitope
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
References Donners *et al.* 2002

- A difference in neutralization patterns between African and European plasma is observed, especially in African women, who tended to have cross-neutralizing Abs against primary isolates. Donners *et al.* [2002]

No. 1120
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Dianzani *et al.* 2002

- Immune complexes(ICs) in the plasma contained HIV RNA (80%-100%) in association with HIV-specific IgG NAbs indicating that the HIV in the plasma of carriers is frequently composed of antibody-neutralized HIV as ICs. Dianzani *et al.* [2002]

No. 1121
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Kimura *et al.* 2002

- Significant neutralization activity against autologous isolates was observed in 13/19 HIV+ patients at initiation of HAART therapy which persisted during therapy, increasing in one patient, and declining in one patient – 3/6 patients with no detectable NAb at the start of therapy developed NAb responses – of the four patients with increased NAb responses, three had low level viral rebounds (blips). Kimura *et al.* [2002]

No. 1122
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing P
Immunogen HIV-1 exposed seronegative
Species (Isotype) human (IgA)
References Devito *et al.* 2000b

- Mucosal and plasma HIV-specific IgA that can neutralize primary isolates is present saliva (11/15 tested) and plasma (11/15) and cervicovaginal fluid (11/14) from highly exposed persistently seronegative (HEPS) individuals. Devito *et al.* [2000b]

No. 1123
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing P
Immunogen HIV-1 exposed seronegative
Species (Isotype) human (IgA)
References Devito *et al.* 2000a

- IgA from the genital tract, saliva and plasma from highly exposed persistently seronegative (HEPS) individuals can inhibit transcytosis of HIV-1 across a transwall system that provides a tight epithelial cell layer—50% of the IgA samples studied were able to inhibit transcytosis of at least one of two primary isolates tested, indicating this may be an important mechanism against sexual acquisition of HIV-1. Devito *et al.* [2000a]

No. 1124
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype A, B, D
Neutralizing P
Immunogen HIV-1 exposed seronegative
Species (Isotype) human (IgA)
References Broliden *et al.* 2001

- IgA isolated from the saliva, genital tract, and plasma of most highly exposed persistently seronegative (HEPS) sex workers in a Kenyan cohort could neutralize a B, A and D clade primary isolates and could inhibit transcytosis of HIV across a transwall model of the human mucosal epithelium. Broliden *et al.* [2001]

No. 1125
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype A, B, D
Neutralizing P
Immunogen HIV-1 exposed seronegative
Species (Isotype) human (IgA)
References Devito *et al.* 2002

- IgA isolated from the saliva, genital tract, and plasma of most highly exposed persistently seronegative (HEPS) Kenyan sex workers mediated broad cross-clade neutralization of primary isolates (A, B, C, D, and CRF01) – 6/10 HEPS individuals that were persistently exposed to a stable HIV+ B clade infected partner showed less breadth of neutralization, and were able to neutralize clade A and B primary isolates, but not clades C, D, or CRF01. Devito *et al.* [2002]

No. 1126
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing P
Immunogen HIV-1 exposed seronegative
Species (Isotype) human (IgA)

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References Mazzoli *et al.* 1999

- Serum HIV-specific IgA is present in highly exposed persistently seronegative individuals (HEPS) in the absence of serum IgG – serum IgA can be found in productively infected individuals and exposed seronegatives at similar titers – 5/15 sera from HEPS had neutralizing activity, 2 of these in purified IgA – HIV-1 specific serum IgA concentrations declined after one year of interruption of at-risk sex. Mazzoli *et al.* [1999]

No. 1127
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing P
Immunogen HIV-1 exposed seronegative
Species (Isotype) human (IgA)
References Beyrer *et al.* 1999

- HIV-specific anti-gp160 IgA is present in cervical lavage from 6/13 HIV-exposed seronegative Thai female sex workers. Beyrer *et al.* [1999]

No. 1128
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade HXB2/Bal
Species (Isotype) mouse
References Chakrabarti *et al.* 2002

- A modified gp140 (gp140ΔCFI), with C-term mutations intended to mimic a fusion intermediate and stabilize trimer formation, retained antigenic conformational determinants as defined by binding to CD4 and to MAbs 2F5, 2G12, F105, and b12, and enhanced humoral immunity without diminishing the CTL response in mice injected with a DNA vaccine. Chakrabarti *et al.* [2002]

No. 1129
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype B
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
References Hioe *et al.* 1997a

- Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D)and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997a]

No. 1130
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype C
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6, B clade IIIB *HIV component:* Env *Adjuvant:* alpha2-macroglobin, Complete Freund's Adjuvant (CFA), GM-CSF, monophosphoryl lipid A
Species (Isotype) mouse
References Liao *et al.* 2002

- HIV-envelope peptides coupled to α2-macroglobin were much more immunogenic when formulated in monophosphoryl lipid A with GM-CSF than in complete or incomplete Freund's adjuvant or in monophosphoryl lipid A with GM-CSF alone. Liao *et al.* [2002]

No. 1131
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing P
Immunogen vaccine
Vector/Type: gp120-CD4 complex, gp140-CD4 complex *Strain:* B clade IIIB *HIV component:* gp120, gp140 *Adjuvant:* QS21
Species (Isotype) macaque
References Fouts *et al.* 2002

- gp120-CD4 and gp140-CD4 complexes were used for i.m. vaccination of rhesus macaques and neutralizing Ig was recovered using affinity chromatography using a chimeric HIV-BAL gp120 with a mimetic peptide that induces a CD4-triggered mimetic structure – the sera and affinity purified Ab were broadly neutralizing against primary X4, R5, and R5X4 isolates from multiple subtypes but did not react as well against lab-adapted isolates. Fouts *et al.* [2002]

No. 1132
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
References Nichols *et al.* 2002

- NYBC-HIVIG derived from patients with high NAb titers and NABI-HIVIG derived from patients with high anti-p24 Ab titers were compared in neutralizing assay against a panel of six primary isolates – both could neutralize all isolates tested but the NYBC-HIVIG dose required for 50% neutralization was of 3.2 fold lower, showing source plasmas influence the effective concentration of NAb present in HIVIG. Nichols *et al.* [2002]

No. 1133
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
References Pastori *et al.* 2002

- HAART initiated during primary infection was studied in seven patients and had different effects on NAb production—in some cases, α-Env Abs were inhibited during primary infection, and in some cases strong NAbs against autologous virus were induced. Pastori *et al.* [2002]

No. 1134
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) chimpanzee (IgG)
References Moore & Burton 1999; Igarashi *et al.* 1999

- The rate of virus clearance in the circulation in rhesus macaques receiving a continuous infusion of cell-free viral dual-tropic virus isolate HIV-1DH12 particles in the presence and absence of virus-specific antibodies was measured – the clearance of physical and infectious viral particles is very rapid in naive animals, with half-lives ranging from 13 to 26 minutes, but clearance cold be acheived with a half life of 3.9-7.2 minutes when chimpanzee neutralizing Abs were present to help to remove virions from the blood. Igarashi *et al.* [1999]
- polyclonal: Commentary discussing this finding noting the particularly high neutralization titer and limited breadth of the chimpanzee sera used in this study. Moore & Burton [1999]

No. 1135
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* gp120, gp41 *Adjuvant:* MF59
Species (Isotype) human
References Gupta *et al.* 2002

- Different HIV strains were used for different regions: gp120 MN and gp41 LAI, rgp120 SF2, protease LAI and gag LAI. Gupta *et al.* [2002]
- Vaccine trial protocol 022A in 150 HIV-1 uninfected adults (130 completed the study) showed high titer ALVAC vaccine in combination with gp120 was safe and immunogenic in HIV-1 negative volunteers – NAb responses were detected in 95% of vaccinees, with higher titers in recipients of sequential versus simultaneous dosing of the two vaccines and in vaccinia naive volunteers. Gupta *et al.* [2002]

No. 1136
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing yes
Immunogen vaccine
Vector/Type: protein *Strain:* B clade 89.6 *HIV component:* gp120, gp140 *Adjuvant:* Cholera toxin (CT), IL-12
Species (Isotype) mouse (IgA, IgG, IgG1, IgG2a)
References Albu *et al.* 2003
Keywords genital and mucosal immunity, mucosal immunity, Th1, Th2

- Mice were intranasally immunized with gp120 or gp140 with IL-12 and Cholera toxin as adjuvants. Adjuvants enhanced NAb stimulation in mucosa and genital tissues and in serum. Albu *et al.* [2003] (**genital and mucosal immunity**, **mucosal immunity**, **Th1**, **Th2**)

No. 1137
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype)
References Berger 2002
Keywords antibody generation, immunotherapy

- This medical hypothesis proposes that HIV shares domains with human proteins, masked from the immune response as they are seen as self. They propose blocking the shared determinants on human proteins in the thymus with antibodies, to allow anti-self responses which are normally inhibited to occur in HIV+ people. Berger [2002] (**antibody generation**, **immunotherapy**)

No. 1138
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype A
Neutralizing yes
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *Strain:* A clade UG5.94UG018 *HIV component:* Gag, gp120

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Species (Isotype) mouse
References Buonaguro *et al.* 2002
Keywords subtype comparisons

• BALB/c mice were immunized with VLPs carrying a subtype A gp120. Humoral immune responses directed against B-clade derived Gag (p24) peptides or gp120-Env V3 loop peptide were readily induced following a multi-dose immunization with VLP particles presenting a gp120 molecule from a HIV-1 isolate of clade A. VLP-immunized mice showed autologous and heterologous (against B-clade HIV-1 IIIB strain) neutralization activity. Proliferative responses and CTL were also observed. Buonaguro *et al.* [2002] (**subtype comparisons**)

No. 1139
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype A, B, D
Neutralizing
Immunogen vaccine
Vector/Type: canarypox, protein *Strain:* B clade LAI, B clade MN *HIV component:* Env, Gag, Protease
Species (Isotype) human
References Cao *et al.* 2003
Keywords subtype comparisons

• 20 Ugandan seronegative individuals were intramuscularly immunized in this study with an ALVAC HIV GagPol and Env vaccine carrying B clade agtigens.3/20 of subjects produced neutralizing antibodies against the autologous HIV-1 clade B strain MN that was T-cell line adapted; 2 also had NAb reactivity against a primary B clade cell line. No NAb cross-reaction was observed with primary viral isolates UG92029 (subtype A) or UG92046 (subtype D). 4/20 had detectable CTL activity against B clade antigen, and one of these cross-reacted with A clade antigen, one with D clade. Cao *et al.* [2003] (**subtype comparisons**)

No. 1140
MAb ID polyclonal
HXB2 Location Env
Author Location gp160
Epitope
Neutralizing
Immunogen SHIV infection
Species (Isotype) macaque
References Crawford *et al.* 1999
Keywords variant cross-recognition or cross-neutralization

• Neutralization assays with rsCD4, MAbs, and serum samples from SHIV-infected macaques and HIV-1 infected individuals were used to characterize the antigenic properties of the env glycoprotein of six primary isolate or TCLA SHIV variants. SHIV infected macaques could neutralize autologous virus very effectively, but serum from HXB2c or 89.6 infected animals could not neutralize heterologous SHIVs. Serum from KU infected animals could neutralize only HXB2c, and serum from 89.6PD infected animals could neutralize 89.6, 89.6P, 89.6PD and KB9 (all derived from 89.6) well. Many sera from the SHIV infected macaques could also neutralize HIV-1 strains MN and SF2. Crawford *et al.* [1999] (**variant cross-recognition or cross-neutralization**)

No. 1141
MAb ID polyclonal
HXB2 Location Env
Author Location gp160
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Crawford *et al.* 1999
Keywords variant cross-recognition or cross-neutralization

• Neutralization assays with rsCD4, MAbs, and serum samples from SHIV-infected macaques and HIV-1 infected individuals were used to characterize the antigenic properties of the env glycoprotein of six primary isolate or TCLA SHIV variants. Serum from 9 HIV-1 infected people were tested for their ability to neutralize SHIVs. KU2 was least sensitive, 89.6, 89.6P, 89.6PD and KB9 (all derived from 89.6) were moderately susceptible, and SHIV HXB2c was less sensitive than IIIB, the strain from which it was derived. Crawford *et al.* [1999] (**variant cross-recognition or cross-neutralization**)

No. 1142
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B, C, CRF01_AE
Neutralizing yes
Immunogen vaccine
Vector/Type: Venezuelan equine encephalitis virus (VEE) *Strain:* B clade R2 *HIV component:* gp160ΔCT
Species (Isotype) rabbit, mouse (IgG)
References Dong *et al.* 2003
Keywords subtype comparisons, variant cross-recognition or cross-neutralization

• Mice and rabbits were immunized with Venezuelan equine encephalitis virus (VEE) replicon system particles expressing HIV-1 Env from the clone R2 that was derived from a virus that was neutralization sensitive and isolated from an individual that made strong NAb resposnes. Stronger and faster NAb responses were induced with replicons expressing gp160 with the cytoplasmic tail deleted than with gp160 or gp140. NAb responses against heterologous strain SF162 were similar in BALB/c and C3H/He mice and enhanced compared to responses elicited in C57BL/6 mice. Serum from mice neutralized 5 primary clade B env proteins, a chinese clade C strain, but not a chinese clade E (CRF-1) strain. Sera from 3/3 immunized rabbits could neutralize SF162, and from 2/3 neutralized the autologous R2 strain. Dong *et al.* [2003] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)

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- Subcutaneous or intradermal immunization with VEE replicons expressing HIV-1 R2 gp140 and with HIV-1 R2 gp160 lacking the cytoplasmic tail. Sera from 3/3 rabbits inhibited SF162 infectivity and 2/3 rabbits were able to neutralize the R2 strain. Dong *et al.* [2003]
- C3H/He mice immunized with replicons expressing RT env protein or the VEE env vector pGP expressing either gp140 or gp160 showed cross-reactive neutralizing Ab responses to five clade B env proteins, a chinese clade C strain and weakly against a chinese clade E (CRF-1) strain. Dong *et al.* [2003]

No. 1143
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype multiple, M, O
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
References Donners *et al.* 2003
Keywords assay development, assay standardization/improvement, co-receptor, kinetics, subtype comparisons

- Plasma samples from six HIV-1 + Belgians showed broad cross-neutralization ability against primary isolates from group M (subtypes A-H) and Group O. Viruses with R5, X4, and R5X4 co-receptor usage were all represented in the test panel. Kinetics of neutralization showed that NAb responses detected using a PBMC assay with a short incubation period could be lost upon extended culture. No preincubation with Ab was needed to see some inhibition of virus replication, indicating that at least partial neutralization occurs post-virus binding to target cells. Donners *et al.* [2003] (**assay development**, **co-receptor**, **kinetics**, **subtype comparisons**, **assay standardization/improvement**)

No. 1144
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Research Contact Rebeca Geffin, Miami School of Medicine
References Geffin *et al.* 2003
Keywords autologous responses, escape, rate of progression, responses in children

- A longitudinal study of NAb responses in perinatally HIV-1 infected infants and children was undertaken, including 7 with rapid progression (RP) and 9 who did not progress rapidly (NRP). A subset of both RPs and NRPs had some plasma samples that could neutralize contemporaneous autologous viral isolates after 6 months of age, but most isolates could not be neutralized by contemporaneous plasma, only by later samples. The non-contemporaneous NAbs would persist for years, had highest titers against earlier isolates, and tended to be more potent in NRP children. This study indicates that there is ongoing NAb escape in HIV-1 + children. No correlation between HIV RNA levels and Ab production was established, although this might have been complicated by treatment. Geffin *et al.* [2003] (**autologous responses**, **escape**, **responses in children**, **rate of progression**)

No. 1145
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype)
Research Contact Mascola2003b
References Mascola & Montefiori 2003
Keywords escape, review

- This paper reviews the paper by Wei *et al.* (Nature 2003) that substantiates the notion that HIV evolves to change the number and position of glycosylation sites in Envelope and this facilitates neutralization escape *in vivo*. This NAb escape mechanism is called a glycan shield. Mascola & Montefiori [2003] (**escape**, **review**)

No. 1146
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) macaque
References Mascola 2003
Keywords immunoprophylaxis, review

- This review dicusses the importance and function of protective antibody responses in animal model studies in the context of effective vaccine development. SHIV models have shown protection using high levels of MAbs can prevent infection, and partial protection that can influence disease course can be obtained from modest levels of NAbs. The binding properties and SHIV challenges studies conducted with infusions of combinations of MAbs b12, 2G12, and 2F5 are reviewed. Mascola [2003] (**immunoprophylaxis**, **review**)

No. 1147
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with virus-like particle (VLP) boost, fowlpoxvirus prime with virus-like particle (VLP) boost *Strain:* B clade 89.6P *HIV component:* Env
Species (Isotype) rabbit
References Radaelli *et al.* 2003
Keywords Th1, Th2

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- Three different immunization protocols using two recombinant fowlpox (FP) constructs and two expression plasmids (SIV mac239 gg/pol or HIV-1 env 89.6P) for priming and VLP particles for boosting were tested for their ability to elicit neutralizing Ab and cell-mediated immune responses. NAb responses against SHIV 89.6P were elicited in all protocols tested. Plasmid DNA (pcDNA3gag/pl SIV) was more efficient than the FP vector (FPgag/polSIV) in inducing Ab responses to the gag core protein (p27). DNA plasmid followed by a VLP boost elicited a Th0 profile. Radaelli *et al.* [2003] (**Th1**, **Th2**)

No. 1148
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype B, CRF01_AE
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Polonis *et al.* 2003
Keywords co-receptor, escape, subtype comparisons

- Neutralization of 49 subtype E HIV-1 isolates from various stages of disease and 21 subtype B viruses was compared using polyclonal Ab pools and single subtype E plasmas. Non-syncytium-inducing (NSI) CRF01 (subtype E) HIV-1 isolates showed increased sensitivity to neutralization (42%) than syncytium-inducing (SI) subtype E isolates (9%). In contrast, the viral phenotype of subtype B isolates did not correlate with neutralizaiton sensitivity. SI viruses were primarily X4 (one X4R5 was identified), NSI were R5. Low CD4+ T cell numbers in subtype E infected patients correlated with concurrent isolate resistance to neutralizing Ab responses. Polonis *et al.* [2003] (**co-receptor**, **escape**, **subtype comparisons**)

No. 1149
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade W61D *HIV component:* gp120, Nef, Tat *Adjuvant:* AS02A (oil-in-water emulsion, 3D-monophosphoryl lipid A, QS21), AS06 (CpG, aluminum hydroxide)
Species (Isotype) macaque (IgG)
References Voss *et al.* 2003
Keywords adjuvant comparison, variant cross-recognition or cross-neutralization

- Monkeys were immunized with different combinations of gp120/NefTat/SIV-Tat three times over a three-month time period and intravenously challenged with SHIV 89.6P four weeks after the last immunzation. Vaccination induced anti-Tat, -Nef and -gp120 Ab responses that decreased until challenge. Neutralizing Ab responses against HIV-1 MN and HIV-1 W61D were observed. Vaccination with the combination of all three proteins reduced viral load and kept animals from a CD4+ T cell decline, preventing AIDS for more than 2.5 years. The adjuvant AS02A elicited NAbs and protected from disease, while AS06 did not. gp120 alone or TatNef/SIV-Tat without gp120 could not protect from disease. Voss *et al.* [2003] (**adjuvant comparison**, **variant cross-recognition or cross-neutralization**)

No. 1150
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Adjuvant:* QS21
Species (Isotype) mouse
References Cunto-Amesty *et al.* 2001
Keywords mimotopes, vaccine antigen design

- Concanavalin A binds to mannose/glucose, and binds to HIV-1. Con A was used to select peptide mimics of carbohydrates that bound to Con A, and the mimetic peptides were then used for BALB/c mouse immunization. Abs raised against the mimetic peptides binds to HIV+ cells, and could weakly neutralize T cell lab adapted strains. Cunto-Amesty *et al.* [2001] (**mimotopes**, **vaccine antigen design**)

No. 1151
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: E. Coli recombinant protein *HIV component:* gp120, gp41 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) mouse
References Li *et al.* 2002
Keywords vaccine antigen design

- A polyepitope vaccine was designed based on a recombinant GST fusion protein containing three repeats of the 2F5 core epitope ELDKWA combined with the V3 region peptide GPGRAFY. Abs raised in mice could recognize the peptides, sgp41, and CHO-WT cells that expressed HIV-1 Env on their surface. Li *et al.* [2002] (**vaccine antigen design**)

No. 1152
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Montefiori *et al.* 2003

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Keywords acute/early infection, autologous responses, escape

- AC10 is a subject who was given treatment early after infection, and had a viral rebound after cessation of therapy, which then declined to a low level. The polyclonal sera from AC10 could potently neutralize the rebound virus, and NAb escape followed with a neutralizing response against the escape variant and subsequent escape from that response. Viral loads remained low in this subject despite escape. The rebound isolate that was potently neutralized by autologous sera was not particularly neutralization sensitive, as it resisted neutralization by sCD4 and MAbs IgG1b12, 2G12 and 2F5, and was only moderately sensitive to sera from other HIV+ individuals that had high titers of NAbs to TCLA strains. Montefiori *et al.* [2003] (**autologous responses**, **acute/early infection**, **escape**)

No. 1153
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (DH012)
Epitope
Neutralizing
Immunogen HIV-1 infection, vaccine
Vector/Type: protein
Species (Isotype) chimpanzee
References Zhu *et al.* 2003
Keywords vaccine-specific epitope characteristics

- This study compares the immunogenicity of the HIV DH012 strain in chimpanzees during a natural infection with DH012 vaccinations. Naturally infected chimpanzees have sera containing potent anti-DH012 neutralization Abs, but the primary epitope is a discontinuous conformational epitope called CEV that involves the V1/V2 region, the bridging sheet, and the V3 loop. Abs that are raised upon gp120 vaccination, in contrast, are primarily against V3. DH012 has preserved the epitopes for the MAbs IgG1b12, 2G12, 17b, however natural DH012 infection in chimpanzees and DH012 gp120 vaccination in guinea pigs does not give rise to Abs against these epitopes. Zhu *et al.* [2003] (**vaccine-specific epitope characteristics**)

No. 1154
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing yes
Immunogen HIV-1 infection
Species (Isotype) human
References Aasa-Chapman *et al.* 2004
Keywords acute/early infection, autologous responses

- Neutralizing Ab responses to autologous virus envelopes were studied in four acutely HIV-1 infected, treatment-naive, homosexual men (MM1,MM2, MM4 and MM8). Detection of gp120 antibodies was rapid using ELISPOT, within a few weeks, but detection of neutralizing antibodies took between 3 and 16 months, precluding involvement of detectable NAbs with resolution of viremia. Heterologous NAb responses arose even later, by 3 months or more, suggesting gradual broadening of the immune response. Aasa-Chapman *et al.* [2004] (**autologous responses**, **acute/early infection**)

No. 1155
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (V3) (IIIB)
Epitope
Subtype B
Neutralizing yes
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, B clade MN *HIV component:* gp120 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) rabbit, guinea pig
References Berman *et al.* 1992
Keywords vaccine-specific epitope characteristics

- Abs derived from immunizations of rabbits and guinea pigs with either IIIB- or MN-gp120 were compared. Both could block gp120 binding to CD4, and this activity was strain-specific. Antisera from IIIB-rgp120 immunizations could only neutralize displayed homologous virus, while sera from MN-rgp120 rabbit vaccinations could neutralize MN 3/8 additional tested viruses. Berman *et al.* [1992] (**vaccine-specific epitope characteristics**)

No. 1156
MAb ID polyclonal
HXB2 Location Env
Author Location Env (YU-2)
Epitope
Subtype B
Neutralizing yes
Immunogen vaccine
Vector/Type: DNA with CMV promotor, DNA prime with protein boost *Strain:* B clade YU2 *HIV component:* gp140 *Adjuvant:* monophosphoryl lipid A, trehalose dicorynomycolate
Species (Isotype) mouse (IgG)
References Bower *et al.* 2004
Keywords adjuvant comparison, vaccine antigen design

- DNA vaccines encoding an uncleaved form of YU-2 gp140 stabilized with a synthetic trimerization domain isolated from the fibritin (FT) protein of the T4 bacteriophage and fused to murine C3d as a molecular adjuvant, could induce low titers of neutralizing antibodies against primary isolates HIV-1 YU-2 and HIV-1 ADA. DNA was administered by gene gun immunization to BALB/c mice, protein boost was performed by intraperitoneal injection. C3d is a component of the innate immune system that can serve as a moelcular adjuvant and had been previously shown to enhance immunogenicity. Bower *et al.* [2004] (**adjuvant comparison**, **vaccine antigen design**)

No. 1157
MAb ID polyclonal
HXB2 Location Env
Author Location Env

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Epitope
Subtype multiple
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB, A clade UG37, B clade HAN2, D clade UG21, F clade BR29 *HIV component:* gp140, gp120ΔV1, V2, and V3 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) rabbit
References Jeffs *et al.* 2004
Keywords subtype comparisons, vaccine antigen design

- A set of oligomeric envelope proteins were made from six primary isolates for potenial use as vaccine antigens: 92/UG/037 (clade A), HAN2/2 (clade B), 92/BR25/025 (clade C), 92/UG/021 (clade D), 93/BR/029 (clade F) and MVP5180 (clade O). This was one of a panel of MAbs used to explore folding and exposure of well characterized epitopes. The clade C isolate BR25 is apparently misfolded, as conformation-dependent antibodies did not bind to it. Polyclonal sera raised in rabbits against the A, B, D and F antigens, which were deemed pure enough for immunization, as well as IIIB and IIIB with the V1, V2 and V3 loops deleted, cross-bound the other antigens, so shared epitopes across clades, but none of the sera had neutralizing activity. Jeffs *et al.* [2004] (**vaccine antigen design**, **subtype comparisons**)

No. 1158
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B, CRF01_AE
Neutralizing
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade MN, B clade GNE8, E clade CM244 *HIV component:* gp120 *Adjuvant:* aluminum hydroxide
Species (Isotype) human
References Lee *et al.* 2001
Keywords assay development, subtype comparisons, vaccine antigen design, vaccine-induced epitopes

- An assay was developed that characterizes antibody binding to primary isolates, and using this system there was a correlation between binding activity and neutralization by sera from HIV-infected people and gp120 vaccinated individuals. The magnitude and breadth of oligomeric, cell surface gp120 binding Abs induced by HIV-1 subtype B vaccines was characterized. The responses in people vaccinated with mono- and bivalent rgp120 vaccines (AIDSVAX B and AIDSVAX B/B AIDSVAX B/E) indicated that increasing the number of antigens increased the cross-binding activities, in support of polyvalent vaccines. Lee *et al.* [2001] (**assay development**, **vaccine antigen design**, **vaccine-induced epitopes**, **subtype comparisons**)

No. 1159
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: gp120-MAb A32 complex *Strain:* B clade 89.6, B clade BaL *HIV component:* gp120-Mab complex *Adjuvant:* Cholera toxin (CT), Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA), Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) guinea pig
References Liao *et al.* 2004
Keywords vaccine antigen design

- A32-rgp120 complexes opened up the CCR5 co-receptor binding site, but did not induce neutralizing antibodies with greater breadth among B subtype isolates than did uncomplexed rgp120 in vaccinated guinea pigs. The vaccine that gave the greatest breadth comparing A32-rgp120 BaL, A32-rgp120 89.6, rgp120 BaL, and rgp120 89.6, was the uncomplexed rgp120 BaL, as it neutralized 9/14 B clade isolates tested (60%). Liao *et al.* [2004] (**vaccine antigen design**)

No. 1160
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (JRFL)
Epitope
Subtype B
Neutralizing yes
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade JRFL *HIV component:* gp120 *Adjuvant:* C3d fusion
Species (Isotype) humanized mouse (IgG)
References Liu *et al.* 2004
Keywords adjuvant comparison

- BALB/c mice were immunized with codon-optimized or C3d-fused DNA vaccine constructs and analyzed for their ability to elicit humoral and cell-mediated immune responses. Each strategy increased binding and gave rise to earlier appearance of neutralizing antibody respones against IIIB and MN viruses, but the combination did not act synergistcally. C3d and codon optimization also gave enhanced CD8+ T cell responses to the epitope SIHIGPGRAFYTTGE. Liu *et al.* [2004] (**adjuvant comparison**)

No. 1161
MAb ID polyclonal
HXB2 Location Env
Author Location Env (SF2)
Epitope
Subtype multiple
Neutralizing yes
Immunogen vaccine

Vector/Type: protein *Strain:* B clade SF2 *HIV component:* gp120 *Adjuvant:* aluminum hydroxide, Incomplete Freund's Adjuvant (IFA), MF59, Other
Species (Isotype) baboon
References Haigwood *et al.* 1992
Keywords adjuvant comparison, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- Baboons were given intramuscular immunization with env 2-3 SF2 (aa Ile-26 to Ala-510) or rgp120SF2. Native, glycosylated rgp120 SF2, gave a broader range of heterologous neutralizing Ab responses than denatured, non-glycosylated env 2-3 SF2. Repeated immunizations with the native rgp120 gave rise to weak but detectable NAbs against two African strains, NDK and ZR6. IFA/MTP-PE gave the highest titer antibodies.of many adjuvant combinations tested. Haigwood *et al.* [1992] (**adjuvant comparison**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **vaccine-specific epitope characteristics**)

No. 1162
MAb ID polyclonal
HXB2 Location Env
Author Location Env (89.6)
Epitope
Subtype B
Neutralizing yes
Immunogen vaccine
Strain: B clade 89.6 *HIV component:* gp140, gp160, gp160ΔV3, gp140ΔV3
Species (Isotype) macaque, mouse
References Lorin *et al.* 2004
Keywords vaccine antigen design, variant cross-recognition or cross-neutralization

- Mice susceptible to MV infection were intraperitoneally immunized with native HIV-1 89.6 env gp160 and gp140 and δV3 HIV-1 89.6 mutants expressed in live attenuated Schwarz measles vector (MV). The gp160ΔV3 construct raised more cross-reactive NAbs to primary isolates than did native gp160, and sera from the gp160ΔV3 animals neutralized SHIV 89.6, clade B strains Bx09, 92US660 and 92US714, and clade A virus 3253 but not to clade B 92HT593, at a 1:30 dilution. A HIVIG/2F5/2G12 combination was used as a positive control and could neutralize all isolates. The vaccine constructs had an additional 2F5 MAb epitope, ELDKWAS, but responses were not directed towards this epitope. Mice and macaques could raise anti-HIV responses in mice and macaques with pre-existing MV immunity. Lorin *et al.* [2004] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1163
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References McCaffrey *et al.* 2004
Keywords antibody binding site definition and exposure, vaccine antigen design

- Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The loss of the glycan within the V3 loop (GM299 V3) and adjacnt to the C-terminal end of the V3 loop (GM329 C3) increased neutralization susceptibility to both sera, but the loss of sites in C2, C4, and V5 did not alter neutralization susceptibility. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure**, **vaccine antigen design**)

No. 1164
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (HXBc2)
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: Con A-NS *Strain:* B clade HXBc2 *HIV component:* Env
Species (Isotype) macaque (IgA, IgG)
References Miyake *et al.* 2004
Keywords genital and mucosal immunity

- Intranasal immunizations of three macaques with SHIV-nanospheres (SHIV-NS) induced vaginal anti-HIV-1 gp120 IgA and IgG antibodies. After intra-vaginal challenge with SHIV KU-2, 1/3 control animals and 1/3 SHIV vaccinated animals were infected, but the SHIV vaccinated animals had low viral loads that fell to undetectable levels. After intravenous re-challenge, all animals were infected, but SHIV immunized animals had lower viral loads. Miyake *et al.* [2004] (**genital and mucosal immunity**)

No. 1165
MAb ID polyclonal
HXB2 Location Env
Author Location gp41 (HXB2)
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Opalka *et al.* 2004
Keywords assay development, assay standardization/improvement

- An antigen panel representing different regions of gp41 was generated, and sera from 23 individuals were screened. Anti-gp41 titers were very high, and sera bound to many regions of gp41, there were no immunologically silent regions. Many individuals had broad responses to diverse regions. High titer responses tended to focus on the N-heptad, C-heptad and 2F5-4E10 regions, but there was no correlation between neutralization capacity of sera and the particular peptides recognized.

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Opalka *et al.* [2004] (**assay development**, **assay standardization/improvement**)

No. 1166
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Research Contact Abraham Pinter, Public Health Research Institute, Newark, NJ, 07103. pinter@phri.o
References Pinter *et al.* 2004
Keywords variant cross-recognition or cross-neutralization

- V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neturalization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. 28 sera were tested – 24/28 sera gave greater than 90% neutralization of SF162 at dilutions of 1:180, while only 2/28 could give 90% neutralization of JRFL, and only 9/28 gave 50% neutralization at dilutions of 1:180. A chimera with SF162 V1V2 in a JRFL Env backbone was neutralization sensitive to most sera at a comparable level to SF162 Env, and in some cases the JRFL-SF162 V1V2 chimera was even more sensitive than JRFL. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)

No. 1167
MAb ID polyclonal
HXB2 Location Env
Author Location Env (gp160)
Epitope
Subtype multiple
Neutralizing
Immunogen vaccine
Vector/Type: DNA, DNA prime with protein boost *Strain:* B clade LAI, A clade 92UG031, C clade 92BR025 *HIV component:* gp160 *Adjuvant:* GM-CSF
Species (Isotype) mouse (IgG)
References Rollman *et al.* 2004
Keywords adjuvant comparison, enhancing activity, Th1, Th2, vaccine antigen design, variant cross-recognition or cross-neutralization

- Vaccination of mice with subtype B Env raised antibodies primarily against subtype B alone, while A+B+C clade Envs raised antibodies that could neutralize the autologous B, C strains, and weakly neutralize the A strain. Serum IgG responses to gp120s including all gp120 variable regions were induced in animals vaccinated with subtypes A, B and C of HIV-1 gp160 with rGM-CSF as adjuvant. Boosting with rgp160 with CpG-ODN enhanced IgG responses, shifted the Th1/Th2 to be more balanced, and these animals made both IgG and Ig2a responses and had expanded recognition of constant regions. The B clade vaccine was LAI, and the A and C clade vaccines were actually V1-V5 of the A and C strains cloned into a LAI backbone. gp41 peptides were also recognized by sera. T cell responses to the multi-clade vaccine had enhanced cross-reactive CD4 T-cell proliferative responses, but diminished gamma IFN CD8 T-cell responses. Rollman *et al.* [2004] (**adjuvant comparison**, **enhancing activity**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **Th1**, **Th2**)

No. 1168
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade IIIB *HIV component:* gp120 *Adjuvant:* C3d fusion
Species (Isotype) mouse (IgG, IgG2a)
References Toapanta & Ross 2004
Keywords adjuvant comparison, Th1, Th2

- Mice [C57BL/6 (H-2b), BALB/c (H-2d), C3H/H3 (H-2k) and CD-1 Swiss] were vaccinated DNA carrying with 2 or 3 complement C3d genes fused to secreted sgp120. Responses were enhanced with C3d, particularly in outbred mice. sgp120-C3d-DNA vaccination induced a primarily IgG1 anti-Env Ab response in inbred mouse strains, while outbred mice had mixed IgG1/IgG2a responses; similarly IL4 (Th2) T-cell responses were observed in inbred mice, and mixed IL4 and IFN gamma (Th1/Th2) responses were observed in outbred mice. An increased avidity maturation of anti-Env Abs in outbred mice was also observed. Toapanta & Ross [2004] (**adjuvant comparison**, **Th1**, **Th2**)

No. 1169
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, Protease
Species (Isotype) human (IgA, IgG)
References Wright *et al.* 2004
Keywords genital and mucosal immunity, vaccine antigen design

- HIV-1 specific responses were seldom detected after systemic or mucosal vaccination with HIV gp120 in a canarypox vector with a rgp120 boost. A limited IgA and CTL response was observed after rectal vaccination, but overall, canary pox virus

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was not an effective mucosal immunogen. Wright *et al.* [2004] (**genital and mucosal immunity**, **vaccine antigen design**)

No. 1170
MAb ID polyclonal
HXB2 Location Env
Author Location Env (735–752)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) human, rabbit
References Kennedy *et al.* 1986
Keywords assay standardization/improvement

- Rabbits intramusculary immunized with peptide KLH ("HTLV-III aa 735-752") produced peptide-specific, serum Ab responses. In an ELISA, AIDS patient derived antisera tested positive for gp41-specific Ab. Kennedy *et al.* [1986] (**assay standardization/improvement**)

No. 1171
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen HIV-1 infection, vaccine
Species (Isotype) human
References Zolla-Pazner 2004
Keywords review, vaccine antigen design

- This review summarizes neutralizing epitopes on Env and their use as vaccine antigens. Most antibodies are not neutralizing, and while some antibodies directed to conserved domains can neutralize the virus, these are generally poorly immunogenic. Variable loops do not elicit much cross-reactive neutralization, although the stem regions of these loops are more conserved so may have some promise. Polyclonal pooled sera from infected people can generally neutralize heterologous virus, suggesting that neutralizing epitopes are yet to be discovered. Polyvalent vaccine design is considered key. Zolla-Pazner [2004] (**vaccine antigen design**, **review**)

No. 1172
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing yes
Immunogen vaccine
Strain: B clade IIIB *HIV component:* gp120, gp160 *Adjuvant:* aluminum hydroxide
Species (Isotype) human, chimpanzee
References Berman *et al.* 1994
Keywords variant cross-recognition or cross-neutralization

- Antisera derived from human or chimpanzee immunized with IIIB-rgp120 showed broad cross-reactivity to HIV-1 isolates MN, IIIB, JRcsf and NY-5 (subtype B), Z6 (subtype D), A244 (subtype E)and Z321 (subtype A). Sera of IIIB-rgp120 chimpanzees cross-reacted with 6/8 V3 peptides derived from HIV-1 isolates (MN, NY5, SF2, RF, CDC4 and IIIB). Human sera only recognized 1/8 V3 peptides, HIV-1 MN. The magnitude, duration, avidity and half-life of IIIB-rgp120-specific Ab-responses were species specific. Sera derived from IIIB-rgp120-immunized humans and chimpanzees inhibited binding of both IIIB- and MN-derived rgp120 to cell-surface CD4. Berman *et al.* [1994] (**variant cross-recognition or cross-neutralization**)

No. 1173
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (V3)
Epitope
Subtype A
Neutralizing
Immunogen vaccine
Vector/Type: hepatitis B surface antigen lipoprotein particles (HsBAg) *Strain:* A clade *HIV component:* CD4BS, V3 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) mouse
References Cruz *et al.* 2004
Keywords variant cross-recognition or cross-neutralization

- Vaccinations with either the subtype A V3 consensus in a Hepatitis B carrier protein, or a multiple antigen peptide (MAP) construct (mixotope) carrying some 5000 V3s representing the diversity of subtype A V3 loops, were compared. Each was combined with a C4 peptide spanning a region involved in CD4 binding. BALB/c mice were used for immunization. The consensus V3 gave higher and more cross-reactive responses than the mixotope. The mixotope response was restricted to the most conserved region of V3, while the consensus antibodies tended to recognize heptamers representing both sides and the tip of the loop. Antibodies against the C4 region were also raised. Cruz *et al.* [2004] (**variant cross-recognition or cross-neutralization**)

No. 1174
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA with CMV promotor, modified vaccinia Ankara (MVA) *Strain:* B clade IIIB *HIV component:* gp120 *Adjuvant:* Cholera toxin (CT)
Species (Isotype) mouse (IgA, IgG, IgG1)
References Gherardi *et al.* 2004

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Keywords adjuvant comparison, genital and mucosal immunity

- Env-specific IgG and IgA Abs were detected in vaginal washings of BALB/c mice (H-2Dd) following intranasal immunization of rMVA + CT in both MVA/MVA and DNA/MVA schemes. Coadministration of CT as adjuvant resulted in an increased responses. Gherardi *et al.* [2004] (**adjuvant comparison**, **genital and mucosal immunity**)

No. 1175
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype B
Neutralizing yes
Immunogen SHIV infection
Species (Isotype) macaque
References Montefiori *et al.* 1998
Keywords variant cross-recognition or cross-neutralization

- Neutralizing antibody responses in rhesus macaques infected with SHIV variants HXB2, 89.6, and 89.6PD were studied. The SHIV infections resulted in induction of high-titer neutralizing Abs to homologous SHIV and HIV-1 strains; heterologous NAbs responses were infrequent and only detected after 40 weeks of infection. Montefiori *et al.* [1998] (**variant cross-recognition or cross-neutralization**)

No. 1176
MAb ID polyclonal
HXB2 Location Env
Author Location gp160 (IIIB)
Epitope
Subtype B
Neutralizing yes
Immunogen vaccine
Vector/Type: DNA prime with gp160 boost *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Incomplete Freund's Adjuvant (IFA), IL-12
Species (Isotype) macaque
References Rasmussen *et al.* 2002
Keywords adjuvant comparison, vaccine-induced epitopes

- DNA prime vaccinations by intradermal or gene-gun delivery were given to neonatal macaques, with or without IL-12, followed by boosting with gp160, or else gp160 was given without the DNA prime. Many of the animals had neutralizing antibodies against autologous Env, and no CTL was detected prior to challenge after DNA inoculation. Autologous SHIV-vpu+ challenge was contained in 4/15 DNA prime-gp160 boost-vaccinated macaques and in 3/4 animals only receiving gp160. Six animals that contained virus were rechallenged with autologous virus, and the virus was rapidly cleared. After an additional challenge with heterologous pathogenic SHIV 89.6P, 4/6 maintained low or limited viral infection and normal CD4 counts. Two animals gave evidence of Gag specific CTL and proliferative responses after pathogenic SHIV challenge with 89.6P, with no other evidence of infection. Rasmussen *et al.* [2002] (**adjuvant comparison**, **vaccine-induced epitopes**)

No. 1177
MAb ID polyclonal
HXB2 Location Env
Author Location gp140 (SF162)
Epitope
Subtype B
Neutralizing yes
Immunogen vaccine
Vector/Type: DNA prime with protein boost *Strain:* B clade SF162 *HIV component:* gp140, gp140ΔV2
Species (Isotype) macaque
Ab Type gp120 C5, gp120 C1-C2, gp120 CD4BS, gp120 V3, gp120 V1-V2
References Srivastava *et al.* 2003
Keywords vaccine antigen design, vaccine-induced epitopes

- Vaccination of macaques with SF162gp140 was compared with vaccination with SF162 deltaV2gp140. V1, V2, V3, CD4BS, C1 and C2 antibodies were elicited by the intact SF612, and the antibodies were able to neutralize some heterologous strains. Deletion of the V2 loop altered the response so that there was a higher ratio of CD4BS antibody made relative to V3 antibody, but did not increase overall amount of CD4BS antibodies. Antibodies against C5 were also elicited by the deltaV2 construct. Overall, the deltaV2 construct was better able to raise antibodies that could cross-neutralize heterologous strains. Using a cleaved versus fused form of gp120 altered the ratio of C1 to C5 antibodies raised, with more C5 response to the fused form. Srivastava *et al.* [2003] (**vaccine antigen design**, **vaccine-induced epitopes**)

No. 1178
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (SF2)
Epitope
Subtype B
Neutralizing yes
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade SF2 *HIV component:* gp120 *Adjuvant:* aluminum hydroxide, Incomplete Freund's Adjuvant (IFA), muramyl-dipeptide base adjuvant (Syntex)
Species (Isotype) human, baboon
References Steimer & Haigwood 1991
Keywords adjuvant comparison, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- Immunization with native glycosylated rgp120SF2 produced Abs directed against linear and conformational epitopes. Denatured, deglycosylated env2-3 (SF2) produced Abs against only linear determinants. Sera from 8/8 rgp120SF2 vs 3/8 env2-3SF2 immunized baboons cross-neutralized HIV-MN. Only 5/8 rgp120SF2 vaccinated animals had neutralizing activity against HIV-HTLV-IIIB and HIV-BRU.

B Cell

Abs from infected people who reacted with rgp120SF2 showed broad cross-neutralization of HIV-1MN, HIV- BRU, HIV-Zr6 and HIV-SF2 isolates, in comparison to env2-3(SF2)immunization, which only neutralized HIV-1 MN. Stronger neutralization potency of Ab responses was observed in baboons using Alum and MF101 as adjuvants. Steimer & Haigwood [1991] (**adjuvant comparison**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **vaccine-specific epitope characteristics**)

No. 1179
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype)
References Balzarini 2005
Keywords antibody binding site definition and exposure

- Author hypothesizes that resistance to drugs that target glycosylation sites of gp120 might stimulate deletions within the glycan shield, thus exposing novel epitopes that enhance neutralization susceptibility. Balzarini [2005] (**antibody binding site definition and exposure**)

No. 1180
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (V3)
Epitope
Subtype multiple
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V3
References Barin *et al.* 2005
Keywords acute/early infection, assay development

- A combination of 4 antigenic regions was used to differentiate between early (<180 days) and chronic infection. These regions were: p24; the gp41 peptide spanning the immunodominant epitope (IDE) of gp41, RVAVERYLKDQQLLGIWGCSGKICTTAV, and a subtype D version of this peptide; 5 V3 consensus peptides including A, B, C, D, and CRF01-AE; and Integrase. V3 and the IDE provide the best discrimination, with >20 fold higher levels in chronic infection when assayed by EIA using dried serum spots. Antibodies to Integrase and p24 were not as distinctive, and people tend to lose, not increase, responses to p24 over time. This assay can be used to identify samples from early infection with high sensitivity and specificity. Barin *et al.* [2005] (**assay development**, **acute/early infection**)

No. 1181
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype A
Neutralizing yes
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *Strain:* A clade 94UG018 *HIV component:* anchored gp120
Species (Isotype) mouse (IgA, IgG)
References Buonaguro *et al.* 2005
Keywords vaccine antigen design, variant cross-recognition or cross-neutralization

- The impact of vaccination routes was studied in BALB/c mice for clade A gp120 in VLPs. I.n. and i.p. vaccination gave a systemic and mucosal IgG and IgA response, and a CTL response. Higher specific IgA titers were detected in i.n. vaccinated mice, and CTL responses were stronger in the i.p. group. The oral route did not induce NAb responses. gp120-Env (V3 loop, TRPYNNTRQSTHIGPGQALYTTNIIGDIRQAHC) specific IgG and IgA Ab were detected at 1-2-dilution lower dilutions than p24 Abs. Neutralizing activity (>50%) against the autologous clade A Ugandan and a heterologous clade B Italian field isolate was observed. No adjuvants were used. Buonaguro *et al.* [2005] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1182
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype multiple
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* natural variants *HIV component:* gp140
Species (Isotype) rabbit
Ab Type RT thumb domain
References Dong *et al.* 2005a
Keywords vaccine antigen design, variant cross-recognition or cross-neutralization

- 2F5 recognizes the epitope ELDKWA, but does not neutralize viruses carrying the commonly found mutated epitope variants: ELDeWA, ELDsWA, ELDnWA, ELDqWA, ELDtWA, or ELnKWA. Peptide cocktails containing ELDKWA, ELnKWA, ELDeWA,and ELeKWA elicit polyclonal antibodies in rabbits that can bind to all of the natural variants that are escape variants for 2F5 expressed in gp41 via WB, as well as ELDrWA. Dong *et al.* [2005a] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1183
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype multiple
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) rabbit

References Dong *et al.* 2005a
Keywords escape, vaccine antigen design, variant cross-recognition or cross-neutralization

- 2F5 recognizes the epitope ELDKWA, but does not neutralize viruses carrying the commonly found mutated epitope, ELDeWA, ELDsWA, ELDnWA, ELDqWA, ELDtWA, or ELnKWA. Peptide cocktails containing ELDKWA, ELnKWA, ELDeWA, and ELeKWA, elicit polyclonal antibodies in rabbits that can bind to all of the natural variants that are escape variants for 2F5 expressed in gp41 via WB, as well as ELDrWA. Dong *et al.* [2005a] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **escape**)

No. 1184
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype CRF02_AG
Neutralizing no
Immunogen vaccine
Vector/Type: virus-like particle (VLP), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* CRF02 IC0928 *HIV component:* Env, Gag, Pol
Species (Isotype) macaque (IgG)
References Ellenberger *et al.* 2005
Keywords vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- Macaques were given a Gag-Pol-Env DNA prime followed by a MVA boost, comparing two DNA constructs, one that resulted mature VLPs with processed Gag (IC48) and one that had a point mutation in Gag that resulted in immature VLPs (IC1-90). Both vaccines gave antibody and T-cell responses to Env and Gag, although negligible neutralizing antibody responses were found. Autologous virus is difficult to neutralize, but the antibodies in the vaccinated macaques also did not neutralize the laboratory adapted B clade MN strain. Ellenberger *et al.* [2005] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **vaccine-specific epitope characteristics**)

No. 1185
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype A, B, C
Neutralizing P
Immunogen vaccine
Vector/Type: DNA, adenovirus *Strain:* B clade HXB2, A clade 92RW020, C clade 97ZA012 *HIV component:* gp140ΔCFI
Species (Isotype) guinea pig
Ab Type gp120 V3
References Chakrabarti *et al.* 2005
Keywords vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- Guinea pigs were immunized with a hybrid HXB2/BaL Env (HIV HXB/BaL gp140δCFI, clade B) in which the tip of the V3 loop (GPGRA) was replaced with the 2F5 epitope LELDKWAS. 2F5 bound to the Env that carried the V3-replacement 2F5 epitope, but antibodies against this construct only neutralized the X4-tropic lab adapted HIV strain IIIB, and not CCR5-HIV BaL or SF162 isolates. This immunogen, a single B clade immunogen, and a mixture of A + B + C clade envelopes, were compared. The single B clade immunogen had neutralizing activity against some B clade viruses. The A+B+C mixture was found to maintain the B clade responses, while eliciting NAbs with greater breadth when tested against a panel 19 A, B and C clade primary isolates. Chakrabarti *et al.* [2005] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **vaccine-specific epitope characteristics**)

No. 1186
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *Strain:* B clade BaL *HIV component:* Env, Gag *Adjuvant:* block copolymer CRL8623
Species (Isotype) guinea pig
References Hammonds *et al.* 2005
Keywords adjuvant comparison, vaccine antigen design

- Adjuvanted (either with a block copolymer or with a CpG aluminum hydroxide adjuvant) pseudovirions and with a recombinant gp120 boost gave significant gp120-specific NAb responses to autologous virus relative to pesudoviruses alone and to 2/5 additional primary isolates (SS1196 and Pvo) tested. Hammonds *et al.* [2005] (**adjuvant comparison**, **vaccine antigen design**)

No. 1187
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* gp120 *Adjuvant:* C3d fusion, Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) mouse (IgG)
References Koch *et al.* 2005
Keywords adjuvant comparison

- Fusion of C3d repeats and the addition of Ribi adjuvant to gp120 variant glycoprotein (gp120δC1/C5(C3d)2 enhanced gp120-specific Ab responses, but Ribi alone gave almost comparable enhancement. Thus C3d as an adjuvant may be of particular value when used alone in conditions where avoiding denaturation and preservation of the native structure is important. Koch *et al.* [2005] (**adjuvant comparison**)

No. 1188
MAb ID polyclonal

B Cell

HXB2 Location Env
Author Location gp120
Epitope
Subtype A, B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V3
References Krachmarov *et al.* 2005
Keywords antibody binding site definition and exposure, subtype comparisons, variant cross-recognition or cross-neutralization

- Sera from 23 subtype A infected individuals from Cameroon have antibodies that react strongly with subtype A and subtype B V3 loops in fusion proteins, and neutralize SF162 pseudotypes, while sera from 47 subtype B infected individuals reacted only with subtype B. The sera from Cameroon do not neutralize primary A or B isolates, due to indirect masking by the V1/V2 domain rather than due to loss of the target epitope. Krachmarov *et al.* [2005] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1189
MAb ID polyclonal
HXB2 Location Env
Author Location Env (JRFT)
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: adenovirus *Strain:* B clade JRFL *HIV component:* Gag, gp140
Species (Isotype) macaque
References Liang *et al.* 2005
Keywords vaccine antigen design, vaccine-induced epitopes

- 4/4 Mamu-A*01-negative rhesus monkeys that were vaccinated with gp140 and challenged intravenously with SHIV-89.6P produced significant neutralizing Ab titers by day 28 realtive to other challenge groups, even though no pre-challenge NAb was detected, suggesting the existance of prechallenge memory neutralizing Ab responses. The viral set point was associated with the strength of the cellular immune response to Gag and Env, but not to Tat. Liang *et al.* [2005] (**vaccine antigen design**, **vaccine-induced epitopes**)

No. 1190
MAb ID polyclonal
HXB2 Location Env
Author Location Env (MN)
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Raviv *et al.* 2005
Keywords vaccine antigen design

- Retrovirus inactivation for vaccine antigen delivery was explored through lipid modification by hydrophobic photoinduced alkylating probe 1.5 iodonaphthylazide (INA). The viral proteins were shown to be structurally intact in the treated non-infectious virus, through the preservation of antibody binding sites for polyclonal anti-gp120 serum, and for broadly neutralizing MAbs 2G12, b12 and 4E10, although the modifications of the lipid disabled viral infection. Raviv *et al.* [2005] (**vaccine antigen design**)

No. 1191
MAb ID polyclonal
HXB2 Location Env
Author Location Env (gp160)
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Bettaieb *et al.* 1992
Keywords mimics

- gp160-specific Abs were detected in platelet elutates from HIV-1 infected patients with immunologic thrombocytopenia purpura (ITP).One patient with high titer anti-gp160/120 Abs had IgG that bound specifically to both gp160/120 and to platelet GPIIb/IIIa, apparent molecular mimicry. The cross-reactive epitope on gp120 has not been defined, however a conformational aspect and/or glycosylation is likely to be involved. Bettaieb *et al.* [1992] (**mimics**)

No. 1192
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Rossi *et al.* 1989
Keywords mother-to-infant transmission

- Abs that bound to gp120 peptides were found to correlate with lack of transmission in infants less than 6 months old and born to HIV+ mothers. Maternal Abs to these same peptides were also enriched in mothers that did not transmit. Rossi *et al.* [1989] (**mother-to-infant transmission**)

No. 1193
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: fixed fusion-intermediate *Strain:* B clade US005.11, FASH isolate *HIV component:* Env
Species (Isotype) mouse
References Zipeto *et al.* 2005
Keywords co-receptor, vaccine antigen design

B Cell

- HIV-1 fusion complexes were prepared from cell lines expressing R5 HIV-1 gp120/gp41 and CD4-CCR5. Fusion complexes were prepared at different temperatures (21, 30 or 37 degrees C) with different fixative combinations, and used to immunize mice. Complexes prepared at 37 degrees were the most immunogenic, suggesting that fixation of multiple conformation intermediates may by helpful. Neutralizing Abs were raised against both R5 (strain BaL) and X4 (strain 213) viruses. Zipeto *et al.* [2005] (**co-receptor**, **vaccine antigen design**)

No. 1194
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade ADA *HIV component:* Env fragments in a pre-fusion state trimer *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) rabbit
References Qiao *et al.* 2005
Keywords antibody binding site definition and exposure, vaccine antigen design, vaccine-specific epitope characteristics

- A gp140 prefusion state trimer composed of gp41 truncated at Lys665, and gp120 C1 and C5 (topless gp140), was engineered and used to immunize rabbits. No NAbs were raised, although the polyclonal sera recognized many regions of the truncated Env. Qiao *et al.* [2005] (**antibody binding site definition and exposure**, **vaccine antigen design**, **vaccine-specific epitope characteristics**)

No. 1195
MAb ID polyclonal
HXB2 Location Env
Author Location Env (Consensus B)
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade consensus, B clade CAAN5342, B clade WITO4160 *HIV component:* Env
Species (Isotype) guinea pig
Research Contact Beatrice Hahn, University of Alabama, Birmingham, bhahn@uab.edu
References Kothe *et al.* 2007
Keywords antibody binding site definition and exposure, co-receptor, neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Four consensus B Env constructs: full length gp160, uncleaved gp160, truncated gp145, and N-linked glycosylation-site deleted (gp160-201N/S) were compared. All were packaged into virions, and all but the fusion defective uncleaved version mediated infection using the CCR5 co-receptor. DNA vaccinations of the four constructs were compared to two wildtype B clade isolates, CAAN5342 and WITO4160. The binding antibody titers elicited by the consensus proteins were 20 to 40 fold higher than to the two wildtype strains. ConB gp145 emerged as the immunogen with the greatest breadth and magnitude of responses, WITO4160 the worst. Con B gp145 and gp160 elicted significantly more potent antibodies than the wild type vaccines against a panel of easier to neutralize tier 1 viruses, but limited neutralization of tier 2 viruses was observed with any of the immunogens. Kothe *et al.* [2007] (**antibody binding site definition and exposure**, **co-receptor**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1196
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype A
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Blish *et al.* 2007
Keywords acute/early infection, neutralization, subtype comparisons

- 15 Pseudovirusus from Envs taken from subtype A infected individuals early in infection had highly variable sensitivity to autologous and heterologous plasma and to sCD4. No patterns of subtype specificity were observed in plasma pools obtained from individuals infected with subtypes A, B, C or D. The Envelopes were generally sensitive to the CCR5 inhibitors PSC-RANTES and TAK-779. Blish *et al.* [2007] (**neutralization**, **acute/early infection**, **subtype comparisons**)

No. 1197
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype A, B
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Dhillon *et al.* 2007
Keywords neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- Neutralizing Ab specificities in broadly neutralizing sera from two clade B and one clade A infected asymptomatic individuals were characterized. Broadly neutralizing activity could exclusively be assigned to the IgG fraction. Abs directed against V1, V2 and V3 and gp41 MPER epitopes were shown not to account for the neutralizing activity, and neutralization was found to result from more than one specificity. These polyspecific cross-neutralizing sera could neutralize clade A, B, C, D and CRF01 AE viruses. Dhillon *et al.* [2007] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

B Cell

No. 1198
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype C
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4i, gp41 MPER (membrane proximal external region)
References Gray *et al.* 2007a
Keywords acute/early infection, antibody interactions, autologous responses, neutralization, variant cross-recognition or cross-neutralization

- This study of 14 individuals infected with subtype C HIV-1 showed that they developed a potent autologous NAb response between 3 and 12 months of infection. The magnitude of this response was associated with shorter V1-V5 envelope lengths and fewer glycosylation sites. Very limited heterologous viral neutralization was observed during the first year of infection. Abs to CD4i epitopes were found in most patients, while MPER antibodies developed later and in fewer individuals. Abs to CD4i or MPER did not confer neutralization breadth to heterologous virus. These results suggest that strain-specific Abs target areas distinct from those targeted by cross-neutralizing Abs. Gray *et al.* [2007a] (**antibody interactions**, **autologous responses**, **neutralization**, **variant cross-recognition or cross-neutralization**, **acute/early infection**)

No. 1199
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Haim *et al.* 2007
Keywords kinetics, neutralization, variant cross-recognition or cross-neutralization

- Controlled attachment of Ab-bound HIV to cells was not affected by the presence of HIVIG. However, the virus was still efficiently neutralized indicating that binding of IgG to the cell-free virus interferes with a step of infection subsequent to cell attachment. Compared to b12, the neutralizing effect of IgG was sustained over extended time frames during the viral entry phase, significantly beyond the stage of CD4 engagement. Haim *et al.* [2007] (**neutralization**, **variant cross-recognition or cross-neutralization**, **kinetics**)

No. 1200
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype B, C
Neutralizing
Immunogen HIV-1 infection, vaccine
HIV component: mimotopes
Species (Isotype) human (IgG)
References Humbert *et al.* 2007
Keywords antibody generation, mimotopes, neutralization, rate of progression, vaccine antigen design, variant cross-recognition or cross-neutralization

- This study showed a significantly higher neutralizing Ab activity against a panel of HIV-1 isolates in LTNPs than in progressors. Random peptide phage libraries were screened with plasma IgGs from the LTNPs and 700 HIV-specific mimotopes were sequenced and analyzed for their capacity to represent conformational epitopes on the surface of gp120 using 3DEX software. Related phage groups were shown to be cross-reactive with the LTNP plasma. Immunization of mice with pools of mimotopes resulted in sera neutralizing various HIV-1 strains (D117III, JR-CSF and MH08). Humbert *et al.* [2007] (**antibody generation**, **mimotopes**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **rate of progression**)

No. 1201
MAb ID polyclonal
HXB2 Location Env
Author Location Env (SHIV SF162P4)
Epitope
Subtype B
Neutralizing L, P
Immunogen SHIV infection
Species (Isotype) macaque
References Kraft *et al.* 2007
Keywords acute/early infection, escape, neutralization, variant cross-recognition or cross-neutralization

- This study tracked neutralizing antibody development in a rhesus macaques. Homologous NAbs were developed in the majority of the animals within the first month of infection while heterologous NAb responses developed over time only in animals with sustained plasma viremia. Viral replication persisted in these animals due to viral escape, and complex quaisispecies developed over two years with mutations distributed over the envelope protein. Breadth of NAb responses was as great in two years in the macaques as is seen in HIV infected patients over 10 years. Kraft *et al.* [2007] (**neutralization**, **variant cross-recognition or cross-neutralization**, **acute/early infection**, **escape**)

No. 1202
MAb ID polyclonal
HXB2 Location Env
Author Location gp140
Epitope
Subtype A, B, C, M
Neutralizing P
Immunogen vaccine
Vector/Type: protein *Strain:* B clade JRFL, Other, B clade BaL, A clade 92RW020, C clade 97ZA012, M group Consensus *HIV component:* gp120, gp140ΔCFI, Other *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

B Cell

Species (Isotype) guinea pig
References Liao *et al.* 2006
Keywords antibody binding site definition and exposure, neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- A group M consensus envelope gene (CON-S) was designed that was central to the M group and a consensus of the consensus sequences of the major clades. The gp140δCFI protein of this virus and gp140CFI and gp140CF proteins of CON6 and other WT viruses were expressed in recombinant vaccinia viruses. The CON-S was shown to induce cross-subtype neutralizing Abs in immunized guinea pigs with greater breadth (neutralizing most A, B and C clade isolates) and titer than the WT proteins. Much of the neutralizing activity induced by CON-S Env was absorbed by the CON-S V3 peptide. Liao *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1203
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (MN)
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade MN *HIV component:* V3 *Adjuvant:* Cholera toxin (CT)
Species (Isotype) mouse (IgA, IgG, IgG1, IgG2a)
Ab Type gp120 V3-C4
References Varona-Santos *et al.* 2006
Keywords adjuvant comparison, genital and mucosal immunity, mucosal immunity, vaccine antigen design

- Mice were immunized intramuscularly and inranasaly with a synthetic C4V3 peptide carrying three HIV-1 gp120 epitopes. It was shown that this peptide could efficiently be produced in E. coli and also induce strong systemic and mucosal anti-HIV-1 specific immune responses in mice. The responses were induced without adjuvant, CT was shown to stimulate mucosal immune responses only when applied with low doses of the protein. Varona-Santos *et al.* [2006] (**adjuvant comparison**, **genital and mucosal immunity**, **vaccine antigen design**, **mucosal immunity**)

No. 1204
MAb ID polyclonal
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with protein boost *HIV component:* Other *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) rabbit, mouse
References Law *et al.* 2007
Keywords neutralization, vaccine antigen design

- High levels of gp120-specific Abs were elicited when mice and rabbits were immunized by DNA priming and protein boosting with G1 and G2 grafts, consisting of 2F5 and 4E10, and 4E10 epitopes, respectivelly, engrafted into the V1/V2 region of gp120. A consistent NAb response against the homologous JR-FL virus was detected in rabbits but not in mice. 4E10 bound to the engrafted construct, but embedding the MPER epitopes in the immunogenic V1/V2 region did not result in eliciting anti-MPER antibodies in mice or rabbits. Law *et al.* [2007] (**neutralization**, **vaccine antigen design**)

No. 1205
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with protein boost *Strain:* B clade *HIV component:* gp140, gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) rabbit (IgG)
References Reynard *et al.* 2007
Keywords acute/early infection, neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- The potential of HIV-1 acute infection Env glycomutants designed from 3D model to elicit neutralizing responses in rabbits was evaluated. Specific potential N-linked glycosylation sites were removed that rendered an Env more neutralization susceptible; these forms were then tested as immunogens in rabbits. It was shown that the protein boosts induced a strong Env-specific antibody response mainly directed against conformational epitopes. The Ab avidity increased constantly through the immunizations. For one glycomutant, the neutralization breadth was increased compared to WT. The WT used as the basis for this study was isolated from a homosexual individual with acute B clade infection. Reynard *et al.* [2007] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **acute/early infection**)

No. 1206
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype C, G
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Rong *et al.* 2007b
Keywords escape, neutralization

- Resistance to NAb in plasma from resistant donor-sensitive recipient pairs was correlated with sequence divergence in the gp120 V1-V4 region and to acquisition of length in the gp120 hypervariable domains in donor plasma. Association between nine amino acid positions in V1-V4 and Ab resistance was found, where five of the positions were located in the alpha-2 helix of the gp120 outer domain. These same 5 positions were found to be under positive selection pressure in subtype C sequences from Los Alamos Sequence Database. However, exchange of the alpha-2 helix between resistant donor and sensitive recipient Envs did not alter NAb phenotype, suggesting that positions within alpha-2 helix must be linked to other domains of Env to utilize NAb escape. Rong *et al.* [2007b] (**neutralization**, **escape**)

No. 1207
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade MN, B clade RF, Other *HIV component:* V3 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) mouse
Ab Type gp120 V3
References Eda *et al.* 2006b
Keywords antibody generation, neutralization, variant cross-recognition or cross-neutralization

- Sequental immunizations of mice with V3 peptides from clade B isolates resulted in an Ab response capable of neutralizing homo- and heterologous forms of the CXCR4-tropic HIV-1 MN and CCR5-tropic HIV-1 JR-CSF. In contrast, repeated immunizations with a single V3 peptide resulted in Ab response that neutralized only type-specific laboratory-adapted homologous viruses. A novel cross-reactive Ab was isolated and humanized, KD-247. Eda *et al.* [2006b] (**antibody generation**, **neutralization**, **variant cross-recognition or cross-neutralization**)

No. 1208
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype B, C
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Li *et al.* 2006a
Keywords acute/early infection, autologous responses, neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- This study examined the course and magnitude of autologous neutralizing Ab response during early HIV-1 infection in patients infected with subtypes B and C. It was found that subtype C infected individuals had a 3.5-fold higher IC50-titers of NAbs in plasma than subtype B infected individuals. The higher NAb titers were associated with the significantly shorter length of the HIV-1 V1-V4 regions of subtype C virus. However, despite the potency of the subtype C NAb response, the response was not found to be directed against the cross-neutralizing epitopes. The intrasubtype cross-neutralizing activity was much more prevalent in subtype B HIV-1. This indicates existence of clade-specific differences of Env-associated immunogenicity or neutralization susceptibility. Li *et al.* [2006a] (**autologous responses**, **neutralization**, **variant cross-recognition or cross-neutralization**, **acute/early infection**, **subtype comparisons**)

No. 1209
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with protein boost *Strain:* B clade YU2 *HIV component:* gp120, gp140 *Adjuvant:* C3d fusion, Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) mouse (IgG, IgG1, IgG2a, IgG2b, IgG3)
References Bower *et al.* 2006
Keywords binding affinity, neutralization, vaccine antigen design

- Mice were vaccinated with high or low dose DNA plasmids expressing Envgp120, Envgp120-mC3d, Envgp140, or Envgp40-mC3d, and boosted with trimeric Envgp140. Mice vaccinated with high dose DNA followed by trimer Envgp140 boost developed highest anti-Env titers and the broadest number of IgG isotypes. However, Envgp140 trimers did not appear to elicit higher titers of Abs that recognized conformational Env epitopes compared to Envgp120 monomers. Mice vaccinated with C3d fused envelopes had Abs with highest avidity, and Envgp140-mC3d was shown to elicit slightly higher neutralization titers for ADA and YU-2 isoaltes than Envgp120. These results indicate that although gp140 trimers are slightly more efficient at eliciting NAb than gp120, the neutralizing ability does not correlate with the induction of conformational antibodies. Bower *et al.* [2006] (**neutralization**, **vaccine antigen design**, **binding affinity**)

No. 1210
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vesicular stomatitis virus (VSV) *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse
References Jiang *et al.* 2006
Keywords neutralization, vaccine antigen design

- Mice immunized intranasally with VSV vector expressing HIV-1 HXB2 gp120 developed anti-HIV-1 response. Mouse sera was shown to be able to neutralize HXB2 and JRFL envelope-pseudotyped viruses. Jiang *et al.* [2006] (**neutralization**, **vaccine antigen design**)

No. 1211
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Cham *et al.* 2006
Keywords neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- Neutralization properties of viruses pseudotyped with Envs derived from individuals with broadly cross-reactive HIV-1 neutralizing sera (BCN) and individuals without BCN sera were examined. All the primary Env-pseudotyped viruses were neutralized by BCN sera while non-BCN sera all failed to neutralize one or more strains tested. The overall geometric mean titers of the BCN sera were higher than those of non-BCN sera. BCN and non-BCN pseudotyped viruses showed similar sensitivity to neutralization by anti-gp120 MAbs while the BCN pseudotyped viruses tended to be more sensitive to the anti-gp41 MAbs. Cham *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1212
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA, peptide *Strain:* A clade, B clade, B clade IIIB, B clade LAI, Other *HIV component:* gp160, mimotopes, Rev *Adjuvant:* cationic liposome
Species (Isotype) mouse (IgA, IgG)
References Hinkula *et al.* 2006
Keywords adjuvant comparison, genital and mucosal immunity, mucosal immunity, neutralization, subtype comparisons, vaccine antigen design

- Mice were immunized with rgp160 DNA-prime and Rev gp41 boost and a novel cationic lipid DNA (N3) was evaluated as adjuvant. It was shown that in the presence of N3 adjuvant, 10-fold less DNA was needed in the immunization to obtain serum IgG and IgA response. gp41 peptide boost in L3 adjuvant increased serum IgG and IgA titers against HIV-1 envelope and clade A, B and C peptides. In addition, the boost resulted in detectable levles of gp160-specific IgA mucosal responses. Immunized mouse serum neutralized clade A, B and C HIV-1 strains. Hinkula *et al.* [2006] (**adjuvant comparison**, **genital and mucosal immunity**, **neutralization**, **vaccine antigen design**, **mucosal immunity**, **subtype comparisons**)

No. 1213
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade *HIV component:* V3 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) guinea pig (IgG)
Ab Type gp120 V3
References Haynes *et al.* 2006
Keywords antibody generation, neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- 29 subtype B V3 peptides were designed and used for immunization of guinea pigs. The most effective peptide was of subtype B consensus sequence and induced Abs that neutralized 31% subtype B isolates but had limited cross-neutralization activity to non-B strains. This study suggests that the neutralizing breadth obtained with selected V3 immunogens is limited. Haynes *et al.* [2006] (**antibody generation**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1214
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BaL *HIV component:* gp120 *Adjuvant:* trehalose dicorynomycolate
Species (Isotype) mouse
References Abdel-Motal *et al.* 2006
Keywords neutralization, vaccine antigen design

- The immunogenicity of gp120 was increased by replacing its multiple sialic acid residues on the carbohydrate chains by alpha-gal epitopes. These epitopes are recognized by the anti-Gal Ab that targets the Ab-gp120 complexes to APC, thereby increasing the uptake of gp120 by APCs. Production of anti-gp120 Abs in mice immunized with the recombinant gp120 was 100-fold higher than the production of anti-gp120 Ab in mice immunized with gp120. Anti-gp120 Abs from mice immunized with the recombinant gp120 effectivelly neutralized HIV-1 lab strain MN while no neutralization activity was observed for Abs from mice immunized with gp120. Abdel-Motal *et al.* [2006] (**neutralization**, **vaccine antigen design**)

No. 1215
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype A, B, C, CRF01_AE
Neutralizing

B Cell

Immunogen vaccine
Vector/Type: Other *Strain:* B clade MN, B clade SF162 *HIV component:* Env, gp140ΔV2, Rev *Adjuvant:* MF59
Species (Isotype) chimpanzee
References Gómez-Román *et al.* 2006
Keywords ADCC, neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- Chimpanzees were immunized with Ad5- and Ad7-HIVenv/rev recombinant prime and gp140deltaV2 protein boost in MF59 adjuvant. The vaccine induced high titers of subtype A, B, C and CRF01_AE gp120-binding Abs. Most of the sera cross-neutralized a heterologous subtype C isolate but not other A, C and CRF01_AE isolates. The vaccine also elicited cross-clade ADCC activity against subtypes A, B, C and CRF01_AE in the majority of sera. Gómez-Román *et al.* [2006] (**ADCC**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1216
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
References Davis *et al.* 2006
Keywords kinetics, neutralization, variant cross-recognition or cross-neutralization

- Neutralization kinetics for sensitive and resistant HIV-1 clade B primary isolates were determined. The neutralization assays were varied for the time of the phase where the virus reacts with the Abs and the subsequent phase where virus-Ab is exposed to target cells. The minority of combinations showed exponentially falling titers as long as the free virions were exposed to Ab. The majority of combinations showed deviations that may be attributed to events after the virion-Ab mixture is added to target cells: significant neutralization with minimal exposure of the free virions to Ab. The neutralization of either free virion or cell-associated virus did not correlate with the resistance/sensitivity properties of primary subtype B isolates. Davis *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **kinetics**)

No. 1217
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Huber *et al.* 2006
Keywords acute/early infection, complement, neutralization, variant cross-recognition or cross-neutralization

- Complement induced lysis activity against autologous virus and a heterologous primary isolate, HIV-1 JR-FL, was shown to be higher in patients in the chronic stage of infection than in patients in the acute stage. However, plasma viral loads during the acute stage of infection were inversely correlated with the autologous complement lysis activity, suggesting that the antibody-mediated virion lysis is effective early in the course of infection. Titers of Abs to gp120 and gp41 increased with increased lysis activity, indicating that early anti-Env responses mediate complement lysis. No association between neutralization and complement lysis activity was observed, suggesting that complement lysis is predominantly caused by non-neutralizing Abs. Huber *et al.* [2006] (**complement**, **neutralization**, **variant cross-recognition or cross-neutralization**, **acute/early infection**)

No. 1218
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen SHIV infection, vaccine
Vector/Type: DNA prime with protein boost *Strain:* B clade SF162 *HIV component:* gp140, gp140ΔV2, Other *Adjuvant:* MF59
Species (Isotype) macaque
References Burke *et al.* 2006
Keywords neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Macaques were immunized with three different SF162 Env-based gp140 immunogens and challenged simultaneously with the homologous SHIV(SF162P4) and heterologous SHIV(SF33A) viruses. The immunization did not protect against infection as all animals were dually infected but it did reduce the viral replication of the homologous virus during primary infection. The immunization elicited neutralizing Ab against the homologous SF162P4 virus. Sera from animals immunized with two of the gp140 immunogens also neutralized heterologous 89.6 and HXB2 viruses while all other heterologous viruses were resistant to neutralization. Burke *et al.* [2006] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1219
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA, DNA prime with protein boost *Strain:* B clade 89.6, B clade HXB2 *HIV component:* gp140ΔCFI *Adjuvant:* Incomplete Freund's Adjuvant (IFA), IL-15, Other
Species (Isotype) rabbit, mouse (IgG, IgG1, IgG2a, IgG2b, IgG3, IgM, IgG2)
References Bolesta *et al.* 2006

B Cell

Keywords ADCC, complement, neutralization, vaccine antigen design

- Rabbits immunized with HXB2 derived gp140deltaCFI plasmid DNA with the most divergent region replaced with the corresponding sequence of 89.6 Env, and boosted with gp140deltaCFI protein developed Ab resonses. The Ab neutralizing activity was detected against homologous 89.6 virus while other HIV-1 isolates were neutralized less effectively. Mice immunized with the gp140deltaCFI construct developed IgM responses with no effect of the presence or absence of IL-15 and IL-21 in the immunization assay. In constrast, coimmunization with IL-15 and IL-21 augmented Env-specific IgG responses, where IL-15 augmented IgG2a and IgG2b responses and IL-21 augmented Env-specific IgG1 Abs. None of the cytokines affected IgG3 Ab responses. The use of IL-15 and IL-21 was also shown to increase Ab-dependent cellular cytotoxicity and complement-dependent lysis of Env-expressing target cells. Bolesta *et al.* [2006] (**ADCC**, **complement**, **neutralization**, **vaccine antigen design**)

No. 1220
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade *HIV component:* gp120 *Adjuvant:* monophosphoryl lipid A
Species (Isotype) hamster (IgG)
References Azizi *et al.* 2006
Keywords neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- Three groups of hamsters were immunized with gp120 protein cloned from subtype B infected individuals, where group 1 received gp120 from one patient, group 2 from 4 patients and group 3 from all 14 patients. Group 3 (polyvalent vaccine) plasma showed higher IgG Ab titer to HIV-1 subtype B isolates MN and SF162 than the other groups, but not to subtypes C and A/E. The polyvalent vaccine showed similar neutralizing activity against the MN strain as the 4-protein group. All vaccines failed to neutralize other primary HIV-1 isolates. Azizi *et al.* [2006] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1221
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Braibant *et al.* 2006
Keywords neutralization, rate of progression, subtype comparisons, variant cross-recognition or cross-neutralization

- Sera from HIV-1 infected long-term non-progressors were tested for neutralization activity against four heterologous primary isolates. 16% of the sera showed broadly neutralizing activity against the four strains. Cross-clade neutralization was detected in some cases but subtype-specific neutralization predominated. Braibant *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**, **rate of progression**)

No. 1222
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype C
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Gray *et al.* 2006
Keywords mother-to-infant transmission, neutralization, responses in children, variant cross-recognition or cross-neutralization

- Env-pseudotyped viruses were constructed from the gp160 envelope genes from seven children infected with subtype C HIV-1. All pseudoviruses except one were neutralized by one or both of the plasma samples tested. Gray *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **responses in children**, **mother-to-infant transmission**)

No. 1223
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein, DNA prime with protein boost *Strain:* B clade JRFL *HIV component:* gp120, Env fragments in a prefusion state trimer *Adjuvant:* QS21, Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) rabbit
References Beddows *et al.* 2007
Keywords neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Rabbits were immunized with either monomeric gp120, trimeric cleavage-defective gp140 or disulfide-stabilized soluble trimeric gp140 with both DNA-prime protein boost and protein prime protein boost immunization formats. All three proteins were shown to induce NAbs against neutralization sensitive strains with limited breadth of activity. Disulfide-stabilized protein most frequently elicited NAbs against the homologous neutralization resistant strain. These Abs were shown not to be directed at the V3 region but targeted other gp120 and non-gp120 epitopes. Beddows *et al.* [2007]

B Cell

(**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1224
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: Other *Strain:* B clade HXB2, B clade NL43 *HIV component:* Gag, gp160, Nef, Pol, Tat, Vif
Species (Isotype) macaque (IgG)
References Luckay *et al.* 2007
Keywords enhancing activity, vaccine antigen design

- Macaques immunized with various two- and three-vector pDNA designes developed serum anti-HIV Env gp120 Ab responses while gp120-specific Ab responses in four-vector group were undetectable. An increase in antibody response was observed with in vivo electroporation. Luckay *et al.* [2007] (**enhancing activity**, **vaccine antigen design**)

No. 1225
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein, virus-like particle (VLP) *Strain:* B clade ADA, B clade BH10 *HIV component:* Env, Gag, gp120, gp140, Protease, Rev, RT, Tat, Vpu *Adjuvant:* CpG immunostimulatory sequence (ISS)
Species (Isotype) mouse (IgA, IgG, IgG1, IgG2a)
References McBurney *et al.* 2007
Keywords mucosal immunity, neutralization, Th1, Th2, vaccine antigen design

- In order to determine if the form and presentation of envelope influence elicited immunity, mice were immunized with either soluble monomeric Env-gp120 or trimeric Env-gp140, or trimeric membrane-retained Env in form of VLPs. It was shown that both VLPs and soluble Envs elicited anti-Env serum Abs. However, only VLP immunized mice elicited high mucosal anti-Env Abs and Abs that blocked viral infection of neutralization-resistant viruses. In addition, VLPs elicited Abs that recognized a broader number of Env-specific peptides at higher titers. McBurney *et al.* [2007] (**neutralization**, **vaccine antigen design**, **mucosal immunity**, **Th1**, **Th2**)

No. 1226
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen SHIV infection, vaccine
Vector/Type: DNA, vaccinia, Other *Strain:* B clade 89.6, B clade 89.6P *HIV component:* complete genome, Env, Gag-Pol
Species (Isotype) macaque
References Blay *et al.* 2006
Keywords antibody binding site definition and exposure, neutralization

- Development of neutralizing Abs and changes to Env gp120 were analyzed in SHIV infected macaques during a period of 1 year. 4 macaques showed little viral divergence while the remaining 7 showed significant env divergence from the inoculum, associated with higher titers of homologous NAbs. 19 highly conserved glycosylation sites were found, of which 10 are also conserved in HIV-1 clade B. Six convergent glycosylation changes occurred independently in multiple macaques, all of which mapped to the neutralizing face of gp120 and were proximal to the CD4bs. Blay *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**)

No. 1227
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen HIV-1 infection, SHIV infection, vaccine
Vector/Type: DNA prime with protein boost *Strain:* B clade SF162 *HIV component:* gp140, gp140ΔV2, Other, gp140ΔV3
Species (Isotype) human, macaque (IgG)
Ab Type gp120 CD4i, gp120 V3, gp120 V1-V2
References Derby *et al.* 2006
Keywords antibody binding site definition and exposure, antibody generation, neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Macaques were immunized with SF162gp140, ΔV2gp140, ΔV2ΔV3gp140 and ΔV3gp140 constructs and their antibody responses were compared to the broadly reactive NAb responses in a macaque infected with SHIV SF162P4, and with pooled sera from humans infected with heterologous HIV-1 isolates. All gp140 immunogens elicited stronger anti-gp120 than anti-gp41 Abs and potent homologous NAbs primarily targeting the V1 loop. Heterologous NAb responses were weak and narrow, or non-existent. Responses from the SHIV-infected macaque and human sera generated similar amounts of anti-gp120 and anti-gp41 Abs, and heterologous NAbs which did not target the V1 loop. A gradual increase in Abs to conformational epitopes was observed in the SHIV-infected macaque, while this was not as evident in the responses to gp140 constructs. Derby *et al.* [2006] (**antibody binding site definition and exposure**, **antibody generation**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1228
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope

B Cell

Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V3
References Zolla-Pazner 2005
Keywords antibody binding site definition and exposure, review, variant cross-recognition or cross-neutralization

- This review summarizes data that indicate that the V3 region of HIV-1 may be an epitope to target for the induction of protective Abs. Data shows that the V3 region can induce broadly-reactive, cross-neutralizing Abs, that it is partially exposed during various stages of the infectious process, and that it is immunogenic. As such, it is suggested that it should constitute a prominent target of the immune response induced with an HIV vaccine. Zolla-Pazner [2005] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **review**)

No. 1229
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B, CRF01_AE
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
References Teeraputon *et al.* 2005
Keywords antibody binding site definition and exposure, neutralization, subtype comparisons

- A T-cell line adapted strain (TCLA) of CRF01_AE primary isolate DA5 (PI) was more neutralization sensitive to MAbs specific to V3, CD4bs and to CD4i epitope than the primary isolate. Mutant virus derived from the PI strain that lacked N-linked glycosylation at position 197 in the C2 region of gp120 was more sensitive to neutralization by pooled sera and MAbs then the PI strain. Deglycosylated subtype B mutants at positions 197 and 234 were significantly more sensitive to neutralization by pooled sera and F105 MAb than the parental strain. In contrast, the mutant at position 295 in V3 did not show any increase in neutralization sensitivity, although glycosylation at this site has been found to provide protection against NAbs in subtype B. This indicates that CRF01_AE viruses can use different N-linked glycosylation sites than subtype B for the protection of their neutralizing epitopes. Teeraputon *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **subtype comparisons**)

No. 1230
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade MN *HIV component:* Other *Adjuvant:* Cholera toxin (CT), Other
Species (Isotype) mouse (IgA, IgG, IgG1, IgG2a, IgM)
Ab Type gp120 V3-C4
References Esquivel-Pérez & Moreno-Fierros 2005
Keywords adjuvant comparison, antibody generation, genital and mucosal immunity, Th1, Th2

- The adjuvant effects of CT and Cry1Ac were tested by immunizations of mice with two hybrid C4/V3 peptides, differing from each other by two amino acids, either in presence or absence of the adjuvants. Immunizations were performed intranasaly or intraperitonealy. The anti-peptide Ab responses were evaluated in serum and at different mucosal sites. The Ab responses differed depending on the adjuvant used, they differed in different compartments and also depended on the immunization route. In addition, the adjuvant effect varied depending on the antigen co-administered and on the number of antigen doses. Esquivel-Pérez & Moreno-Fierros [2005] (**adjuvant comparison**, **antibody generation**, **genital and mucosal immunity**, **Th1**, **Th2**)

No. 1231
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype multiple
Neutralizing
Immunogen vaccine
Vector/Type: DNA, protein, vaccinia *Strain:* B clade, Other *HIV component:* gp120, gp140, gp41
Species (Isotype) macaque
References Zhan *et al.* 2005
Keywords neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Multi-envelope vaccine using three different delivery systems was used to immunize rhesus macaques. The vaccine elicited humoral immune responses of wide breadth in all animals, including both binding and neutralizing Abs. The elicited NAbs showed significant activities towards a variety of heterologous viruses, with exception toward viruses that were hard to neutralize in general. All animals became infected upon challenge with the heterologous SHIV 89.6, but the vaccinated animals experienced significantly lower virus titers and better CD4 T-cell control. HIV-1-specific Ab responses were far superior post-challenge in the vaccinated group compared to the pre-challenge responses in this group, and compared to control animals. Zhan *et al.* [2005] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1232
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen vaccine

Vector/Type: DNA prime with gp120 boost, protein, DNA prime with protein boost *Strain:* B clade JRFL *HIV component:* gp120, gp140 *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (Isotype) rabbit (IgG)
References Wang *et al.* 2005b
Keywords neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Serum from rabbits immunized with either gp120 or gp140 DNA vaccines showed similar sporadic neutralization of JR-FL, and neutralization of SF162, and the neutralizing activity increased following a gp120 protein boost. Env DNA alone and gp120 protein alone did not result in effective neutralization of JR-FL, but were both capable of generating Abs that neutralized the highly neutralization-sensitive SF162 strain. Wang *et al.* [2005b] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1233
MAb ID polyclonal
HXB2 Location Env
Author Location gp140
Epitope
Subtype B, D
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with vaccinia boost, DNA prime with protein boost *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA), Other
Species (Isotype) mouse (IgA, IgG1, IgG2a, IgG2b)
References Stambas *et al.* 2005
Keywords mucosal immunity, neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Immune responses were evaluated in mice successively immunized with DNA, recombinant vaccinia virus, and recombinant protein (D-V-P), and three forms of protein inoculations were analyzed: purified protein i.m. with CFA, purified protein i.n., and purified protein conjugated to oxidized mannan i.n. All three regimens elicited a diversity of Ab isotypes in serum and at mucosal surfaces, and responses were sustained for at least 12 months post-immunization. Serum and mucosal IgA responses were most prominent in mice boosted with the protein-mannan conjugate. Durable serum Abs correlated with presence of antibody forming cells in the bone-marrow of immunized mice. Sera from immunized mice showed cross-clade neutralization ability. Stambas *et al.* [2005] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **mucosal immunity**)

No. 1234
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: Other *Strain:* B clade MN *HIV component:* V3
Species (Isotype) macaque
Ab Type gp120 V3
References Someya *et al.* 2005
Keywords neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- Macaques immunized with recombinant Mycobacterium bovis expressing HIV-1 V3 antigen (rBCG Env V3) developed strong type-specific V3 NAb response with the levels of NAbs maintained for 24 weeks with no diminishment in titer. Sera from immunized animals neutralized primary HIV-1 isolates with homologous V3 sequences in vitro, but not viruses with heterologous V3 sequences nor isolates from clade A. Low-dose challenge with homologous SHIV-MN resulted in reduced viral load in rBCG Env V3 immunized animals and sterile protection in 3/5 animals. Protected animals showed higher levels of NAbs. Challenge with heterologous SHIV-89.6PD was not affected by immunizations. Someya *et al.* [2005] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1235
MAb ID polyclonal
HXB2 Location Env
Author Location Env (gp160)
Epitope
Subtype B
Neutralizing P
Immunogen vaccine
Vector/Type: adenovirus, adenovirus type 5 (Ad5) *Strain:* B clade MN *HIV component:* gp160
Species (Isotype) chimpanzee
References Peng *et al.* 2005
Keywords ADCC, neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Chimpanzees were sequentially primed with different serotypes of replicating- or nonreplicating- adenovirus/HIVEnv (Ad/HIV) recombinants, and boosted with oligomeric gp140ΔV2 protein. The replicating Ad/HIV recombinants were better at eliciting HIV-specific immune responses than the nonreplicating Ad/HIV. Replicating Ad/HIV elicited higher titers of anti-envelope binding and neutralizing Abs and induced better ADCC. A greater number of animals immunized with the replicating Ad/HIV developed NAbs against heterologous viruses. Peng *et al.* [2005] (**ADCC**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1236
MAb ID polyclonal
HXB2 Location Env
Author Location gp41
Epitope

B Cell

Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: liposome *HIV component:* gp41
Species (Isotype) mouse (IgA, IgG1, IgG2a)
References Lenz *et al.* 2005
Keywords neutralization, vaccine antigen design

- Mice were immunized with a trimeric gp41 construct comprising the env transmembrane domain and the extracellular C-terminal region (gp41ctm), either alone or incorporated into liposomes. All the mice immunized with gp41ctm-liposomes developed IgG1 and IgG2a-specific immune response against gp41ctm and 2 out of 5 mice developed low IgA responses. 3 out of 5 mice immunized with gp41ctm alone showed weak responses against gp41ctm. No significant neutralization activity could be observed in sera from either gp41ctm or gp41ctm-liposome immunized mice. Lenz *et al.* [2005] (**neutralization**, **vaccine antigen design**)

No. 1237
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade ADA *HIV component:* gp120, oligomeric gp140 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) guinea pig
References Kim *et al.* 2005
Keywords neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Guinea pigs were immunized with either trimeric recombinant gp140 or monomeric gp120, and both immunogens generated high titers of Env-specific binding Abs and equivalent titers of V3-specific binding Abs. Both immunogens also generated neutralizing Ab responses, however, these were significantly higher in sera from gp140-immunized animals. Sera from gp140-immunized animals also showed a broader neutralization of heterologous HIV-1 strains. Addition of an ADA-V3 peptide to sera from gp120-immunized animals completely blocked its neutralizing activity against ADA, while the sera from gp140-immunized animals were insensitive to ADA-V3 presence. Kim *et al.* [2005] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1238
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein, Other *Strain:* B clade YU2 *HIV component:* gp120, oligomeric gp140, gp160ΔCT *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI), monophosphoryl lipid A
Species (Isotype) rabbit (IgG)
References Grundner *et al.* 2005
Keywords neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Rabbits were immunized with monomeric gp120, trimeric gp140 (-/GCN4), and cleavage defective gp160ΔCT glycoproteins expressed on solid-phase proteoliposomes (EnvPLs). Animals immunized with trimeric gp140 (-/GCN4) expressed the greatest degree of both homologous and heterologous neutralization mainly not associated with activity against the V3 loop. The EnvPL immunizations induced Abs that had slightly less breadth of neutralization then trimeric gp140 (-/GCN4), and a slightly greater level of V3-loop directed neutralizing Abs. Monomeric gp120 induced the weakest neutralizing activity. Repeated boosting with the trimeric constructs resulted in increased neutralizing potency and increased neutralization breadth. Grundner *et al.* [2005] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1239
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA *HIV component:* gp120 *Adjuvant:* Other
Species (Isotype) mouse (IgG)
References Garzón *et al.* 2005
Keywords adjuvant comparison, mucosal immunity, vaccine antigen design

- Immunization of mice with a single inoculation of 100 microgram of gp120 DNA in complex with polyethylenimine (PEI) resulted in optimal Ab response that was similar to response in mice immunized with three doses of naked DNA. Administration of higher or lower doses of gp120-PEI resulted in lower Ab responses. Vaccination with gp120-PEI resulted in protective immune response for both mucosal and systemic challenge with a sublethal dose of recombinant vaccinia virus expressing gp120. Garzón *et al.* [2005] (**adjuvant comparison**, **vaccine antigen design**, **mucosal immunity**)

No. 1240
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype multiple
Neutralizing
Immunogen vaccine

B Cell

Vector/Type: protein *Strain:* M group Consensus *HIV component:* gp120, gp140 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) guinea pig
References Gao *et al.* 2005a
Keywords kinetics, neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Guinea pigs were immunized with a synthetic group M consensus (CON6) gp120 or gp140CF protein. Sera from both gp120 and gp140CF immunized animals were able to neutralize two subtype B primary isolates (BXO8 and SF162), but showed weak or no neutralization of other subtype B, A, C, D and CRF01_AE isolates. For the primary isolate BXO8, Abs distinct from the V3 Abs were responsible for the majority of CON6-induced neutralization activity, while the neutralizing activity for HIV MN was predominantly against the V3 loop. Sera from patients infected with HIV-1 subtypes A through G reacted well with CON6 gp120 protein, indicating preservation of cross-reactive epitopes on the CON6 protein. Gao *et al.* [2005a] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **kinetics**)

No. 1241
MAb ID polyclonal
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein, Semliki-Forest Virus *Strain:* B clade YU2 *HIV component:* gp140 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) rabbit, mouse (IgG1, IgG2a)
References Forsell *et al.* 2005
Keywords neutralization, Th1, Th2, vaccine antigen design, variant cross-recognition or cross-neutralization

- Mice immunized with two inoculations of gp140(-GCN4) protein developed consistent antibody response, while only 50% of mice immunized with three inoculations of rSFV-gp140(-GCN4) yielded antibody responses. Boosting rSFV-gp140(-GCN4) immunizations with gp140(-GCN4) protein resulted in similar end-point Ab titers as in protein-only immunized mice. Immunizations with gp140(-GCN4) resulted in an IgG1 Th2-biased response, while immunizations with rSFV-gp140(-GCN4) resulted in an IgG2a Th1-biased response. Immunizations with rSFV-gp140(-GCN4) or gp140(-GCN4) in rabbits resulted in similar neutralization Ab potency and breadth. Sera from immunized rabbits neutralized MN, HxB2 and SF162 isolates, but did not neutralize YU2, 89.6 and JR-CSF. Forsell *et al.* [2005] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **Th1**, **Th2**)

No. 1242
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with protein boost *Strain:* Other *HIV component:* gp120, gp140, gp160 *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (Isotype) rabbit, mouse (IgG)
References Doria-Rose *et al.* 2005
Keywords neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- An ancestral subtype B Env gene sequence was designed and gp160 (AN1-EnvB) and gp140 proteins were produced that were able to be recognized by anti-HIV Abs from sera derived from HIV-1 infected individuals. Mice and rabbits immunized with AN1-EnvB developed high titers of Env-binding Abs, and sera from immunized rabbits neutralized heterologous HIV-1 strains to a modest degree, and a variety of primary isolates at a low degree. The breadth and potency of Ab neutralizing capability was similar for AN1-EnvB gp160, gp140, gp120 and for the natural isolate SF162 immunized rabbits. Doria-Rose *et al.* [2005] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1243
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with gp120 boost, DNA, protein, DNA prime with protein boost *Strain:* B clade JRFL *HIV component:* gp140 *Adjuvant:* QS21, Other
Species (Isotype) rabbit
References Beddows *et al.* 2005a
Keywords neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- gp120 antibody responses in rabbits immunized with a soluble, cleaved trimeric gp140 (SOSIP gp140) were three-fold lower than those elicited with gp120 monomer immunization, but were somewhat higher than Ab responses elicited by priming with membrane-bound SOSIP gp140. The strongest neutralization of HIV-1 MN was seen with sera from animals immunized with soluble SOSIP gp140 prime and boost, and corresponded to responses seen by gp120 boosting. NAb were also induced against primary JR-FL strain, but only after extended immunizations. The ability of rabbit sera to neutralize heterologous strains of subtype B was modest, and no neutralization was observed for subtype A and C viruses. Beddows *et al.* [2005a] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1244
MAb ID polyclonal
HXB2 Location Env

B Cell

Author Location gp140
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade R2 *HIV component:* gp120, oligomeric gp140 *Adjuvant:* AS02A (oil-in-water emulsion, 3D-monophosphoryl lipid A, QS21)
Species (Isotype) rabbit (IgG)
References Zhang *et al.* 2007
Keywords neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Sera from rabbits immunized with either soluble oligomeric gp140 or gp120, both from the R2 subtype B strain, and both with adjuvant AS02A, showed broad cross-neutralizing activity. 20% of tested HIV-1 strains were neutralized by IgG Abs induced by immunizations with gp120, while gp140 immunizations induced cross-reactive neutralization of all the strains tested, including A, B, C, D, H, F, CRF01_AE, CRF11_cpx and CRF06cpx. Levels and affinities of the most extensively cross-reactive Abs induced by gp140 continued to increase throughout the immunization regimen. Zhang *et al.* [2007] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1245
MAb ID polyclonal
HXB2 Location Env
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (Isotype) human (IgG)
References Wilflingseder *et al.* 2007
Keywords complement, dendritic cells

- In contrast to HIV coated with complement fragments (C-HIV), HIV coated with HIV-specific IgG in the absence (IgG-HIV) or in the presence of complement coating (C-IgG-HIV) showed significantly impaired infection and provirus formation in dendritic cells. These dendritic cells were also unable to promote long-term transmission of HIV to susceptible T cells. Wilflingseder *et al.* [2007] (**complement**, **dendritic cells**)

No. 1246
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade YU2 *HIV component:* gp140 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI), Other
Species (Isotype) guinea pig (IgG)
References Li *et al.* 2006d
Keywords adjuvant comparison, neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Guinea pigs were immunized with monomeric gp120 or trimeric gp140 proteins in adjuvants Ribi or GlaxoSmithKline (GSK) family of adjuvants AS01B, AS02A and AS03. gp140 elicited higher-titer neutralizing Abs against homo- and heterologous isolates than gp120. GSK adjuvants induced higher level of neutralizing Abs than Ribi for both gp120 and gp140. Homologous neutralization activity of gp120 was V1-focused while gp140-immunized sera was not and neutralized heterologous isolates more eficiently. Li *et al.* [2006d] (**adjuvant comparison**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1247
MAb ID polyclonal
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41 MPER *Adjuvant:* aluminum hydroxide, Cholera toxin (CT)
Species (Isotype) mouse (IgA, IgG, IgG1, IgG2a)
References Matoba *et al.* 2006
Keywords adjuvant comparison, genital and mucosal immunity, immunodominance, mucosal immunity, vaccine antigen design

- Mice were immunized with a fusion protein consisting of cholera toxin B (CTB) and the MPR of gp41 ectodomain peptide in the presence or absence of adjuvant and through different prime-boost routes. It was shown that mucosal priming with CT adjuvant followed by systemic boosting induced best response of vaginal IgA and serum IgG Abs specific to MPR-peptide. Systemic priming with boost induced strong serum anti-MPR IgG responses but was less effective in inducing secretory anti-MPR IgA. Co-immunization with CT mucosal adjuvant resulted in higher proportion of IgG2a while its absence skewed the Ab responses towards IgG1. Matoba *et al.* [2006] (**adjuvant comparison**, **genital and mucosal immunity**, **vaccine antigen design**, **immunodominance**, **mucosal immunity**)

No. 1248
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: canarypox *Strain:* B clade LAI, B clade MN, B clade GNE8 *HIV component:* Gag, gp120, gp41, Nef, Protease *Adjuvant:* aluminum hydroxide
Species (Isotype) human
References McFarland *et al.* 2006
Keywords mother-to-infant transmission, neutralization, responses in children, vaccine antigen design

B Cell

- HIV-1-negative infants born to mothers infected with HIV-1 were immunized with the ALVAC-HIV-1 vaccine (1452) alone or in combination with rgp120 vaccine. Both vaccines induced gp120-specific binding serum Abs distinguishable from maternal Abs. In 50% of the 1452+gp120-immunized subjects neutralizing activity to homologous strain was observed, indicating that young infants can generate functional HIV-1 specific Abs active against homologous virus in response to HIV-1 vaccine. McFarland *et al.* [2006] (**neutralization**, **vaccine antigen design**, **responses in children**, **mother-to-infant transmission**)

No. 1249
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Pan *et al.* 2006
Keywords acute/early infection, assay development, neutralization

- A neutralization test was used to detect early Abs to native gp41/160 in sera from 12 high-risk patients. The neutralization test detected early HIV-1 IgG Abs in the sera of 10 of 12 patients while the EIA and WB tests that use denatured antigens missed the early diagnosis in 12 of 13 patients, indicating that native HIV antigens can detect polyclonal HIV neutralizing Abs earlier than currently available tests. Pan *et al.* [2006] (**assay development**, **neutralization**, **acute/early infection**)

No. 1250
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype C
Neutralizing
Immunogen vaccine
Strain: Other *HIV component:* gp120
Species (Isotype) human (IgG, IgM)
References Sheppard *et al.* 2007a
Keywords complement, neutralization

- Patients immunized with NYVAC expressing clade C gp120 developed Env-specific IgG and IgM in 60% of the cases. The serum sample with highest IgM titre but undetectable IgG neutralized the homologous isolate indicating that vaccine-induced IgM may have antiviral activity. Sheppard *et al.* [2007a] (**complement**, **neutralization**)

No. 1251
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: Other *HIV component:* mimotopes
Species (Isotype) guinea pig (IgG, IgM)
References Kusov *et al.* 2007
Keywords neutralization

- Marmosets infected with a chimeric hepatitis A virus carrying dominant gp41 epitope 2F5 at the surface developed both anti-HAV and anti-2F5 epitope immune response. A weak HIV-neutralizing antibody response was detected in guinea pigs immunized with the HAV-gp41 particles. Kusov *et al.* [2007] (**neutralization**)

No. 1252
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* Other *HIV component:* gp120
Species (Isotype) mouse
References Chen *et al.* 2007a
Keywords vaccine antigen design

- 2 glycosylation site additions to asparagines 295 and 392 on the clade C gp120 backbone (gp120CN54+) were used to reconstruct the 2G12 epitope. Mice were immunized with gp120CN54+, with an Fc tagged gp120CN54+ (gp120CN54+-Fc) and with an Fc tagged outer domain of gp120CN54+ (ODCN54+-Fc). Both Fc tagged proteins elicited significant gp120 titers while gp120CN54+ was very poorly immunogenic. The serum response for ODCN54+-Fc showed a predominant anti V3C3 response. (**vaccine antigen design**)

No. 1253
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Sheppard *et al.* 2007b
Keywords antibody interactions, binding affinity

- Polyclonal HIV Ig and polyclonal serum ARP422 were used in the analysis of clade C gp140 (97CN54) antigenicity and were shown to bind to this molecule. Binding of these Abs was not significantly affected by Abs N3C5 or N03B11. Sheppard *et al.* [2007b] (**antibody interactions**, **binding affinity**)

No. 1254
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with protein boost *Strain:* B clade, B clade NL43, Other, B clade BaL *HIV component:* Env, Gag *Adjuvant:* QS21

B Cell

Species (Isotype) macaque
References Pal *et al.* 2006
Keywords neutralization, SIV, subtype comparisons, variant cross-recognition or cross-neutralization

- Macaques immunized with DNA-prime encoding Env and Gag from multiple HIV-1 subtypes developed persistent level of gp120-binding Abs markedly enhanced following gp120 protein-boost. Although gene gun admnistration of the DNA-prime elicited higher Abs than the ID administration, the Ab responses became comparable in both routes of administration after the protein boosts. The macaque-sera neutralizied homologous and to a lesser degree heterologous HIV-1 isolates. 4 of 6 animals were protected against infection following SHIV challenge while two showed reduced viral load. Pal *et al.* [2006] (**neutralization**, **SIV**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1255
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse (IgG)
References Ponomarenko *et al.* 2006
Keywords antibody generation, assay development

- Pathogen-free SJL mice susceptible to experimental autoimmune encephalomyelitis were immunized with gp120 fused with encephalitogenic peptide MBP. Polyclonal IgGs were induced in mice with the ability to degrade gp120. A dominant proteolysis site in gp120 was demonstrated and the sequence surrounding this site is present in nearly half of the HIV-1 variants. Ponomarenko *et al.* [2006] (**antibody generation**, **assay development**)

No. 1256
MAb ID polyclonal
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Rey-Cuillé *et al.* 2006
Keywords antibody binding site definition and exposure, HIV-2, optimal epitope

- It is shown that anti-CBD (calveolin binding domain) antibodies are directed against the conserved calveolin-1 binding motif WNNMTWMQW in the CBD1 epitope of the gp41 region of HIV-1. However, anti-CBD1 Abs do not react with the CBD2 peptide corresponding to the CBD in HIV-2. This is suggested to be because of the presence of a proline residue upstream of the CBD in HIV-2 that might affect the presentation of the CBD motif. Rey-Cuillé *et al.* [2006] (**antibody binding site definition and exposure**, **HIV-2**, **optimal epitope**)

No. 1257
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype A
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Sagar *et al.* 2006
Keywords acute/early infection, autologous responses, escape, neutralization

- It was shown that V1-V2 loops of sequences isolated during chronic infection were significantly longer and had significantly higher number of potential N-linked glycosylation sites than sequences isolated early in infection. Pseudotyped viruses with V1-V2 sequences from early infection showed higher neutralization sensitivity to autologous plasma samples than pseudotyped viruses with V1-V2 from chronic infection, suggesting that changes in V1-V2 contribute to Ab escape. No difference was observed in neutralization sensitivity of early and chronic infection viruses to heterologous plasma. Sagar *et al.* [2006] (**autologous responses**, **neutralization**, **acute/early infection**, **escape**)

No. 1258
MAb ID polyclonal
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide in liposome *Strain:* Other *HIV component:* gp41 *Adjuvant:* liposome, Other
Species (Isotype) rabbit (IgG, IgG1, IgG2a, IgG2b, IgG3)
References Singh & Bisen 2006
Keywords adjuvant comparison

- Rabbits were immunized with liposomes bearing gp41 epitopes and gp41 epitopes + PEG on the surface, as well as with free antigenic epitope. The free epitope was unable to elicit an immune response while liposomes carrying gp41 epitopes elicited a gp41-specific Ab response. The immune response was further enhanced by liposomes carrying gp41 epitopes and protected by PEG by increasing the Ab titer and extending the persistence of the Abs. The isotypic distribution of IgG1:IgG2a ratio was shown to be 1:2.5 while no detectable levels of IgG2b and IgG3 were found. Singh & Bisen [2006] (**adjuvant comparison**)

No. 1259
MAb ID polyclonal
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG, IgM)
References Vieillard *et al.* 2006

- Antibodies against the 3S motif (anti-3S Abs) from the gp41 were detected in 28.5% of HIV-1 infected patients. Anti-3S Abs were positively correlated to CD4 cell counts and inversely correlated to the expression of NKp44L. Inhibition of lysis of CD4 NKp44L cells by NK cells was observed in relationship to anti-3S Ab titers. It is suggested that these Ab can affect disease course by inhibiting CD4 sensitivity to NK lysis. Vieillard *et al.* [2006]

No. 1260
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: formaldehyde-fixed whole-cell *Strain:* B clade *HIV component:* gp120, gp41
Species (Isotype) mouse
References Zipeto *et al.* 2006
Keywords neutralization

- Mice were immunized with fusion complexes of co-cultivated CHO cells expressing CD4-CCR5 and gp120/gp41 produced at diffrent temperatures and fixative combinations. It was shown that fusion complexes prepared at 21, 30 or 37 degrees C were immunogenic and induced neutralizing Abs against heterologous isolates, however, complexes prepared at 37 degrees C were more immunogenic and induced higher titers of NAbs. The fixative used was shown not to affect the NAb titer except for the ineffective glutaraldehyde. Zipeto *et al.* [2006] (**neutralization**)

No. 1261
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype A, B, C, CRF01_AE, D, F, G
Neutralizing
Immunogen HIV-1 infection, vaccine
Vector/Type: DNA prime with protein boost *Strain:* A clade, B clade, Other, C clade 92BR025 *HIV component:* gp120 *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (Isotype) rabbit (IgG)
References Wang *et al.* 2006a
Keywords neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- Rabbits immunized with DNA vaccines expressing one, three or eight primary HIV-1 isolates from different clades followed by gp120 protein boost developed substantial levels of Ab responses against gp120. Neutralization assays against primary isolates of clades A, B, C, D and E showed that the rabbit sera neutralized 7 of 10 and 12 of 14 viruses in the assays. Sera immunized with polyvalent Envs were able to neutralize a significantly higher percentage of viruses than the monovalent vaccine. Wang *et al.* [2006a] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1262
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA, adenovirus type 5 (Ad5) *Strain:* Other, B clade BaL, A clade 92RW020, C clade 97ZA012 *HIV component:* gp140ΔCFI
Species (Isotype) guinea pig
References Wu *et al.* 2006
Keywords neutralization, subtype comparisons, vaccine antigen design

- Guinea pigs were immunized with chimeric immunogens prepared from different clades of HIV-1 with modifications in variable regions. It was observed that the V3-specific neutralization activity induced by a clade B immunogen was limited to clade B viruses and was blocked by clade B V3 peptide but not by clade A and C peptides. The V3 region of clade C was shown to elicit Abs that neutralized some clade A, B and C isolates, suggesting that immunization with clade C V3 might induce more cross-reactive Abs than with subtype B. A V1-specific immune response was described that might be partially responsible for strain-specific neutralization responses. Wu *et al.* [2006] (**neutralization**, **vaccine antigen design**, **subtype comparisons**)

No. 1263
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with protein boost *Strain:* B clade SF162 *HIV component:* gp120, gp140, gp140ΔV2, Other
Species (Isotype) rabbit
References Sharma *et al.* 2006
Keywords antibody binding site definition and exposure, vaccine antigen design

- Plasmids containing gp120 (monomer), gp120deltaV2 (trimer), gp140 (monomer) and gp140deltaV2 (trimer) from subtype B SF162 were constructed and rabbits were immunized. Animals primed with gp140 and gp140deltaV2 induced a higher proportion of Abs directed towards conformational epitopes while animals primed with gp120deltaV2 induced highest Ab titers towards linear V3 epitopes. Sharma *et al.* [2006] (**antibody binding site definition and exposure**, **vaccine antigen design**)

No. 1264
MAb ID polyclonal
HXB2 Location Env
Author Location

B Cell

Epitope
Subtype C
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Li *et al.* 2006c
Keywords acute/early infection, neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- Subtype C env-pseudotyped viruses were obtained from individuals in acute/early stage of HIV-1 infection with subtype C. Each clone was broadly sensitive to neutralization by individual subtype C plasma samples and by subtype-specific plasma pools but the level of sensitivity was lower than that of MN and SF162.LS. The sensitivity of the clones was also greater to neutralization by subtype C plasma pool than to plasma pools of subtypes A, B and D. Li *et al.* [2006c] (**neutralization**, **variant cross-recognition or cross-neutralization**, **acute/early infection**, **subtype comparisons**)

No. 1265
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Pantophlet & Burton 2006
Keywords antibody binding site definition and exposure, antibody generation, review, structure, variant cross-recognition or cross-neutralization

- This review describes the strucural organization and topological features of gp120 as well as its molecular structure. Furthermore, it describes different viral defense mechanisms for Ab evasion, binding sites and Ab epitopes on gp120, and different antigen design strategies used to elicit cross-neutralizing anti-gp120 Abs. Pantophlet & Burton [2006] (**antibody binding site definition and exposure**, **antibody generation**, **variant cross-recognition or cross-neutralization**, **review**, **structure**)

No. 1266
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Yang *et al.* 2006
Keywords binding affinity, neutralization

- An Ab against an artificial FLAG epitope inserted in the V4 region of three HIV-1 strains with different neutralization sensitivities was shown to inhibit all three viruses equivalently. Viruses bearing inserted artificial epitopes of FLAG in the V4 region were as sensitive to neutralization by IgG as the parental viruses, which exhibited following senstitivity to neutralization; HXBc2>JR-FL>YU2. A clear relationship between neutralization potency and the affinity of the anti-FLAG antibody for its cognate epitope was observed. Yang *et al.* [2006] (**neutralization**, **binding affinity**)

No. 1267
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade 89.6 *HIV component:* gp41, Other
Species (Isotype) mouse (IgG)
References Ye *et al.* 2006
Keywords antibody generation, neutralization, vaccine antigen design

- Mice were immunized with a DNA vaccine encoding HA/gp41 chimeric protein. Significant levels of Ab response against gp41 was induced in all mice. The sera from immunized mice were able to neutralize SF162 pseudoviruses, however, at low levels. The HA/gp41 chimeric protein was shown to form trimers on cell surfaces and does not form post-fusion six-helix bundle structure which may make it more effective in eliciting neutralizing Ab. Ye *et al.* [2006] (**antibody generation**, **neutralization**, **vaccine antigen design**)

No. 1268
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgA, IgG)
References Yuste *et al.* 2006
Keywords neutralization, SIV

- Epitope recognition sequences for Abs 2F5 and 4E10 were introduced into the corresponding region of SIVmac239. SIVmac239/4E10 was neutralized by a LTNP plasma. IgG and IgA were purified from the LTNP plasma but either failed to neutralize SIVmac239/4E10 virus (IgG) or modestly neutralized it (IgA) suggesting that a majority of the neutralizing activity does not appear to be Ab mediated. Yuste *et al.* [2006] (**neutralization**, **SIV**)

No. 1269
MAb ID polyclonal
HXB2 Location Env
Author Location gp160
Epitope
Subtype B
Neutralizing
Immunogen vaccine

B Cell

Vector/Type: protein, virus-like particle (VLP) *Strain:* B clade ADA, B clade HXB2, B clade JRFL, B clade SF162, B clade BaL *HIV component:* gp120, gp160, gp160ΔCT *Adjuvant:* CpG immunostimulatory sequence (ISS), QS21

Species (Isotype) guinea pig
References Crooks *et al.* 2007
Keywords adjuvant comparison, neutralization, vaccine antigen design

- Guinea pigs were immunized with three types of VLPs containing disulfide-shackled functional trimers (SOS-VLP), uncleaved nonfunctional Env (UNC-VLP), naked VLP bearing no Env, and also with gp120 protein alone. SOS- and UNC-VLPs elicited anti-gp120 Abs focused primarily on the nonfunctional forms of Env, the V3 loop and the gp120 coreceptor binding site, possibly on gp120/gp41 monomers and not trimers. Some of the VLP sera from the immunized animals neutralized primary isolates at modest titers. Non-Env specific Abs in the sera were found to be able to nonspecifically neutralize the virus, and even enhance infection. Crooks *et al.* [2007] (**adjuvant comparison**, **neutralization**, **vaccine antigen design**)

No. 1270
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BaL *HIV component:* gp120, Other *Adjuvant:* QS21
Species (Isotype) macaque
Ab Type gp120 CD4i
References DeVico *et al.* 2007
Keywords binding affinity, neutralization, vaccine antigen design

- Macaques were immunized with either CD4, gp120, cross-linked gp120-human CD4 complex (gp120-CD4 XL), and with single chain complex containing gp120 rhesus macaque CD4 domains 1 and 2 (rhFLSC). Animals immunized with rhFLSC showed accelerated decline and clearance of plasma viremia, and absence of viremia in tissue. The control of viral replication correlated with relatively stronger anti-CD4i epitope responses. When these animals were challenged with SHIV162P3, the anti-CD4 epitope responses were boosted. Animals immunized with gp120-CD4 XL raised anti-CD4 epitope responses less efficiently then rhFLSC animals, and failed to control infection. Neutralization activity against HIV731A/V434M was detected in three out of four rhFLSC immunized macaques, and in two out of four gp120-CD4 XL immunized macaques. The control of infection did not correlate with neutralization activity. DeVico *et al.* [2007] (**neutralization**, **vaccine antigen design**, **binding affinity**)

No. 1271
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype)
References Blish *et al.* 2008
Keywords antibody binding site definition and exposure, escape

- This study explored features of Env that would enhance exposure of conserved HIV-1 epitopes. The changes in neutralization susceptibility, mediated by two mutations, T569A (in the HR1) and I675V (in the MPER), were unparalleled in their magnitude and breadth on diverse HIV-1 Env proteins. The variant with both TA and IV mutations was >360-fold more susceptible to 2F5, >180-fold more susceptible to 4E10, 2.8-fold more susceptible to b12, >780-fold more susceptible to sCD4 and resulted in 18-fold enhanced susceptibility to autologous plasma and >35-fold enhanced susceptibility to the plasma pool. Blish *et al.* [2008] (**antibody binding site definition and exposure**, **escape**)

No. 1272
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Strain: B clade SF162 *HIV component:* gp140
Species (Isotype) macaque
References Ching *et al.* 2008
Keywords neutralization

- The study explores how the V1 loop of Env influences the neutralization susceptibilities of heterologous viruses to antibodies elicited during immunization of macaques with the SF162gp140 immunogen. Generally, when the V1 loop of the heterologous isolates was replaced by the V1 loop present on the DF162go140 immunogen, these isolates became highly susceptible to neutralization, indicating that the V1 loop as expressed on the surface of virion-associated Env trimers plays a major role in the resistance of heterologous viruses to neutralization by gp140-elicited NAbs. Ching *et al.* [2008] (**neutralization**)

No. 1273
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Bunnik *et al.* 2008
Keywords acute/early infection, autologous responses, escape

B Cell

- Autologous NAb responses were studied in 5 typical R5 progressors in relation to viral NAb escape and molecular changes in the viral envelope (Env) in the period from seroconversion until 5 after AIDS diagnosis. Particularly early in infection, NAbs had a large effect on the evolution of Env. Reversion of NAb-induced changes was observed late in infection in the face of declining neutralizing immunity, suggestive of an effect of these changes on the viral fitness. Bunnik *et al.* [2008] (**autologous responses**, **acute/early infection**, **escape**)

No. 1274
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Hu *et al.* 2007
Keywords escape, neutralization

- HIV-1 env clones resistant to cyanovirin (CV-N), a carbohydrate binding agent, showed amino acid changes that resulted in deglycosylation of high-mannose type residues in the C2-C4 region of gp120. These viruses demonstrated significantly enhanced sensitivity to IgG pooled from HIV-1 infected individuals compared to the wildtype virus, indicating that high-mannose depletion in CV-N escape viruses may increase exposure of neutralization epitopes on gp120. Hu *et al.* [2007] (**neutralization**, **escape**)

No. 1275
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Laakso *et al.* 2007
Keywords neutralization

- V3 loop deletions were introduced into three different primary HIV-1 strains: R3A, DH12, and TYBE. The deletions included: ΔV3(12,12) containing the first and the last 12 residues of the V3 loop, ΔV3(9,9) containing first and last 9 residues, and ΔV3(6,6) ontaining first and last 6 residues. Only HIV-1 R3A ΔV3(9,9) was able to support cell fusion. Passaging of this virus resulted in a virus strain (TA1) that replicated with wildtype kinetics, and that acquired several adaptive changes in gp120 and gp41 while retaining the V3 loop truncation. TA1 was efficiently neutralized by four different HIV positive human sera, in contrast to R3A, which was neutralized inefficiently. Virions bearing a V1/V2 truncation were neutralized by three out of four human sera. Laakso *et al.* [2007] (**neutralization**)

No. 1276
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Li *et al.* 2007b
Keywords antibody binding site definition and exposure, neutralization

- 32 human HIV-1 positive sera neutralized most viruses from clades A, B, and C. Two of the sera stood out as particularly potent and broadly reactive. A fraction of Abs from the two sera were directed against the functionally conserved CD4-binding site of gp120. These Abs were able to neutralize viruses partially or fully resistant to neutralization by b12, indicating that novel Abs to the CD4-binding site are elicited in some HIV-1 infected individuals. Li *et al.* [2007b] (**antibody binding site definition and exposure**, **neutralization**)

No. 1277
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* Other *HIV component:* gp120
Species (Isotype)
References Forsman *et al.* 2008
Keywords neutralization, variant cross-recognition or cross-neutralization

- Two llamas were immunized with recombinant gp120 from the CRF07_BC primary isolate CN54. Llamas produce heavy chain Abs devoid of light chains (VHH), and it was hypothesized that the small size of the VHH, in combination with their protruding CDR3 loops, and their preference for cleft recognition and binding into active sites, may allow for recognition of conserved motifs on gp120 that are occluded from conventional Abs. Antienvelope Abs were present in serum samples from both animals, and weak neutralization activity against HIV-1 subtype C was observed in serum and plasma from one of the animals. Forsman *et al.* [2008] (**neutralization**, **variant cross-recognition or cross-neutralization**)

No. 1278
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide, protein *Strain:* B clade YU2 *HIV component:* gp120
Species (Isotype) rat (IgG)
References Martin *et al.* 2008
Keywords assay development, variant cross-recognition or cross-neutralization

B Cell

- A new purification method was developed using a high affinity peptide mimicking CD4 as a ligand in affinity chromatography. This allowed the separation in one step of HIV envelope monomer from cell supernatant and capture of prepurified trimer. The miniCD4-purified gp120 was used to immunize rats and was shown to induce Ab directed against the HIV envelope. IgG purified from rat sera recognized envelope monomers from subtypes B and C but were less efficient in recognizing gp140 trimers from subtypes B, C and F. Martin *et al.* [2008] (**assay development**, **variant cross-recognition or cross-neutralization**)

No. 1279
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen SHIV infection
Species (Isotype) macaque
References Tasca *et al.* 2008
Keywords co-receptor, neutralization

- The neutralization profile of early R5, intermediate R5X4, and late X4 viruses from a rhesus macaque infected with SHIV-SF162P3N was assessed. The early R5 and the intermediate R5X4 viruses were equally sensitive to neutralization with Abs present in the R5 SHIV serum. The parental R5 virus was resistant to neutralization with serum Abs from an X4 SHIV-infected macaque, while the R5X4 virus was efficiently neutralized, and the final X4 virus was the most neutralization sensitive of all. The dual-tropic R5X4 viruses from the macaque were found to be temporal, evolutionary, functional, and antigenic intermediates in the pathway to coreceptor switch in rhesus macaques. Tasca *et al.* [2008] (**coreceptor**, **neutralization**)

No. 1280
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype B, C
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgA, IgG, IgM)
Ab Type gp120 CD4BS, gp120 CD4i, gp120 V3, gp41 MPER (membrane proximal external region)
References Tomaras *et al.* 2008
Keywords acute/early infection, antibody generation, autologous responses, complement

- To investigate B-cell responses immediately following HIV-1 transmission, env-specific Ab responses to autologous and consensus Envs in plasma donors were determined. The first detectable B-cell response was in the form of Ab-virus immune complexes 8 days after T0 (plasma virus detection), while the first free plasma IgG anti-HIV-1 Ab was to gp41 and appeared 13 days after T0. gp120-specific Abs appeared 28 days after T0 and were mainly directed to the V3 loop. Abs against p24 and p55 appeared 18 days after T0, Abs against p66 appeared 21 days after T0, and Abs against p17 and p31 appeared 33 and 53 days after T0, respectively. Abs that did not appear within 40 days after T0 were anti-MPER, CD4bs, and CD4i Abs. As with IgG responses, the first IgM Ab targeted gp41 and appeared 13 days after T0. IgM anti-gp41 was detected at the same time as IgG and IgA anti-gp41 Abs. IgM responses were transient and decayed over a period of 20 to 40 days while IgG responses rose over the same period. Anti-gp41 Env Abs were also found to activate complement. In a cohort of patients from Trinidad and Tobago (subtype B), CD41, CD4bs, and cluster II MPER Abs arose 5-10 weeks postenrollment into the acute infection study. Tier 1 neutralizing Abs appeared 8 weeks after infection and were primarily V3-directed. Autologous neutralizing Abs arose 32 weeks after infection in the clade B cohort, and 19 weeks after infection in a subtype C patient cohort. The early Abs were shown to have little functional consequence for the control of viremia. Tomaras *et al.* [2008] (**antibody generation**, **autologous responses**, **complement**, **acute/early infection**)

No. 1281
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype A, B, C
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgA, IgG)
Ab Type gp120 V1-V2
References Granados-Gonzalez *et al.* 2008

- The study evaluated the influence of glycosylation within the V1/V2 domain on antibody recognition. Recombinant proteins, demonstrated to be folded in native conformation, were produced following transfection of CHO cells by plasmids expressing V1/V2 domains from primary isolates of different clades. From a cohort of HIV-seropositive patients, serum IgA and IgG and SIgA antibodies with anti-V1/V2 specificity demosntrated a good recognition of these recombinant proteins that were dependent on glycosylation. Declycosylation of the recombinant proteins increased the reactivity of the serum IgG to the clade A and C but not to clade B V1/V2 domain. Granados-Gonzalez *et al.* [2008]

No. 1282
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype multiple
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Chong *et al.* 2008
Keywords neutralization, subtype comparisons

- The goal of the study was to measure NAb responses in patients infected with HIV-1 prevalent subtypes in China. g160 genes from plasma samples were used to establish a pseudovirus-based neutralization assay. 43 HIV-1 positive samples, comprising BC, B and AE subtypes, were tested with subtype BC,B and AE pseudoviruses. There were significant differences in the cross-neutralization activities between subtypes. Chong *et al.* [2008] (**neutralization**, **subtype comparisons**)

No. 1283
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype B, C
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with Ad5 boost *Strain:* B clade, Other *HIV component:* Other
Species (Isotype) guinea pig
References Wu *et al.* 2008
Keywords neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- Sera from guinea pigs immunized with subtype B or C Envs containing a deletion of the V1V2 loop and two small deletions on both arms of the V3 stem were previously shown to contain high amounts of anti-V3 neutralizing Abs. To test whether the conformation change of Env induced by CD4 affects the breadth and the neutralization potency of these anti-V3 Abs, the sera were tested in the presence or absence of sCD4 in neutralization of a panel of 12 subtype B and 12 subtype C Env-pseudoviruses. Without sCD4, subtype B- and C-immunized sera neutralized fewer HIV isolates than with sCD4 present, indicating that neutralization resistance of some viruses to anti-V3 Abs is due to a lack of exposure of the V3 loop. Neutralization of JRFL, ADA, and YU2 isolates by the sera increased with increased dose of sCD4. Wu *et al.* [2008] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1284
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype C
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* C clade 97CN54 *HIV component:* Other *Adjuvant:* Other
Species (Isotype) mouse
Ab Type gp120 V3
References Chen *et al.* 2008a
Keywords neutralization, vaccine antigen design

- Mice were immunized with three constructs of the outer domain (OD) of gp120 of subtype C, fused with Fc. All the OD constructs were immunogenic in the Fc-bound format, but the overall reactivity was severely reduced in sera from mice immunized with OD(DL3)-Fc (has 29 residues from the centre of the V3 loop removed) and with OD(2F5)-Fc (has the same deletion reconstructed to contain the sequence of 2F5 epitope), compared to the parental OD-Fc molecule. Despite the low titer response of the OD(DL3)-Fc and OD(2F5)-Fc, the fine specificity of polyclonal sera response showed that much of the OD immunogenicity resided in the V3 loop. The polyclonal sera from the immunized mice failed to neutralize both subtype C CN54 and subtype B MN isolates, and showed only a marginal ability to prevent entry of the highly sensitive 93MW965.26 isolate. Chen *et al.* [2008a] (**neutralization**, **vaccine antigen design**)

No. 1285
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection, vaccine
Vector/Type: protein *Strain:* B clade YU2 *HIV component:* gp140 *Adjuvant:* Other
Species (Isotype) human, macaque, rabbit, humanized rabbit
Ab Type gp120 CD4i, gp120 V3
References Forsell *et al.* 2008
Keywords neutralization, vaccine antigen design

- Requirements for elicitation of CD4i Abs were examined by immunizing non-primate monkeys, rabbits, and human-CD4 transgenic (huCD4) rabbits with trimeric gp140. Similar HIV-1 neutralization breadth was elicited in both monkeys and rabbits, however, CD4i Abs were elicited only in monkeys and huCD4-rabbits, indicating requirement of primate CD4 presence for the elicitation of CD4i Abs. This was confirmed by the detection of high-titer CD4i Abs in all sera derived from human volunteers inoculated with recombinant gp120. The results also indicate that the naive B-cell receptor does not recognize the gp120 co-receptor site in the absence of CD4. Forsell *et al.* [2008] (**neutralization**, **vaccine antigen design**)

No. 1286
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS, gp120 CD4i
References Wang *et al.* 2008
Keywords escape, rate of progression

- Concentrations of neutralizing Abs in long-term non-progressors (LNTPs) were significantly higher than the concentrations in asymptomatic subjects and subjects with AIDS, with no statistically significant difference between the two latter groups. Amino acid substitutions at the conserved neutralization epitopes in the gp120 C2-C4 region were observed in both asymptomatic subjects and subjects with AIDS, while no such mutations were found among LNTPs. The mutations found were 370Q/K and 412R in the CD4bs, and 370Q/K, 419K, and 421R in the epitopes for CD4i Abs. There was no significant difference in mutation rates of the conserved neutralization epitopes for CD4bs and CD4i among LNTPs,

B Cell

asymptomatic subjects, and subjects with AIDS. Wang *et al.* [2008] (**escape**, **rate of progression**)

No. 1287
MAb ID polyclonal
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide keyhole limpet hemocyanin (KLH) conjugate, Other *HIV component:* gp41 MPER *Adjuvant:* Complete Freund's Adjuvant (CFA), liposome
Species (Isotype) rabbit (IgA, IgG)
Ab Type gp41 cluster II
References Matoba *et al.* 2008
Keywords neutralization, vaccine antigen design

- Rabbits immunized with CTB-MPR649-684 (cholera toxin subunit B and residues 649-684 of gp41 MPER region) and boosted with a second MPR649-684-based immunogen elicited a productive anti-MPR649-684 Ab response. The majority of the raised Abs targeted the N-terminal portion of the MPR peptide, away from the 2F5 and 4E10 epitopes, and were not effective in neutralizing infection of CD4+ cells. These Abs, however, strongly blocked the epithelial transcytosis of a primary subtype B HIV-1 isolate, indicating that non-neutralizing Abs may play a role in stopping mucosal transmission and infection of target cells. Matoba *et al.* [2008] (**neutralization**, **vaccine antigen design**)

No. 1288
MAb ID polyclonal
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Vincent *et al.* 2008
Keywords antibody binding site definition and exposure, neutralization

- The majority of sera from HIV-1 infected patients reacted significantly with HR1/HR2 complexes, but did not react, or reacted to a lower extent, to the recombinant proteins tested separately. Purified sera IgG Abs that recognized HR1/HR2 complexes also recognized specifically N36/C34 complex but not peptides N36, C34 and 4759 separately. The HR1/HR2-specific IgG Abs were able to neutralize HIV-1 primary isolates from clades A, B, C, D and E. Vincent *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**)

No. 1289
MAb ID polyclonal
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Penn-Nicholson *et al.* 2008
Keywords binding affinity, neutralization

- For assessment of gp41 immunogenic properties, five soluble GST-fusion proteins encompassing C-terminal 30, 64, 100, 142, or 172 (full-length) amino acids of gp41 ectodomain were generated from M group consensus env sequence. The proteins were recognized by polyclonal HIV-Ig from pooled patient sera. Plasma samples from 44 HIV-1-infected individuals were also assessed separately and showed great variation in Ab reactivity against GST-gp41-100, -64, and -30 fragments, both in terms the magnitude and binding patterns. The strongest Ab responses were detected against the 100aa fragment. Patients considered as slow progressors generally exibited larger Ab reactivity against the 30aa fragment, indicating that these Abs target MPER region and exhibit 2F5- and 4E10-like properties. Plasma from these patients also exhibited broader and more potent neutralizing activity against several HIV-1 isolates. Plasma from a patient with the strongest neutralizing activity also neutralized clade A, B, and C viruses. Plasma from 8 of 44 patients had 2F5-like Abs, plasma from 6 patients had Z13-like Abs, and plasma from 4 patients had 4E10-like Abs, indicating that patients that mount Abs against epitopes that are near, or overlapping with, 2F5 or 4E10, may not be as rare as previously thought. Penn-Nicholson *et al.* [2008] (**neutralization**, **binding affinity**)

No. 1290
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Pugach *et al.* 2008
Keywords co-receptor, escape, neutralization

- In order to assess whether small molecule CCR5 inhibitor resistant viruses were more sensitive to neutralization by plasma NAbs, two escape mutant viruses, CC101.19 and D1/85.16, were tested for their sensitivity to neutralization by pooled human sera, compared to the sensitivity of CC1/85 parental isolate and the CCcon.19 control isolate. The CC101.19 escape mutant has 4 sequence changes in V3 while the D1/85.16 has no sequence changes in V3 and relies on other sequence changes for its resistance. A subset of sera neutralized the CCR5 inhibitor-resistant viruses more potently than the two sensitive viruses. 6/16 sera neutralized D1/85.16 at higher than expected titers, while only 2/16 sera did so against the CC101.19 mutant. This suggests that CCR5 inhibitor-resistant viruses are likely to be somewhat more sensitive to neutralization than their parental viruses. Pugach *et al.* [2008] (**coreceptor**, **neutralization**, **escape**)

No. 1291
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype B

B Cell

Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with gp120 boost *Strain:* B clade consensus *HIV component:* Other
Species (Isotype) mouse (IgA, IgG)
References Raska *et al.* 2008
Keywords neutralization, vaccine antigen design

- Hydrodynamic i.v. immunization of mice with plasmid DNA encoding ConB gp120 + exon 1-coded fragment of mannan binding lectin (MBL) followed by gp120 protein boost induced significantly higher gp120-specific Ab titers (40-fold) than other immunization routes. High levels of long-lasting IgG gp120-specific Abs were found in serum of immunized mice, and both IgG and IgA Abs were induced in the genital tract secretions. Abs with the most effective neutralizing activity were induced by the DNA-prime protein-boost hydrodynamic immunization, although the levels of neutralization were low. Raska *et al.* [2008] (**neutralization**, **vaccine antigen design**)

No. 1292
MAb ID polyclonal
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade HXB2 *HIV component:* gp41 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) guinea pig
References Sadler *et al.* 2008
Keywords mimics, neutralization, vaccine antigen design

- Quaternary structure of gp41 helical domains N-HR and C-HR was mimicked by 3α N-HR and 3α C-HR mimetic proteins consisting of covalently linked trimeric coiled-coil bundle, which is a truncated version of the gp41 prehairpin. The 3α mimetics were immunogenic and elicited Abs in guinea pigs specific for gp41. The sera from immunized animals neutralized viral R5 and X4-tropic viruses at 31.5 degrees C, indicating that the elicited Abs bind to a transition state between pre- and postfusion of the six-helix bundle. Addition of a Th epitope to the 3α mimetics did not increase the quantity of Ab produced, but did increase the inhibitory activity of the sera. Sadler *et al.* [2008] (**mimics**, **neutralization**, **vaccine antigen design**)

No. 1293
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B, C
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Srivastava *et al.* 2008
Keywords subtype comparisons

- Trimeric envelope glycoproteins with a partial deletion of the V2 loop derived from subtype B SF162 and subtype C TV1 were compared. Sera from HIV-1 infected individuals recognized both subtype B and C proteins, indicating similar exposure and preservance of the immunodominant epitopes on the B and C trimers. Subtype C trimer had many biophysical, biochemical, and immunological characteristics similar to subtype B trimer, except for a difference in the three binding sites for CD4, which showed cooperativity of CD4 binding in subtype C but not in subtype B. Srivastava *et al.* [2008] (**subtype comparisons**)

No. 1294
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with gp120 boost, protein *Strain:* B clade JRFL *HIV component:* gp120 *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
Species (Isotype) rabbit
Ab Type gp120 carbohydrates at glycosylation residues in C2, C3, C4, and V4, gp120 CD4BS, gp120 CD4i, gp41 cluster I, gp120 V3
References Vaine *et al.* 2008
Keywords neutralization, subtype comparisons, vaccine antigen design

- DNA prime-protein boost regimen was shown to be more effective than a protein-alone vaccination in inducing Abs targeting the V3 loop and the CD4 binding site (CD4bs). High-level V3 Abs were responsible for neutralizing activities against the neutralization sensitive isolate SF162, while the CD4bs Abs were responsible for the neutralizing activity against more resistant HIV primary isolates. Sera from rabbits immunized with DNA prime-protein boost regimen also recognized a region at the junction of the V5 and C5, a region that is highly conserved among different HIV clades, while sera from protein-alone immunized rabbits did not. Rabbit immune sera showed different binding preferences for subdomains of the V3 loops from gp120 from different clades, indicating that the V3 loops of different HIV clades are oriented differently and elicit different Ab specificities. Vaine *et al.* [2008] (**neutralization**, **vaccine antigen design**, **subtype comparisons**)

No. 1295
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: Other *Strain:* B clade LAI *HIV component:* gp120-Mab complex

B Cell

Species (Isotype) mouse (IgA, IgG1)
Ab Type gp120 V3
References Visciano *et al.* 2008b
Keywords neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Mice immunized with gp120/anti CD4bs mAb complexes produced higher titers of gp120-specific serum IgG1 and IgA than mice immunized with other gp120/mAb complexes or gp120 alone. Immunization with gp120/anti-CD4bs mAb complexes enhanced the Ab response to V3, while responses to other gp120 regions were comparable. Abs elicited by gp120/anti-CD4bs mAb complex immunization reacted preferentially with homologous V3 peptide, and sera from immunized mice potently neutralized homologous, but not heterologous, HIV-1 isolates. The results indicate that the gp120/anti-CD4bs mAb complexes elicit the production of V3-specific neutralizing Abs, but that those Abs are skewed towards V3 epitopes not shared among different HIV-1 isolates. Visciano *et al.* [2008b] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1296
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype A, B, C
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with protein boost *Strain:* A clade, B clade, Other *HIV component:* gp120, V3
Species (Isotype) rabbit
References Zolla-Pazner *et al.* 2008
Keywords neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Rabbits immunized with gp120 DNA prime from clade A and /or C Env and boosted with one or more fusion proteins containing V3 sequences from clades A, B, and/or C developed cross-clade neutralizing Ab responses focused on the V3 epitope of gp120 that were better than, or comparable to, those induced by Env immunogens possessing a multitude of B cell epitopes. The broadest and most potent neutralizing responses were elicited by clade C DNA prime and a combination of V3-fusion protein boost from clades A, B and C. V3 proteins with GPGR were immunodominant over GPGQ in eliciting Ab responses when used in combination with each other. Zolla-Pazner *et al.* [2008] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1297
MAb ID polyclonal
HXB2 Location Env
Author Location gp140
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein, protein-Ab complex *Strain:* B clade IIIB, B clade LAI, B clade NL43 *HIV component:* gp120-Mab complex, gp140 *Adjuvant:* Incomplete Freund's Adjuvant (IFA), Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) mouse (IgA, IgG, IgM)
Ab Type gp120 CD4BS, gp120 V3
References Visciano *et al.* 2008a
Keywords kinetics, vaccine-induced epitopes

- To test inhibitory significance of anti CD4bs Abs in vivo, mice were immunized with recombinant envelope proteins with or without CD4-binding activity. CD4bs Abs were generated only in animals immunized with CD4bs+ Env, and their presence was associated with with lower levels of envelope-specific lymphoploriferation. In addition, mice were immunized with gp120 in the presence of anti-CD4bs Ab or anti-C5 Ab. Mice immunized with gp120/anti-CD4 mAb complex showed lower levels of lymphoproliferation, indicating that anti-CD4bs Abs supress the induction of CD4 T cell responses in vivo. However, mice immunized with gp120/anti-CD4bs Ab displayed faster kinetics and higher levels of gp120-specific serum IgG and IgA, but not IgM, indicating that immunization with gp120 in the presence of anti-CD4 Ab alters the immunogenicity of gp120 such that the immune response is dominated by anti-gp120 IgG. Visciano *et al.* [2008a] (**vaccine-induced epitopes**, **kinetics**)

No. 1298
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype A, B, C, D
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Babaahmady *et al.* 2008
Keywords neutralization, subtype comparisons

- Dose dependent inhibition studies of HIV-1 subtypes A, B, C and D with polyclonal human sera with Abs to gp120, HLA class I or II, and 70kDa heat shock protein (HSP70) showed that combination of three antisera resulted in highest maximum inhibition. The triple Ab HLA-II+HIVgp120+HSP70 combination yielded highest maximum inhibition of subtype B HIV-1 replication of 96.7%, followed by triple HLA-I+gp120+HSP70 combination (92.8% inhibition). Similar results were seen for HIV-1 subtypes C and D but not for subtype A HIV-1 inhibition. Babaahmady *et al.* [2008] (**neutralization**, **subtype comparisons**)

No. 1299
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen vaccine

B Cell

Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp140ΔV2 *Adjuvant:* MF59, LTK63
Species (Isotype) macaque (IgA, IgG)
References Barnett *et al.* 2008
Keywords mucosal immunity, neutralization, vaccine antigen design

- Macaques were immunized with an HIV-1 SF162 envelope protein administered systematically (intramuscularly, IM), or mucosally (intranasally, IN), or as a combination of both (IM/IN, IN/IM). Animals immunized mucosally followed by systematic immunizations developed the highest mucosal and systemic Ab responses as measured by serum IgA, vaginal, nasal, and saliva IgG. IN/IM, IM/IN, and IM only immunizations protected against intravaginal challenge with SHIV, while intranasally immunized animals displayed a substantial decrease in plasma viral load. Macaques immunized IN/IM, IM/IN or IM only showed serum neutralization titers against the homologous SHIV to varying degrees, while IN immunized animals showed very little or no neutralizing activity. Barnett *et al.* [2008] (**neutralization**, **vaccine antigen design**, **mucosal immunity**)

No. 1300
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Keele *et al.* 2008
Keywords acute/early infection, neutralization

- A mathematical model was developed and used to derive transmitted or founder Env sequences from individuals with acute HIV-1 subtype B infection. Transmitted or early founder Envs were biologically functional and sensitive to neutralization by HIVIG. The neutralization profiles of the transmitted or early founder Envs was comparable to primary HIV-1 strains. Keele *et al.* [2008] (**neutralization**, **acute/early infection**)

No. 1301
MAb ID polyclonal
HXB2 Location Env
Author Location gp41
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide, protein *Strain:* B clade HXB2 *HIV component:* Other *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) rabbit (IgG)
Ab Type gp41 cytoplasmic domain
References Lu *et al.* 2008
Keywords antibody binding site definition and exposure

- Rabbits were immunized with purified recombinant protein LLP1-2 (lentivirus lytic peptide of the gp41 cytoplasmic tail region including two α-helical domains LLP1 and LLP2) or with LLP2 peptide alone. LLP2-specific IgG predominated over the LLP1-specific IgG in the LLP1-2 immunized animals. Anti-LLP1-2 and anti-LLP2 IgGs recognized LLP1-2 and LLP2 but did not react with gp41, nor with peptides N36 and C34 or with the 6-HB formed by N36/C34. Both LLP1-2 and LLP2-specific IgGs, but not LLP1-specific IgGs, bound with the effector cells in the presence of target cells at 31.4 degrees C, but not at 37 degrees C. These results suggest that LLP2, but not LLP1 domain, may be exposed on the surface of the effector cell during its interaction with the target cell for cell-to-cell fusion. Furthermore, both LLP1-2 and LLP2-specific IgGs showed potent inhibitory activity against Env-mediated syncytium formation, indicating that binding of the Abs to the LLP2 domain interferes with gp41 CT-mediated cell-cell fusion. These results indicate that the LLP2 domain, which is located inside the viral membrane, is transiently exposed on the membrane surface during the fusion process. Lu *et al.* [2008] (**antibody binding site definition and exposure**)

No. 1302
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Willey & Aasa-Chapman 2008
Keywords ADCC, complement, enhancing activity, escape, review

- The various effects that neutralizing and non-neutralizing anti-envelope Abs have on HIV infection are reviewed, such as Ab-mediated complement activation and Fc-receptor mediated activities, that both can, through various mechanisms, increase and decrease the infectivity of the virus. The importance of these mechanisms in vaccine design is discussed. Willey & Aasa-Chapman [2008] (**ADCC**, **complement**, **enhancing activity**, **escape**, **review**)

No. 1303
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade YU2 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) rabbit (IgG)
Ab Type gp120 CD4BS, gp120 CD4i, gp120 V1, gp120 V3
References Dey *et al.* 2007b
Keywords neutralization, vaccine antigen design

B Cell

- Sera from rabbits immunized with trimeric gp120 proteins with double mutation T257S+S375W, which alters the cavity at the epicenter of the CD4 binding region, had more potent neutralizing responses against many of the HIV-1 isolates tested compared to sera from rabbits immunized with wildtype monomeric or trimeric gp120. No or little of the responses were V1 or V3-specific, and some of the wildype gp120 responses were due to elicitation of CD4-blocking Abs. The double-mutant virus induced CD4i-specific responses. Dey *et al.* [2007b] (**neutralization**, **vaccine antigen design**)

No. 1304
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype C
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Kirchherr *et al.* 2007
Keywords assay development, neutralization

- A new high throughput method was developed for neutralization analyses of HIV-1 env genes by adding cytomegalovirus (CMV) immediate enhancer/promoter to the 5' end of the HIV-1 rev/env gene PCR products. The PCR method eliminates cloning, transformation, and plasmid DNA preparation steps in the generation of HIV-1 pseudovirions and allows for sufficient amounts of pseudovirions to be obtained for a large number of neutralization assays. Pseudovirions generated with the PCR method showed similar sensitivity to six HIV-1 positive sera, indicating that the neutralization properties are not altered by the new method. Kirchherr *et al.* [2007] (**assay development**, **neutralization**)

No. 1305
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype A, B, C, CRF02_AG, CRF01_AE, D
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS, gp120 V3, gp41 MPER (membrane proximal external region)
References McKnight & Aasa-Chapman 2007
Keywords neutralization, review, variant cross-recognition or cross-neutralization

- This review summarizes data on possible vaccine targets for elicitation of neutralizing Abs and discusses whether it is more practical to design a clade-specific than a clade-generic HIV-1 vaccine. Development of a neutralizing Ab response in HIV-1 infected individuals is reviewed, including data that show no apparent division of different HIV-1 subtypes into clade-related neutralization groups. Also, data on modulation of a virion's susceptibility to Ab-mediated neutralization is summarized. McKnight & Aasa-Chapman [2007] (**neutralization**, **variant cross-recognition or cross-neutralization**, **review**)

No. 1306
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: Venezuelan equine encephalitis virus (VEE) *Strain:* B clade *HIV component:* gp160
Species (Isotype) mouse (IgG1, IgG2a)
References Ljungberg *et al.* 2007
Keywords vaccine antigen design

- Mice immunized with Venezuelan equine encephalitis (VEE) DNA encoding HIV-1 gp160 had a significantly increased Ab responses than mice immunized with a conventional DNA vaccine. The Ab subclasses revealed a Th1-type response. Using VEE vaccine as a prime and a VRP (VEE replicon particle) as a boost induced increasing humoral immunity compared to VEE immunization only. In addition, immunization with VEE DNA did not induce any anti-VRP neutralizing Abs. Only a few sera from immunized mice were able to neutralize HIV-1. Ljungberg *et al.* [2007] (**vaccine antigen design**)

No. 1307
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade MN *HIV component:* Other
Species (Isotype) mouse (IgG)
References Nishiyama *et al.* 2007
Keywords neutralization, vaccine antigen design

- Mice immunized with E-PND, a peptide corresponding HIV gp120 residues 306-328 with 4 eletrophilic phosphonate diester groups, developed polyclonal Abs that formed complexes with intact virions and were poorly or not at all dissociable. Sera from mice immunized with E-PND were able to neutralize HIV MN with 44-272-fold greater potency than sera from mice immunized with the same peptide but without the eletrophilic phosphonate diester groups. None of the sera neutralized HIV subtype C. Analyses confirmed presence of anti-E-PND Abs with increased nucleophilic reactivity and their importance in prolonging immune complex longevity. These results indicate that inclusion of eletrophilic phosphonate diester groups in the immunogenic peptide may increase Ab neutralization potency. Nishiyama *et al.* [2007] (**neutralization**, **vaccine antigen design**)

No. 1308
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing

B Cell

Immunogen vaccine
Vector/Type: virus-like particle (VLP) *Strain:* B clade 89.6 *HIV component:* Env
Species (Isotype) mouse (IgG, IgG1, IgG2a, IgG2b, IgG3)
Ab Type gp120 V3
References Quan *et al.* 2007
Keywords neutralization, vaccine antigen design

- Mice were immunized with SHIV virus like particles (VLPs) containing mutant HIV Env with reduced glycosylation (3G), V1V2 deletions (dV1V2), or both (3G-dV2-1G). Mice immunized with 3G-dV2-1G showed the highest level of IgG binding to HIV Env. IgG1, IgG2a, IgG2b, IgG3 and IgA were found in all immunized mice. Levels of V3 binding Abs were significantly higher in mice immunized with dV1V2. The highest neutralization activity against the homologous HIV 89.6 strain was found in sera from mice immunized with 3G, while the highest neutralizing activity against the heterologous YU2 and IIIB strains was found in sera from mice immunized with 3G-dV2-1G vaccine. These results indicate that immunizations with VLPs can induce neutralizing activity against homologous as well as heterologous strains, which can be increased by V1V2 deletions or deglycosylations. Quan *et al.* [2007] (**neutralization**, **vaccine antigen design**)

No. 1309
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype C
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Rong *et al.* 2007a
Keywords autologous responses, escape, neutralization

- Subtype C HIV-1 from four heterosexually infected pairs was cloned and sequenced. The donor and the recipient Envs were sensitive to autologous neutralization by contemporaneous plasma from the donors. Chimeric Envs were constructed where the V1V2 domains from the neutralization sensitive recipient Envs were replaced with donor V1V2. The neutralization sensitivity of the Envs was regulated by V1V2 domain length but also glycosylation, primary sequences, and V1V2-independent mechanisms. One residue was found to be associated with neutralization sensitivity of Env, Lys at position 309, where the Env became six-fold less sensitive to NAb when this residue was changed to Glu. Rong *et al.* [2007a] (**autologous responses**, **neutralization**, **escape**)

No. 1310
MAb ID polyclonal
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Adjuvant:* gp41 N-HR and C-HR helical peptides
Species (Isotype) rabbit (IgG)
Ab Type C-HR, gp41 NHR (N-heptad repeat), gp41six-helix bundle
References Golding *et al.* 2002b; de Rosny *et al.* 2001

- The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – the preincubation 31.5 C step did not alter anti-C-HR Abs inability to inhibit fusion. Golding *et al.* [2002b]
- A panel of Abs against gp41 heptad repeats N-HR, C-HR, and self-assembled stable N-HR and C-HR six helix bundles were generated. de Rosny *et al.* [2001]

No. 1311
MAb ID 101-342
HXB2 Location Env
Author Location gp120 (476–505 HAM112, O group)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* O group HAM112 *HIV component:* gp160
Species (Isotype) mouse (IgG2aκ)
Ab Type C-term
References Scheffel *et al.* 1999

- 101-342: Overlapping peptides based on group O HAM112 Env were tested for MAb reactivity. Scheffel *et al.* [1999]

No. 1312
MAb ID 101-451
HXB2 Location Env
Author Location gp120 (498–527 HAM112, O group)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* O group HAM112 *HIV component:* gp160
Species (Isotype) mouse (IgG2bκ)
Ab Type C-term
References Scheffel *et al.* 1999

- 101-451: Overlapping peptides based on group O HAM112 Env were tested for MAb reactivity. Scheffel *et al.* [1999]

No. 1313
MAb ID 120-1
HXB2 Location Env
Author Location gp120 (503–532)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: peptide
Species (Isotype) mouse (IgMκ)
Ab Type C-term
References Dalgleish *et al.* 1988; Chanh *et al.* 1986

No. 1314
MAb ID T26
HXB2 Location Env

B Cell

Author Location gp41
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein
Species (Isotype) mouse
Ab Type C-term
Research Contact Patricia Earl, National Institute of Allergy and Infectious Diseases
References Usami *et al.* 2005; Kilgore *et al.* 2003; Earl *et al.* 1997; Earl *et al.* 1994
Keywords antibody binding site definition and exposure, antibody generation, rate of progression, variant cross-recognition or cross-neutralization

- T26: T26 was found to predominantly bind to oligomeric gp41 and not to monomeric gp41. Binding of this Ab to H9/IIIB-infected cells gave a weak signal which was slightly increased by sCD4 pretreatment. Binding to H9/MN-infected cells gave no signal regardless of sCD4 pretreatment. Sera from both long-term survivors (LTS) and AIDS patients inhibited binding of T26 to H9/IIIB-infected cells, however, sera from the AIDS patients inhibited T26 more efficiently than the sera from LTS. Usami *et al.* [2005] (**antibody binding site definition and exposure**, **rate of progression**)
- T26: Mab is restricted in its binding to gp41 of the LAI isolate and not to gp41 of the MN, Ada and RF isolates. Antibody specificity may be determined by LAI residues D637E, N641D and H648Y. T26 binds to the N-terminal half of the C helix (aa630-680) of the LAI envelope, specifically targeting a confomational epitope within the six-helix bundle of gp41. Addition of the C-helical peptide inhibitor from LAI (T26 reactive) rescued the binding activity of MAb T26 to cell-surface expressed RF envelope (T26 non-reactive) triggered with sCD4 or cell-surface expressed receptors in a surface immunoprecipitation assay. This supports that C-peptide entry inhibitors bind to the gp41 N-helical coiled-coil, disrupting native six-helix bundles. Kilgore *et al.* [2003] (**antibody binding site definition and exposure**)
- T26: T26 was raised against the gp140 tetramer, binds to gp41 and is a highly strain specific. Earl *et al.* [1997] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- T26: A panel of 138 MAb raised against different forms of soluble Env. Earl *et al.* [1994] (**antibody generation**)

No. 1315
MAb ID D33
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4BS, C-term, N-term
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1994

- D33: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D33 is part of a group of MAbs labeled A1 – all A1 MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, blocked CD4 binding, were sensitive to mutations in gp120 positions 368 and 370 that directly contact CD4 – D33 was unusual for the group of A1 MAbs, because while it blocked CD4 binding completely, but competed with MAbs that did not in a BIAcore assay – both the N- and C-terminal ends of gp120 are involved in D33 binding. Sugiura *et al.* [1999]
- D33: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1316
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgA)
Ab Type gp120 CD4BS, C-term, gp120 V3-C4
References Vincent *et al.* 2004
Keywords genital and mucosal immunity

- IgA derived from sera and saliva from 5 HIV-1 infected patients undergoing ART therapy reacted to peptide antigens corresponding to the C3-V4 region of gp120 and the C-terminal part of gp41. HIV-1-specific IgA obtained in 6/26 sera and 5/25 saliva samples inhibited gp120-sCD4 protein binding. Vincent *et al.* [2004] (**genital and mucosal immunity**)

No. 1317
MAb ID 212A
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 C1
Research Contact James Robinson, Tulane University, LA
References Pantophlet *et al.* 2004; Pantophlet *et al.* 2003b; Binley *et al.* 1998; Sullivan *et al.* 1998b; Parren *et al.* 1997b; Wyatt *et al.* 1997; Ditzel *et al.* 1997; Fouts *et al.* 1997; Binley *et al.* 1997a; Moore & Sodroski 1996; Moore *et al.* 1994d; Robinson *et al.* 1992
Keywords vaccine antigen design

- 212A: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 212A. Pantophlet *et al.* [2004] (**vaccine antigen design**)

- 212A: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- 212A: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
- 212A: Does not compete with binding of MAb generated in response to gp120-CD4 complex, CG10. Sullivan *et al.* [1998b]
- 212A: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – 212A bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997]
- 212A: Does not neutralize TCLA strains or primary isolates. Parren *et al.* [1997b]
- 212A: Binds efficiently to sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding – does not bind to HXBc2 gp120 if the 19 C-term amino acids are deleted. Wyatt *et al.* [1997]
- 212A: Binding enhanced by anti-V3 MAb 5G11 – reciprocal inhibition with anti-C1 MAbs. Moore & Sodroski [1996]
- 212A: Mutations that inhibit binding: C1 (45 W/S) and V5 (463 N/D) – and enhance binding: V2 (179/180 LD/DL) and C5 (495 G/K). Moore *et al.* [1994d]

No. 1318
MAb ID 522-149
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Env
Species (Isotype) mouse
Ab Type gp120 C1
Research Contact G. Robey, Abbott Inc.
References Pantophlet *et al.* 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Yang *et al.* 2000; Binley *et al.* 1998; Trkola *et al.* 1996a; Moore & Sodroski 1996
Keywords antibody interactions, vaccine antigen design

- 522-149: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 522-149. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- 522-149: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- 522-149: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a C1-binding Fab that had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
- 522-149: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000]
- 522-149: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
- 522-149: Binding is enhanced by C5 antibodies M91 and 1C1 – mutual binding-inhibition with anti-C1 antibody 133/290 – binding is destroyed by a W/L (position 61, LAI) gp120 amino acid substitution – other C1 antibodies enhance binding to gp120. Moore & Sodroski [1996]
- 522-149: Does not neutralize JR-FL nor block gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]

No. 1319
MAb ID CA1 (ARP3117)
HXB2 Location Env
Author Location Env
Epitope
Subtype A
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia prime with gp120 boost *Strain:* A clade *HIV component:* Env
Species (Isotype) mouse
Ab Type gp120 C1
References Jeffs *et al.* 2004
Keywords subtype comparisons, vaccine antigen design

B Cell

- CA1: A set of oligomeric envelope proteins were made from six primary isolates for potenial use as vaccine antigens: 92/UG/037 (clade A), HAN2/2 (clade B), 92/BR25/025 (clade C), 92/UG/021 (clade D), 93/BR/029 (clade F) and MVP5180 (clade O). This was one of a panel of MAbs used to explore folding and exposure of well characterized epitopes. The clade C isolate BR25 is apparently misfolded, as conformation-dependent antibodies did not bind to it. CA1 is a MAb that binds to a linear epitope in the C1 region of gp120 that was raised against clade A variant 92/UG/029. CA1 was subtype-specific and bound only to the antigen from all clade A. Polyclonal sera raised in rabbits against these antigens cross-bound the other antigens, but none of the sera had neutralizing activity. Jeffs *et al.* [2004] (**vaccine antigen design**, **subtype comparisons**)

No. 1320
MAb ID L19
HXB2 Location Env
Author Location gp120 (HXBc2)
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
Ab Type gp120 C1
References Ditzel *et al.* 1997

- L19: gp120 immobilized on solid phase by capture with anti-CD4 BS MAb L72 was used for the selection of Fabs – six N-term Fabs, L19 L34, L35, L52, L59, and L69, were obtained that have a similar epitope to Fab p7. Ditzel *et al.* [1997]

No. 1321
MAb ID M90
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein *HIV component:* Env
Species (Isotype) (IgG1)
Ab Type gp120 C1
Research Contact Fulvia di Marzo Veronese
References Koefoed *et al.* 2005; Pantophlet *et al.* 2003b; Yang *et al.* 2000; Binley *et al.* 1999; Binley *et al.* 1998; Wyatt *et al.* 1997; Ditzel *et al.* 1997; Moore & Sodroski 1996; DeVico *et al.* 1995; di Marzo Veronese *et al.* 1992
Keywords antibody binding site definition and exposure

- M90: IgG antibody phage display libraries were created from HIV-1 + individuals after pre-selection of PBMC with gp120, as an alternative to using bone marrow for generating libraries. M90 was among a set of Abs used for competition studies to define the binding sites of the newly isolated MAbs, and has a conformational C1 epitope. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**)
- M90: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b]
- M90: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000]
- M90: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999]
- M90: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
- M90: Binds efficiently to sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding – does not bind to HXBc2 gp120 if the 19 C-term amino acids, in conjunction with C1 positions 31-82, are deleted. Wyatt *et al.* [1997]
- M90: Reciprocal inhibition of binding of other anti-C1 MAbs – inhibits CD4 binding site MAbs – enhances binding of V2 MAbs G3-4 and SC258. Moore & Sodroski [1996]
- M90: Reacted with both non-reduced (but not denatured) covalently cross-linked gp120-CD4 complex. DeVico *et al.* [1995]
- M90: Reactive only with native gp120, so binds to a discontinuous epitope – reacts with multiple strains. di Marzo Veronese *et al.* [1992]

No. 1322
MAb ID MAG 104
HXB2 Location Env
Author Location gp120

B Cell

Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 C1
Research Contact C. Y. Kang, IDEC Inc
References Kang *et al.* 1994

- MAG 104: Only observed amino acid substitution that reduces binding: 88 N/P and 106 E/A – does not bind to C1 region 20 mer peptides, tentative classification conformationally sensitive anti-C1 MAb. Kang *et al.* [1994]

No. 1323
MAb ID MAG 45 (#45, MAG45)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 C1
Research Contact C. Y. Kang, IDEC Inc, or Dr. Hariharam, IDEC Pharmaceuticals Corporation, La Jolla, CA
References Koefoed *et al.* 2005; Yang *et al.* 2000; Wyatt *et al.* 1997; Moore & Sodroski 1996; Kang *et al.* 1994
Keywords antibody binding site definition and exposure

- MAG 45: IgG antibody phage display libraries were created from HIV-1 + individuals after pre-selection of PBMC with gp120, as an alternative to using bone marrow for generating libraries. MAG 45 was among a set of Abs used for competition studies to define the binding sites of the newly isolated MAbs, representing a MAb with a C1 epitope. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**)
- MAG 45: Called #45 – a combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000]
- MAG 45: Called #45 – binds to efficiently sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding – does not bind to HXBc2 gp120 if the 19 C-term amino acids, in conjunction with C1 positions 31-50, are deleted. Wyatt *et al.* [1997]
- MAG 45: Reciprocal binding inhibition with anti-C1-C5 and anti-C1-C4 discontinuous MAbs – binding enhanced by anti-V3 5G11 – inhibits binding of anti-CD4 binding site MAbs. Moore & Sodroski [1996]
- MAG 45: Only observed amino acid substitution that reduces binding: 88 N/P – does not bind to C1 region 20 mer peptides, tentative classification conformationally sensitive anti-C1 MAb. Kang *et al.* [1994]

No. 1324
MAb ID MAG 95
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 C1
Research Contact C. Y. Kang, IDEC Inc
References Kang *et al.* 1994

- MAG 95: Only observed amino acid substitution that reduces binding: 88 N/P – does not bind to C1 region 20 mer peptides, tentative classification conformationally sensitive anti-C1 MAb. Kang *et al.* [1994]

No. 1325
MAb ID MAG 97
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 C1
Research Contact C. Y. Kang, IDEC Inc
References Kang *et al.* 1994

- MAG 97: Only observed amino acid substitution that reduces binding: 88 N/P – does not bind to C1 region 20 mer peptides, tentative classification conformationally sensitive anti-C1 MAb. Kang *et al.* [1994]

No. 1326
MAb ID P35
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 C1
References Zwick *et al.* 2003; Kwong *et al.* 2002
Keywords antibody binding site definition and exposure, antibody interactions

- P35: called p35. scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of

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the V1/V2 and V3 loops restrict CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a C1-binding Fab with a discontinuous epitope that had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)

- P35:Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-299) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Authors describe the epitope as N-terminal, linear. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)

No. 1327
MAb ID T9
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen vaccine
HIV component: oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 C1
Research Contact Patricia Earl and Christopher Broder, NIH
References Golding *et al.* 2002b; Earl *et al.* 1997; Broder *et al.* 1994
Keywords antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization

- T9 database comment: There are two HIV-Abs with the name T9, one binds to gp41, one to gp120.
- T9: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – the preincubation 31.5 C step did not alter the inhibitory activity of neutralizing Abs anti-gp41 2F5, or anti-gp120 2G12, IG1b12, 48d, and 17b – nor did it alter two gp41 MAbs, T9 and D61, inability to inhibit fusion. Golding *et al.* [2002b] (**antibody binding site definition and exposure**)
- T9: This antibody, along with 7 others (M10, D41, D54, T6, T4, T10 and T35), can block the linear murine MAb D61, and the human MAb 246-D, which both bind to the immunodominant region near the two Cys in gp41 – most of these antibodies are oligomer dependent – all of the MAbs are reactive with ten different HIV-1 strains – members of this competition group are blocked by sera from HIV-1 + individuals. Earl *et al.* [1997] (**antibody binding site definition and exposure**)
- T9: One of five MAbs (T4, T6, T9, T10 and T35) in a competition group that bind to a conformation-dependent epitope in gp41 and is oligomer specific – neutralizes IIIB and SF2. Broder *et al.* [1994] (**antibody generation**, **variant cross-recognition or cross-neutralization**)

No. 1328
MAb ID p7
HXB2 Location Env
Author Location gp120 (HXBc2)
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
Ab Type gp120 C1
References Crooks *et al.* 2008; Moore *et al.* 2006; Parren *et al.* 1997b; Ditzel *et al.* 1997
Keywords antibody binding site definition and exposure, antibody generation, binding affinity, neutralization

- P7: The study compared Ab neutralization against the JR-FL primary isolate and trimer binding affinities judged by native PAGE. There was direct quantitative relationship between monovalent Fab-trimer binding and neutralization, implying that neutralization begins as each trimer is occupied by one Ab. In BN-PAGE, neutralizing Fabs and sCD4 were able to shift JR-FL trimers, In contrast, most non-neutralizing Fabs, P7 in particular, bound to monomer, but their epitopes were conformationally occluded on trimers, confirming the exclusive relationship of trimer binding and neutralization. Crooks *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- P7: In addition to gp120-gp41 trimers, HIV-1 particles were shown to bear nonfunctional gp120-gp41 monomers and gp120-depleted gp41 stumps on their surface. P7 was found to bind to nonfunctional monomers. Monomer binding did not correlate with neutralization, but it did correlate with virus capture. It is hypothesized that the nonfunctional monomers on the HIV-1 surface serve to divert the Ab response, helping the virus to avoid neutralization. Moore *et al.* [2006] (**antibody binding site definition and exposure**)
- p7: gp120 immobilized on solid phase by capture with sCD4 was used for selection of Fabs – three novel N-term Fabs were obtained that bind to similar epitopes, p7, p20, and p35 – a C1 W/S substitution at position 45 abolished binding, a Y/D at position 45 reduced binding, and C5 region substitutions 475 M/S and 493 P/K enhanced binding – compete with MAbs M85, M90 and 212A, but not M91 and G3-299. Ditzel *et al.* [1997] (**antibody generation**)
- p7: Does not neutralize TCLA strains or primary isolates. Parren *et al.* [1997b]

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No. 1329
MAb ID L100
HXB2 Location Env
Author Location gp120 (HXBc2)
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
Ab Type gp120 C1-C2
References Kwong *et al.* 2002; Parren & Burton 1997; Parren *et al.* 1997b; Ditzel *et al.* 1997
Keywords antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization

- L100: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-299) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Authors describe the epitope as N-terminal, discontinuous. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- L100: gp120 immobilized on solid phase by capture with sCD4 and then masked with Fab p7 allowed selection of a new Fab, L100, with a novel specificity for C1 and C2 – gp120 C1 substitutions 69 W/L and 76 P/Y abolish L100 binding, and C2 substitutions 252 R/W, 256 S/Y, 262 N/T and 267 E/L abolish or strongly inhibit L100 binding – inhibits binding of MAbs M90 and G3-299, but not M85, 212A, and M91. Ditzel *et al.* [1997]; Parren & Burton [1997] (**antibody binding site definition and exposure**, **antibody generation**)
- L100: Does not neutralize TCLA strains or primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)

No. 1330
MAb ID 2/11c (211c, 2.11c, 211/c, 2-11c)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L (weak)
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 C1-C4
Research Contact James Robinson, Tulane University, LA
References Yuan *et al.* 2006; Yuan *et al.* 2005; Pancera & Wyatt 2005; Kwong *et al.* 2002; Xiang *et al.* 2002a; Binley *et al.* 1998; Wyatt *et al.* 1997; Li *et al.* 1997; Fouts *et al.* 1997; Binley *et al.* 1997a; Trkola *et al.* 1996a; Moore & Sodroski 1996
Keywords antibody binding site definition and exposure, antibody interactions, binding affinity, neutralization

- 2/11c: Interactions of this Ab with gp120 monomer and two cleavage-defective gp140 trimers were studied. It was shown that 2/11c recognized the soluble monomer more efficiently than the soluble trimers and that treatment of the proteins with GA (cross-linking) further decreased the interactions of this Ab with the trimers to low levels, indicating that the access of the 2/11c epitope was affected by cross-linking of the trimers but not the monomer. Yuan *et al.* [2006] (**antibody binding site definition and exposure**, **antibody interactions**, **binding affinity**)
- 211c: R-FL and YU2 HIV-1 strains were not neutralized by 211c. 211c and other non-neutralizing Abs only recognized JR-FL cleavage-defective glycoproteins, while the neutralizing Abs (2G12 and IgG1b12) recognized both cleavage competent and cleavage-defective glycoproteins. It is suggested that an inefficient env glycoprotein precursor cleavage exposes non-neutralizing determinants, while only neutralizing regions remain accessible on efficiently cleaved spikes. For YU2, both cleavage-competent and -defective glycoproteins were recognized by both neutralizing and non-neutralizing Abs. Abs able to neutralize lab-adapted isolates displayed enhanced viral entry at higher Ab concentrations, whereas Abs that cannot neutralize any virus, such as 211c, did not display such enhancement. Pancera & Wyatt [2005] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- 2/11c: A substantial fraction of soluble envelope glycoprotein trimers contained inter-subunit disulfide bonds. Reduction of these disulfide bonds decreased binding of 2/11c to the glycoprotein, indicating that the inter-S-S bonds contribute to the exposure of the 2/11c epitope. Yuan *et al.* [2005] (**antibody binding site definition and exposure**)
- 2/11c: Called 211/c. Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-299) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate

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masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Authors describe the epitope as N-terminus, discontinuous. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)

- 2/11c: Used as a negative control in a study of CD4i MAbs. Xiang *et al.* [2002a]
- 2/11c: Called 211/c – a panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
- 2/11c: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric env binding – 2/11c bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997]
- 2/11c: Called 2.11c – One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env – 50% neutralization could not be achieved at a maximal concentration of 67 mug/ml. Li *et al.* [1997]
- 2/11c: Binds efficiently to sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding – does not bind to HXBc2 gp120 if the 19 C-term amino acids, in conjunction with C1 positions 31-74, are deleted. Wyatt *et al.* [1997]
- 2/11c: Inhibits binding of anti-C1, -C5, -C4, -V3 and anti-CD4 binding site MAbs – induces binding of some anti-V2 and CD4i MAbs (48d and 17b) – similar reactivity pattern to A32, but less cross-reactive and lower affinity – A32 and 211/c are unique among known human and rodent MAbs. Moore & Sodroski [1996]
- 2/11c: Called 211c – does not neutralize JR-FL nor block gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]

No. 1331
MAb ID A32
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
Ab Type gp120 C1-C4, gp120 adjacent to CD4BS
Research Contact James Robinson, Tulane University, New Orleans, LA, USA
References Dey *et al.* 2008; Gray *et al.* 2007b; Gao *et al.* 2007; DeVico *et al.* 2007; Lam *et al.* 2006; Liao *et al.* 2006; Haynes & Montefiori 2006; Yuan *et al.* 2005; Selvarajah *et al.* 2005; Robinson *et al.* 2005; Haynes *et al.* 2005a; Gao *et al.* 2005a; Pantophlet *et al.* 2004; Liao *et al.* 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Kwong *et al.* 2002; Grundner *et al.* 2002; Yang *et al.* 2002; Finnegan *et al.* 2001; Yang *et al.* 2000; Binley *et al.* 1999; Binley *et al.* 1998; Sullivan *et al.* 1998b; Parren *et al.* 1997b; Boots *et al.* 1997; Wyatt *et al.* 1997; Burton & Montefiori 1997; Fouts *et al.* 1997; Binley *et al.* 1997a; Trkola *et al.* 1996a; Wu *et al.* 1996; Moore & Sodroski 1996; Moore & Ho 1995; Wyatt *et al.* 1995; Moore *et al.* 1994b
Keywords antibody binding site definition and exposure, antibody generation, antibody interactions, assay development, assay standardization/improvement, binding affinity, co-receptor, enhancing activity, HAART, ART, kinetics, mimotopes, neutralization, review, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- A32: Five amino acids in the gp41 N-terminal region that promote gp140 trimerization (I535, Q543, S553, K567 and R588) were considered. Their influence on the function and antigenic properties of JR-FL Env expressed on the surfaces of pseudoviruses and Env-transfected cells was studied. Various non-neutralizing antibodies bind less strongly to the Env mutant, but neutralizing antibody binding is unaffected. A32 bound minimally, but comparably to both pseudoviruses, and A32 failed to inhibit infection by either pseudovirus. Dey *et al.* [2008] (**binding affinity**)
- A32: Macaques were immunized with either CD4, gp120, cross-linked gp120-human CD4 complex (gp120-CD4 XL), and with single chain complex containing gp120 rhesus macaque CD4 domains 1 and 2 (rhFLSC). Sera from the gp120-CD4 XL immunized animals showed highest competition titers, being able to block gp120-CD4 complex interactions with A32 more efficiently than sera from animals immunized with the three other proteins. DeVico *et al.* [2007] (**neutralization**)
- A32: This review summarizes data on the development of HIV-1 centralized genes (consensus and ancestral) for induction of neutralizing antibody responses. Functionality and conformation of native epitopes in proteins based on the centralized genes was tested and confirmed by binding to A32 and other MAbs. Binding of A32 following CD4 also indicated presence of functionally relevant conformational changes of the proteins. Gao *et al.* [2007] (**antibody binding site definition and exposure**, **review**)
- A32: Addition of a glycosylation site at position V295N in three different subtype C envelope clones did not have any impact on binding of A32 to gp120, indicating that the mutation did not cause a substantial conformational change. Gray *et al.* [2007b] (**binding affinity**)
- A32: This review describes the effectiveness of the current HIV-1 immunogens in eliciting neutralizing antibody responses to different clades of HIV-1. It also summarizes different evasion and antibody escape mechanisms, as well as the most potent neutralizing MAbs and their properties. MAbs reviewed in this article are: 2G12, IgG1b12, 2F5, 4E10, A32, 447-52D and, briefly, D50. Novel immunogen design strategies are also discussed. Haynes & Montefiori [2006] (**antibody binding site definition and exposure**, **enhancing activity**)

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- A32: This Ab was used in a microcantilever deflection assay to detect gp120 from solution. Deflection twice that of the baseline was detected upon specific binding of gp120 to cantilevers decorated on one side with A32. Lam *et al.* [2006] (**assay development**, **assay standardization/improvement**)
- A32: The gp140δCFI protein of CON-S M group consensus protein and gp140CFI and gp140CF proteins of CON6 and WT viruses from HIV-1 subtypes A, B and C were expressed in recombinant vaccinia viruses and tested as immunogens in guinea pigs. A32 was shown to bind specifically to all recombinant proteins except for the one derived from subtype C virus. It also bound specifically to the two subtype B gp120 proteins. The specific binding of A32 to CON-S indicated that its conformational epitope was intact. Liao *et al.* [2006] (**antibody binding site definition and exposure**, **vaccine antigen design**, **subtype comparisons**)
- A32: Monomeric gp120 and trimeric gp140CF proteins synthesized from an artificial group M consensus Env gene (CON6) bound with high affinity to A32, indicating correct exposure of the A32 epitope. A32 induced conformational changes of gp120 and gp140CF required for binding of MAb 17b. Gao *et al.* [2005a] (**antibody binding site definition and exposure**, **kinetics**, **binding affinity**)
- A32: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)
- A32: A reverse capture assay was developed to asses what kind of human MAbs were produced in EBV B-cell transformation assays performed on PBMC sampled at different timepoints from three HIV-1 infected patients on HAART. The reverse capture assay was validated by the solid phase MAbs that could not capture biotin-MAbs of the same or overlapping specificity when reacted with patient virus envelope glycoproteins preincubated with or without sCD4. Reverse capture assay showed that the produced Abs from the patients were able to block binding of biotin-labeled A32, however the blocking was low, indicating presence of relatively few A32-like Abs. Robinson *et al.* [2005] (**antibody generation**, **assay development**, **HAART, ART**)
- A32: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. V1/V2/V3 MAb 4KG2, C1-C4 MAb A32, C1-C5 MAb C11, and HIVIG all either did not bind or had significantly diminished binding to both antigen constructs. Selvarajah *et al.* [2005] (**vaccine antigen design**, **vaccine-specific epitope characteristics**)
- A32: A substantial fraction of soluble envelope glycoprotein trimers contained inter-subunit disulfide bonds. Reduction of these disulfide bonds decreased binding of A32 to the glycoprotein, indicating that the inter-S-S bonds contribute to the exposure of the A32 epitope. Yuan *et al.* [2005] (**antibody binding site definition and exposure**)
- A32: A32-rgp120 complexes opened up the CCR5 coreceptor binding site, but did not induce neutralizing antibodies with greater breadth among B subtype isolates than did uncomplexed rgp120 in vaccinated guinea pigs. Liao *et al.* [2004] (**vaccine antigen design**)
- A32: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including A32. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- A32: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- A32: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. A32 is described as having a C1-C4 discontinuous CD4i epitope, and had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
- A32: HIV-1 gp160deltaCT (cytoplasmic tail-deleted) proteoliposomes (PLs) containing native, trimeric envelope glycoproteins from R5 strains YU2 and JRFL, and X4 strain HXBc2, were made in a physiologic membrane setting as candidate immunogens for HIV vaccines – 2F5 bound to gp160deltaCT with a reconstituted membrane ten-fold better than the same protein on beads – anti-CD4BS MAbs IgG1b12 and F105, A32 (C1-C4), C11 (C1-C5), and 39F (V3) MAbs bound gp160deltaCT PLs indistinguishably from gp160deltaCT expressed on the cell surface – non-neutralizing MAbs C11 and A32 bound with lower affinity than NAb IgG1b12 – the MAb 17b was sCD4 inducible on gp160deltaCT PL. Grundner *et al.* [2002] (**vaccine antigen design**)
- A32: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neu-

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tralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-299) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Authors describe the epitope as N-terminal, discontinuous. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)

- A32: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibritin – stabilized oligomer gp140 delta683(-FT) showed strong preferential recognition by NAbs IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAbs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002] (**antibody binding site definition and exposure**)
- A32: Using a cell-fusion system, it was found CD4i antibodies 17b, 48d, and CG10 reacted faintly with Env expressing HeLA cells even in the absence of sCD4 or CD4 expressing target cells. Reactivity increased after sCD4 addition, but not after CD4 expressing target cell addition, and binding was not increased at the cell-to-cell CD4-Env interface. This suggests the CD4i co-receptor binding domain is largely blocked at the cell-fusion interface, and so CD4i antibodies would not be able access this site and neutralize cell-mediated viral entry. However, CD4i MAbs 8F101 and A32, that bind outside the co-receptor domain, had a different pattern. They reacted after the formation of gp120-CD4-CXCR4 tri-complexes, so co-receptor interactions allowed exposure of their epitopes. Finnegan *et al.* [2001] (**antibody binding site definition and exposure**)
- A32: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000] (**vaccine antigen design**)
- A32: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999] (**antibody binding site definition and exposure**)
- A32: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998] (**antibody binding site definition and exposure**)
- A32: Enhances binding of CD4i MAbs 17b and 48d, and a MAb generated in response to gp120-CD4 complex, CG10. Sullivan *et al.* [1998b] (**antibody interactions**)
- A32: Abs that recognize discontinuous epitopes can identify mimotopes from a phage peptide display library – A32 has a unique epitope involving mostly C2 but C1 and C4 contribute – six quite variable phage inserts were recognized, with a consensus of LPWYN – a central Trp was the most conserved element, consistent with W427 being an important residue for binding gp120. Boots *et al.* [1997] (**antibody binding site definition and exposure**, **mimotopes**)
- A32: Review. Burton & Montefiori [1997] (**review**)
- A32: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric env binding – A32 bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
- A32: Does not neutralize TCLA strains or primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- A32: Binds efficiently to sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
- A32: Reciprocal inhibition of binding of anti-C1, -C5, -C4, -V3 and anti-CD4 binding site MAbs – induces binding of some anti-V2 and sCD4 inducible MAbs (48d and 17b) – very similar competition pattern between 2/11c, A32 and 211/c are unique among known human and rodent MAbs. Moore & Sodroski [1996] (**antibody binding site definition and exposure**, **antibody interactions**)
- A32: Does not neutralize JR-FL, or any strain strongly – partial inhibition of gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a] (**co-receptor**)
- A32: Not neutralizing – binds domains that interact with gp41 – MIP-1alpha binding to CCR-5 expressing cells can be inhibited by gp120-sCD4 and binding of A32 does not block this inhibition. Wu *et al.* [1996] (**antibody binding site definition and exposure**)

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- A32: Review: epitope is distinct from CD4BS MAbs, 48d and 17b, and 2G12. Moore & Ho [1995] (**antibody binding site definition and exposure**)
- A32: Epitope is better exposed upon CD4 binding to gp120 – binding of A32 enhances binding of 48d and 17b – studies using a V1/V2 deletion mutant demonstrated that enhanced binding of 48d in the presence sCD4 involves the V1/V2 loops, with more significant involvement of V2. Wyatt *et al.* [1995] (**antibody binding site definition and exposure**, **antibody interactions**)
- A32: Reacted with virtually every gp120 monomer of every clade tested, most conserved gp120 monomer epitope known. Moore *et al.* [1994b] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1332
MAb ID C11 (c11)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 C1-C5
Research Contact James Robinson, Tulane University, LA
References Pacheco *et al.* 2008; DeVico *et al.* 2007; Yuan *et al.* 2006; Yang *et al.* 2006; Bowley *et al.* 2007; Moore *et al.* 2006; Yuan *et al.* 2005; Selvarajah *et al.* 2005; Robinson *et al.* 2005; Pancera *et al.* 2005; Pancera & Wyatt 2005; Kim *et al.* 2005; Haynes *et al.* 2005a; Pantophlet *et al.* 2004; Pantophlet *et al.* 2003b; Ohagen *et al.* 2003; Raja *et al.* 2003; Kwong *et al.* 2002; Basmaciogullari *et al.* 2002; Grundner *et al.* 2002; Yang *et al.* 2002; Binley *et al.* 1999; Sullivan *et al.* 1998b; Parren *et al.* 1997b; Wyatt *et al.* 1997; Fouts *et al.* 1997; Binley *et al.* 1997a; Wu *et al.* 1996; Trkola *et al.* 1996a; Moore & Sodroski 1996; Moore *et al.* 1994d; Robinson *et al.* 1992
Keywords antibody binding site definition and exposure, antibody generation, antibody interactions, assay development, assay standardization/improvement, binding affinity, brain/CSF, co-receptor, HAART, ART, neutralization, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- C11: Two HIV-1 isolates, NL4-3 and KB9, were adapted to replicate in cells using the common marmoset receptors CD4 and CXCR4. The adaptation resulted in a small number of changes of env sequences in both isolates. None of the adaptation-associated changes in the HIV-1 env glycoproteins affected isolate recognition by the C11 Ab. Pacheco *et al.* [2008] (**antibody binding site definition and exposure**)
- C11: Yeast display was compared to phage display and shown to select all the scFv identified by phage display and additional novel antibodies. Biotinylated C11 and 2G12 were used to minimize selection of non-gp120 specific clones from the yeast displayed antibody library; these MAbs were used as they have unique epitopes with limited overlap with with most known epitopes. Bowley *et al.* [2007] (**assay standardization/improvement**)
- C11: Macaques were immunized with either CD4, gp120, cross-linked gp120-human CD4 complex (gp120-CD4 XL), and with single chain complex containing gp120 rhesus macaque CD4 domains 1 and 2 (rhFLSC). Sera from all the immunized animals were able to block gp120-CD4 complex interactions with C11 equally. DeVico *et al.* [2007] (**neutralization**)
- c11: In addition to gp120-gp41 trimers, HIV-1 particles were shown to bear nonfunctional gp120-gp41 monomers and gp120-depleted gp41 stumps on their surface. c11 recognizes monomeric gp120. c11 was unable to neutralize or capture the VLPs studied, indicating that no forms of Env exist on the particles that resemble monomeric gp120 dissociated from gp41. Moore *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**)
- C11: Viruses bearing inserted artificial epitopes of FLAG in the V4 region were as sensitive to neutralization by this Ab as the parental viruses. A clear relationship between neutralization potency and the affinity of the anti-FLAG antibody for its cognate epitope was observed. Yang *et al.* [2006] (**neutralization**, **binding affinity**)
- C11: Interactions of this Ab with gp120 monomer and two cleavage-defective gp140 trimers were studied. It was shown that C11 recognized the soluble monomer more efficiently than the soluble trimers and that treatment of the proteins with GA (cross-linking) further decreased the interactions of this Ab with the trimers to undetectable levels, indicating that the access of the C11 epitope was affected by cross-linking of the trimers but not the monomer. Yuan *et al.* [2006] (**antibody binding site definition and exposure**, **antibody interactions**, **binding affinity**)
- C11: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. C11 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)
- C11: A trimeric recombinant gp140 construct was developed for immunization studies. Its structural integrity was assessed by a panel of MAbs. The trimeric gp140 was poorly recognized by C11 compared to monomeric gp120, suggesting poor accessibility of the C11 epitope on the construct. Kim *et al.* [2005] (**antibody binding site definition and exposure**)
- C11: R-FL and YU2 HIV-1 strains were not neutralized by C11.C11 and other non-neutralizing Abs only recognized JR-FL cleavage-defective glycoproteins, while the neutralizing Abs (2G12 and IgG1b12) recognized both cleavage competent and cleavage-defective glycoproteins. It is suggested that an inefficient env glycoprotein precursor cleavage exposes non-neutralizing determinants, while only neutralizing regions remain accessible on efficiently cleaved spikes. For YU2, both cleavage-competent and -defective glycoproteins were recognized by both neutralizing and non-neutralizing Abs. Abs able

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to neutralize lab-adapted isolates displayed enhanced viral entry at higher Ab concentrations, whereas Abs that cannot neutralize any virus, such as C11, did not display such enhancement. Pancera & Wyatt [2005] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)

- C11: A stable trimerization motif, GCN4, was appended to the C terminus of YU2gp120 to obtain stable gp120 trimers (gp120-GCN4). Each trimer subunit was capable of binding IgG1b12, indicating that they were at least 85% active. D457V mutation in the CD4 binding site resulted in a decreased affinity of the gp120-GCN4 for CD4 and for C11. Pancera *et al.* [2005] (**binding affinity**)
- C11: A reverse capture assay was developed to asses what kind of human MAbs were produced in EBV B-cell transformation assays performed on PBMC sampled at different timepoints from three HIV-1 infected patients on HAART. The reverse capture assay was validated by the solid phase MAbs that could not capture biotin-MAbs of the same or overlapping specificity when reacted with patient virus envelope glycoproteins preincubated with or without sCD4. Reverse capture assay showed that the produced Abs from the patients were able to block binding of biotin-labeled C11, indicating presence of C11-like Abs. Robinson *et al.* [2005] (**antibody generation**, **assay development**, **HAART, ART**)
- C11: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. V1/V2/V3 MAb 4KG2, C1-C4 MAb A32, C1-C5 MAb C11, and HIVIG all either did not bind or had significantly diminished binding to both antigen constructs. Selvarajah *et al.* [2005] (**vaccine antigen design**, **vaccine-specific epitope characteristics**)
- C11: A substantial fraction of soluble envelope glycoprotein trimers contained inter-subunit disulfide bonds. Reduction of these disulfide bonds decreased binding of C11 to the glycoprotein, indicating that the inter-S-S bonds contribute to the exposure of the C11 epitope. Yuan *et al.* [2005] (**antibody binding site definition and exposure**)
- C11: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including C11. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- C11: Env genes derived from uncultured brain biopsy samples from four HIV-1 infected patients with late-stage AIDS were compared to env genes from PBMC samples. Brain isolates did not differ in the total number or positions of N-glycosylation sites, patterns of coreceptor usage, or ability to be recognized by gp160 and gp41 MAbs. C11 recognized most variants,some from each of the four individuals, by gp120 immunoprecipitation. Ohagen *et al.* [2003] (**brain/CSF**, **variant cross-recognition or cross-neutralization**)
- C11: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- C11: This paper shows that binding of CD4BS MAbs to Env blocks the conformational shift that allows co-receptor CCR5 binding and CD4-independent mediated cell fusion. C11 was used as a negative control, as C11 binding did not alter binding of CD4-independent gp120 to CCR5, nor binding to CCR5-expressing Cf2Th cells. Raja *et al.* [2003] (**co-receptor**)
- C11: gp120 mutants were used to define the CXCR4 binding site using CXCR4 displayed on paramagnetic proteoliposomes (PMPLs) to reduce non-specific gp120 binding – basic residues in the V3 loop and the beta19 strand (RIKQ, positions 419-422) were involved, and deletion of the V1-V2 loops allowed CD4-independent CXCR4 binding – MAbs 17b (CD4i) and F105 (CD4BS) were used to study conformational changes in the mutants – C11 was used to detect gp120 binding to CXCR4 or CCR5 on PMPLs. Basmaciogullari *et al.* [2002] (**antibody binding site definition and exposure**)
- C11: HIV-1 gp160deltaCT (cytoplasmic tail-deleted) proteoliposomes (PLs) containing native, trimeric envelope glycoproteins from R5 strains YU2 and JRFL, and X4 strain HXBc2, were made in a physiologic membrane setting as candidate immunogens for HIV vaccines – 2F5 bound to gp160deltaCT with a reconstituted membrane ten-fold better than the same protein on beads – anti-CD4BS MAbs IgG1b12 and F105, A32 (C1-C4), C11 (C1-C5), and 39F (V3) MAbs bound gp160deltaCT PLs indistinguishably from gp160deltaCT expressed on the cell surface – non-neutralizing MAbs C11 and A32 bound with lower affinity than NAb IgG1b12 – the MAb 17b was sCD4 inducible on gp160deltaCT PL. Grundner *et al.* [2002] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- C11: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-299) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutraliz-

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ing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Authors describe the epitope as N-term and C-term binding. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)

- C11: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibritin – stabilized oligomer gp140 delta683(-FT) showed strong preferential recognition by NAbs IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAbs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002] (**antibody binding site definition and exposure**)
- C11: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999] (**vaccine antigen design**)
- C11: Does not compete with binding of MAb generated in response to gp120-CD4 complex, CG10. Sullivan *et al.* [1998b] (**antibody interactions**)
- C11: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – C11 bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
- C11: Does not neutralize TCLA strains or primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- C11: Binds efficiently to sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding – partial re-exposure if sCD4 was bound – does not bind to HXBc2 gp120 if the 19 C-term amino acids are deleted. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
- C11: Binding enhanced by anti-V3 MAb 5G11 – reciprocal inhibition with anti-C1 MAbs. Moore & Sodroski [1996] (**antibody interactions**)
- C11: Does not neutralize JR-FL nor block gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a] (**antibody binding site definition and exposure**)
- C11: Did not block ability of gp120-sCD4 complexes to inhibit MIP-1alpha binding – binds to gp41-binding domain. Wu *et al.* [1996] (**antibody binding site definition and exposure**)
- C11: Mutations that inhibit binding: C1 (45 W/S, 88 N/P) – V5 (463 N/D) – and C5 (491 I/F, 493 P/K and 495 G/K) and enhance binding: C1 (36 V/L) – V1-V2 (152/153 GE/SM) – and DeltaV1/V2/V3. Moore *et al.* [1994d] (**antibody binding site definition and exposure**)

No. 1333
MAb ID L81
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
Ab Type gp120 C1-C5
References Parren *et al.* 1997b; Ditzel *et al.* 1997

- L81: gp120 immobilized on solid phase by capture with anti-CD4 BS MAb L72 was used for selection of Fabs – L81 binding is abolished by C1 substitution 45 W/S, C5 substitution 491 I/F, and C3 substitution L/A. Ditzel *et al.* [1997]
- L81: Does not neutralize TCLA strains or primary isolates. Parren *et al.* [1997b]

No. 1334
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 C3
References Wang *et al.* 2002b

- Autologous NAbs were studied in 3 patients on HAART that rebounded – phylogenetic analysis of env (V1-V5) sequences indicated that rebound viruses had evolved from or preexisted in baseline populations – HIV-1 rebound viruses from all 3 patients were resistant to neutralization by autologous IgG, unlike the baseline viruses – mutations in the C3 region was responsible for conferring neutralization resistance against autologous antibody in 2 of 3 patients. Wang *et al.* [2002b]

No. 1335
MAb ID 1024
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 C4
References Berman *et al.* 1997

- 1024: Binds to 1/7 isolates from breakthrough cases from a MN gp120 vaccine trial. Berman *et al.* [1997]

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No. 1336
MAb ID 4KG5 (4KG.5)
HXB2 Location Env
Author Location gp120 (JR-FL)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 V1-V2-V3
References Cham *et al.* 2006; Bowley *et al.* 2007; Selvarajah *et al.* 2005; Zwick *et al.* 2003
Keywords antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, assay standardization/improvement, binding affinity, neutralization, structure, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- 4KG5: Called 4KG.5. A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. 4KG5 was identified using both methods, and binds to a unique epitope that depends on V1, V2 and V3. Bowley *et al.* [2007] (**antibody binding site definition and exposure**, **antibody generation**, **binding affinity**, **antibody sequence variable domain**, **assay standardization/improvement**)
- 4KG5: This Ab was shown to infrequently neutralize cloned Envs (clades A, B, C, D, F1, CRF01_AE, CRF02_AG, CRF06_cpx and CRF11_cpx) derived from donors with and without broadly cross-reactive neutralizing antibodies. Cham *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 4KG5: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. V1/V2/V3 MAb 4KG2, C1-C4 MAb A32, C1-C5 MAb C11, and HIVIG all either did not bind or had significantly diminished binding to both antigen constructs. Selvarajah *et al.* [2005] (**vaccine antigen design**, **vaccine-specific epitope characteristics**)
- 4KG5: 4KG5, a single-chain Fv (scFv), reacts with a conformational epitope that is formed by the V1, V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. 4KG5 was derived from the serum of HIV-1 infected patient FDA2, who showed broad neutralizng activity, but is not itself neutralizing. Denaturation of gp120 abolished binding of 4KG5 and Fab b12. Addtionally, binding of 4KG5 was abrogated when any of the V1, V2 or V3 loops were deleted. Of a panel of Abs tested, only NAb b12 enhanced 4KG5 binding to gp120 JR-FL. MAbs to the following regions diminished or abrogated binding: V2 loop MAbs (G3-4, G3-136), V3 loop MAbs (19b, 447-52D, hNM01, AH48, loop2, F425 B4e8, 694-88D), V3-C4 (G3-299, G3-42, G3-519, G3-537), CD4BS (b6, b3, F91, F105, 15e, L33, 1008-D, 654-30D, 559-64D, 1027-30D, Ia3, Ia7, FG39, Fbb14). MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1, V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. 4KG5 recognized HIV-1 envelope proteins derived from JR-FL, JR-CSF, BaL, ADA and R2, but not MN, DH123, HxB2, YU2, SF2 and 89.6. Binding of 4KG5 to different strains of HIV-1 env is probably due to sequence differences in V3 and C4, rather than V1 or V2. Zwick *et al.* [2003] (**antibody binding site definition and exposure**, **antibody generation**, **antibody interactions**, **variant cross-recognition or cross-neutralization**, **structure**)

No. 1337
MAb ID 23A (2.3A)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen
Species (Isotype)
Ab Type gp120 C5
Research Contact James Robinson, Tulane University, LA
References Schulke *et al.* 2002; Binley *et al.* 1999; Fouts *et al.* 1997; Trkola *et al.* 1996a; Wu *et al.* 1996; Thali *et al.* 1993; Thali *et al.* 1992a

- 23A: Ab binding characteristics of SOS gp140 were tested using SPR and RIPA – SOS gp140 is gp120-gp41 bound by a disulfide bond – NAbs 2G12, 2F5, IgG1b12, CD4 inducible 17b, and 19b bound to SOS gp140 better than uncleaved gp140 (gp140unc) and gp120 – non-neutralizing MAbs 2.2B (binds to gp41 in gp140unc) and 23A (binds gp120) did not bind SOS gp140. Schulke *et al.* [2002]
- 23A: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999]

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- 23A: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric env binding – 23A bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997]
- 23A: C5 binding MAb – does not inhibit gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]
- 23A: Called 2.3A – Did not block ability of gp120-sCD4 complexes to inhibit MIP-1alpha binding – binds to gp41-binding domain of gp120. Wu *et al.* [1996]

No. 1338
MAb ID D7324
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
HIV component: gp120
Species (Isotype) sheep
Ab Type gp120 C5
Research Contact Aalto BioReagents Ltd, Dublin, Ireland or Cliniqa Inc., Fallbrook, CA, USA
References Stricher *et al.* 2008; Martin *et al.* 2008; Sheppard *et al.* 2007b; Martín-García *et al.* 2005; Koefoed *et al.* 2005; Jeffs *et al.* 2004; Zwick *et al.* 2003; Herrera *et al.* 2003; Poignard *et al.* 2003; Basmaciogullari *et al.* 2002; Xiang *et al.* 2002a; Gram *et al.* 2002; Sanders *et al.* 2002; Binley *et al.* 1998; Mondor *et al.* 1998; Ugolini *et al.* 1997; Ditzel *et al.* 1997; Trkola *et al.* 1996a; Wyatt *et al.* 1995; Moore *et al.* 1993b; Moore *et al.* 1993a; Sattentau & Moore 1991; Moore 1990
Keywords antibody binding site definition and exposure, antibody interactions, assay development, binding affinity, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- D7324: A new purification method was developed using a high affinity peptide mimicking CD4 as a ligand in affinity chromatography. This allowed the separation in one step of HIV envelope monomer from cell supernatant and capture of pre-purified trimer. The identity of gp120SF162 purified by miniCD4 method was confirmed by D7324-binding. D7324 was also used to normalize the concentration of gp120SF162 envelopes for comparison between the miniCD4 affinity chromatography and a reference method. Binding of D7324 to gp120SF162 purified by the miniCD4 affinity chromatography and a multi-step method was comparable, suggesting that the miniCD4 allows the separation of HIV-1 envelope with intact D7324 epitope. Martin *et al.* [2008] (**assay development**, **binding affinity**)
- D7324: Binding of gp120 in the presence or absence of CD4, or in the presence of synthetic miniproteins with HIV-1 gp120 binding surface of the CD4 receptor incorporated, were evaluated using D7324 Ab. Phenylalanine derivatives of the miniproteins were more capable of inducing a CCR5-binding conformation of gp120. Stricher *et al.* [2008]
- D7324: This Ab was shown not to bind to clade C gp140 (97CN54). Sheppard *et al.* [2007b] (**variant cross-recognition or cross-neutralization**)
- D7324: IgG antibody phage display libraries were created from HIV-1 + individuals after pre-selection of PBMC with gp120, as an alternative to using bone marrow for generating libraries. D7324 was among a set of Abs used for competition studies to define the binding sites of the newly isolated MAbs, representing a MAb with a C5 epitope. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**)
- D7324: The HIV-1 Bori-15 variant was adapted from the Bori isolate for replication microglial cells. Bori-15 had increased replication in microglial cells and a robust syncytium-forming phenotype, ability to use low levels of CD4 for infection, and increased sensitivity to neutralization by sCD4 and 17b. Four amino acid changes in gp120 V1-V2 were responsible for this change. Protein functionality and integrity of soluble, monomeric gp120-molecules derived from parental HIV-1 Bori and microglia-adapted HIV-1 Bori-15 was assessed in ELISA binding assays using F105, IgG1b12, 17b and 48d, 2G12 and 447-52D. Association rates of sCD4 and 17b were not changed, but dissociation rates were 3-fold slower for sCD4 and 14-fold slower for 17b. The kinetics of D7324 binding were tested as a control, and were unchanged. Martín-García *et al.* [2005] (**antibody binding site definition and exposure**)
- D7324: A set of oligomeric envelope proteins were made from six primary isolates for potenial use as vaccine antigens: 92/UG/037 (clade A), HAN2/2 (clade B), 92/BR25/025 (clade C), 92/UG/021 (clade D), 93/BR/029 (clade F) and MVP5180 (clade O). This was one of a panel of MAbs used to explore folding and exposure of well characterized epitopes. The clade C isolate BR25 is apparently misfolded, as conformation-dependent antibodies did not bind to it. D7324 bound to clade A, B, C, D and F HIV-1 primary isolates, but not to the group O protein. Polyclonal sera raised in rabbits against these antigens cross-bound the other antigens, but none of the sera had neutralizing activity. Jeffs *et al.* [2004] (**vaccine antigen design**, **subtype comparisons**)
- D7324: Used to capture gp120 onto solid phase for epitope mapping. Basmaciogullari *et al.* [2002]; Binley *et al.* [1998]; Ditzel *et al.* [1997]; Herrera *et al.* [2003]; Moore *et al.* [1993a,b]; Poignard *et al.* [2003]; Sanders *et al.* [2002]; Xiang *et al.* [2002a]
- D7324: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a C5-binding polyclonal Ab that had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
- D7324: Called NEA9205 – gp120 capture ELISAs with MAbs D7324 (anti-C-term) or 9205 (anti-V3) were compared in a study of orientation of glycosylation sites – CD4 binding could only inhibit deglycosylation when gp120 was bound to the plate by D7324, not by 9205, while Abs from HIV-1 in-

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fected people inhibited deglycosylation most effectively when gp120 was caught by 9205. Gram *et al.* [2002]

- D7324: Epitope in C5 – Does not neutralize JR-FL nor block gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]
- D7324: Binds to the last 15 amino acids in gp120 – used for antigen capture ELISA. Wyatt *et al.* [1995]
- D7324: Binding unaltered by gp120 binding to sCD4, in contrast to 110.5, 9284, 50-69 and 98-6. Sattentau & Moore [1991]

No. 1339
MAb ID 10/46c
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* gp120
Species (Isotype) rat
Ab Type gp120 CD4BS
References Peet *et al.* 1998; Jeffs *et al.* 1996; Cordell *et al.* 1991

- 10/46c: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind – 10/46c was not affected by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]
- 10/46c: Increased binding when V1/V2 or V1/V2 and V3 were deleted from gp120. Jeffs *et al.* [1996]

No. 1340
MAb ID 1008-D
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU Med Center, NY, NY
References Zwick *et al.* 2003; Zolla-Pazner *et al.* 1995
Keywords antibody interactions

- scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)

No. 1341
MAb ID 1027-30-D (1027-30D, 1027/30D, 1027)
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype) human (IgG1κ)
Ab Type gp120 CD4BS
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Visciano *et al.* 2008a; Visciano *et al.* 2008b; Gorny & Zolla-Pazner 2004; Zwick *et al.* 2003; Hioe *et al.* 2000
Keywords antibody interactions, review

- 1027/30D: A significantly higher level of anti-V3 Abs (694/98D) and anti-C1 mAb (EH21) bound to gp120 complexed with 1027/30D mAb than to gp120 alone or in complex with other non-CD4bs Abs, indicating that binding of 1027/30D to gp120 increases exposure of specific V3 and C1 mAb epitopes. Visciano *et al.* [2008b]
- 1027: A mouse CD4 T cell clone proliferated well in response to gp120 alone but this response was inhibited by more than 80% when gp120 was complexed with mAb 1027. These results indicate that anti-CD4bs Abs inhibit CD4 T cell responses to gp120 in the murine system. Visciano *et al.* [2008a]
- 1027-30D: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 1027-30-D: Called 1027-30D. scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- 1027-30-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – anti-CD4 binding site MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – CD4BS MAbs 654-D, 559/64-D, 588-D, 830-D, 1027-30-D, and 1202-30D strongly diminished proliferation. Hioe *et al.* [2000]

No. 1342
MAb ID 1125H (1125h)
HXB2 Location Env
Author Location gp120

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Epitope
Neutralizing L (MN)
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 CD4BS
Research Contact Shermaine Tilley, Public Health Research Institute, USA
References Yang *et al.* 1998; Alsmadi & Tilley 1998; Wyatt *et al.* 1998; Pincus *et al.* 1996; Warrier *et al.* 1996; D'Souza *et al.* 1995; Pinter *et al.* 1993b; Wyatt *et al.* 1992; Thali *et al.* 1992a; Tilley *et al.* 1991a; Tilley *et al.* 1991b

- 1125H: A study of 6 anti-Env MAbs and their ability to bind or direct ADCC against target cells infected with IIIB, MN, SF-2, and RF – bound and directed lysis against all four strains. Alsmadi & Tilley [1998]
- 1125H: Called 1125h – summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAb binding – probable mechanism of neutralization by CD4BS Ab is direct interference with CD4 binding. Wyatt *et al.* [1998]
- 1125H: A neutralization assay was developed based on hemi-nested PCR amplification of the LTR (HNPCR) – LTR-HNPCR consistently revealed HIV DNA and was shown to be a rapid, specific and reliable neutralization assay based on tests with 6 MAbs and 5 isolates. Yang *et al.* [1998]
- 1125H: A panel of immunotoxins were generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but killing was not directly proportional to binding. Pincus *et al.* [1996]
- 1125H: Synergistic neutralization of HIV-1 when combined with anti-V2 MAb C108G. Warrier *et al.* [1996]
- 1125H: Neutralization was MN specific – failed to neutralize JRCSF, and 2 B subtype and 1 D subtype primary isolates in a multi-laboratory study involving 11 labs. D'Souza *et al.* [1995]
- 1125H: Binding to soluble gp120 enhanced by the presence of an anti-V3 HuMAb, 41148D. Pinter *et al.* [1993b]
- 1125H: Amino acid substitutions in HXB2 that strongly inhibit binding: 88, 102, 117, 113, 257, 368, 370, 421, 427, 457, 470, 480. Thali *et al.* [1992a]
- 1125H: Precipitation of Delta 297-329 env glycoprotein, with has a deleted V3 loop, is much more efficient that precipitation of wild type. Wyatt *et al.* [1992]
- 1125H: Binding to gp120 inhibited by CD4 – epitope is destroyed by reduction, but not by removal of N-linked sugars – potent neutralization of MN, RF, SF-2 and IIIB – neutralization synergy with anti-V3 MAb 4117C. Tilley *et al.* [1991a]

No. 1343
MAb ID 1125H (1125h)
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing L (MN)
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 CD4BS
Research Contact Shermaine Tilley, Public Health Research Institute, USA
References Wilkinson *et al.* 2007; Tuen *et al.* 2005; Pinter *et al.* 2004; Gorny & Zolla-Pazner 2004; Yang *et al.* 1998; Alsmadi & Tilley 1998; Wyatt *et al.* 1998; Pincus *et al.* 1996; Warrier *et al.* 1996; D'Souza *et al.* 1995; Pinter *et al.* 1993b; Wyatt *et al.* 1992; Thali *et al.* 1992a; Tilley *et al.* 1991a; Tilley *et al.* 1991b
Keywords ADCC, antibody binding site definition and exposure, antibody generation, antibody interactions, assay development, binding affinity, immunotoxin, review, structure, subtype comparisons, variant cross-recognition or cross-neutralization

- 1125H: This Ab was used to screen a phage peptide library but no positive clones were observed. Wilkinson *et al.* [2007] (**antibody generation**)
- 1125H: This Ab bound with an intermediate affinity to gp120IIIb, it did not prevent uptake of gp120 by APCs, and it had a weak inhibitory effect on gp120 antigen presentation by MHC class II. 1125H readily disassociated from gp120 at acidic pH. Lysosomal enzyme digestion of gp120 treated with 1125H yielded fragmentation similar to that of gp120 alone, and digestion rate was intermediate, between the rapid digestion of gp120 alone and the slow digestion of gp120 in complex with high-affinity Ab5145A. It is thus concluded that CD4bs Ab 1125H does not have a strong inhibitory effect on gp120 processing and presentation. Tuen *et al.* [2005] (**antibody interactions**, **binding affinity**)
- 1125H: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 1125H: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neturalization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Three anti-CD4BS MAbs were tested, including IgG1b12 which neutralizes both JRFL and SF162. The affinities for IgG1b12 and 5145A were similar for both JRFL and SF612, but 1125A bound with 2.5 fold higher affinity to SF162. 5145A and 1125H both preferentially neutralize SF162, but not JRFL, and the CD4BS is more sensitive to neutralization in the context of the SF162 V1V2 loop. This was also true for neutralization by sCD4. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 1125H: A study of 6 anti-Env MAbs and their ability to bind or direct ADCC against target cells infected with IIIB, MN, SF-2, and RF – bound and directed lysis against all four strains. Alsmadi & Tilley [1998] (**ADCC**)
- 1125H: Called 1125h – summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAb bind-

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ing – probable mechanism of neutralization by CD4BS Ab is direct interference with CD4 binding. Wyatt *et al.* [1998] (**structure**)

- 1125H: A neutralization assay was developed based on hemi-nested PCR amplification of the LTR (HNPCR) – LTR-HNPCR consistently revealed HIV DNA and was shown to be a rapid, specific and reliable neutralization assay based on tests with 6 MAbs and 5 isolates. Yang *et al.* [1998] (**assay development**)
- 1125H: A panel of immunotoxins were generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but killing was not directly proportional to binding. Pincus *et al.* [1996] (**immunotoxin**)
- 1125H: Synergistic neutralization of HIV-1 when combined with anti-V2 MAb C108G. Warrier *et al.* [1996] (**antibody interactions**)
- 1125H: Neutralization was MN specific – failed to neutralize JRCSF, and 2 B subtype and 1 D subtype primary isolates in a multi-laboratory study involving 11 labs. D'Souza *et al.* [1995] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 1125H: Binding to soluble gp120 enhanced by the presence of an anti-V3 HuMAb, 41148D. Pinter *et al.* [1993b] (**antibody interactions**)
- 1125H: Amino acid substitutions in HXB2 that strongly inhibit binding: 88, 102, 117, 113, 257, 368, 370, 421, 427, 457, 470, 480. Thali *et al.* [1992a] (**antibody binding site definition and exposure**)
- 1125H: Precipitation of Delta 297-329 env glycoprotein, with has a deleted V3 loop, is much more efficient that precipitation of wild type. Wyatt *et al.* [1992] (**antibody binding site definition and exposure**)
- 1125H: Binding to gp120 inhibited by CD4 – epitope is destroyed by reduction, but not by removal of N-linked sugars – neutralization of MN, RF, SF-2 and IIIB – neutralization synergy with anti-V3 MAb 4117C. Tilley *et al.* [1991a] (**antibody binding site definition and exposure**, **antibody interactions**, **variant cross-recognition or cross-neutralization**)

No. 1344
MAb ID 120-1B1
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen
Species (Isotype) human
Ab Type gp120 CD4BS
Research Contact Virus Testing Systems Corp., Houston, TX
References Gorny & Zolla-Pazner 2004; Watkins *et al.* 1993
Keywords antibody binding site definition and exposure, review

- 120-1B1: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 120-1B1: A neutralization escape mutant (HXB2 A281V) was selected by growth of HXB2 in the presence of broadly neutralizing sera – 120-1B1 was not affected by this mutation. Watkins *et al.* [1993] (**antibody binding site definition and exposure**)

No. 1345
MAb ID 1202-D (1202-30-D)
HXB2 Location Env
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype) human (IgG1κ)
Ab Type gp120 CD4BS
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Hioe *et al.* 2000; Nyambi *et al.* 1998
Keywords review, subtype comparisons

- 1202-D: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 1202-D: Called 1202-30D – Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – anti-CD4 binding site MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – CD4BS MAbs 654-D, 559/64-D, 588-D, 830-D, 1027-30-D, and 1202-30D strongly diminished proliferation. Hioe *et al.* [2000]
- 1202-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 CD4BS MAbs – CD4BS MAbs bound consistently to most isolates of clade D, but poorly to isolates of other clades with the exception of broadly reactive MAb IgG1b12. Nyambi *et al.* [2000] (**subtype comparisons**)
- 1202-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – CD4-BS Abs tended to bind weakly without clade specificity to virions, but bound well to soluble gp120 – 1202-D did not bind to any B clade viruses, and weakly bound A, C, and G clade isolates – 559/64-D, 558-D and 1202-D had similar reactivities. Nyambi *et al.* [1998] (**subtype comparisons**)

No. 1346
MAb ID 1331E
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 CD4BS
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)

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References Gorny & Zolla-Pazner 2004; Gorny *et al.* 2000
Keywords antibody binding site definition and exposure, review

- 1331E: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 1331E: Inhibits sCD4 binding to rec gp120 LAI – binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – CD4BS MAbs 559/64-D, 654-D, 729-D, 9CL and 1331E bound with a 5-13 fold preference for the oligomer. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)

No. 1347
MAb ID 1570 (1570A, 1570C, 1570D)
HXB2 Location Env
Author Location Env (PR12, BH10)
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
References Gorny & Zolla-Pazner 2004; Jeffs *et al.* 2001
Keywords antibody binding site definition and exposure, antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 1570: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 1570: BH10 was mutated to form the PR12 protein with the first 74 C-terminal amino acids and the V1, V2 and V3 hypervariable loops deleted and a very well exposed CD4 binding domain (CD4bd) – this proteins was used to select three new human CD4BS MAbs 1570, 1595 and 1599 – three MAbs were isolated from one individual, 1570A, C and D but all were determined to have the same V(H)3 region – 1570 was able to bind to a panel of recombinant proteins from the A, B, C, D, and E subtypes. Jeffs *et al.* [2001] (**antibody binding site definition and exposure**, **antibody generation**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1348
MAb ID 1595
HXB2 Location Env
Author Location Env (PR12, BH10)
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
References Gorny & Zolla-Pazner 2004; Jeffs *et al.* 2001
Keywords antibody binding site definition and exposure, antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 1595: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 1595: BH10 was mutated to form the PR12 protein with the first 74 C-terminal amino acids and the V1, V2 and V3 hypervariable loops deleted and a very well exposed CD4 binding domain (CD4bd) – this proteins was used to select three new human CD4BS MAbs 1570, 1595 and 1599 – 1595 was able to bind gp120 from the A, B, and D clades from a panel of recombinant proteins from the A, B, C, D, and E subtypes. Jeffs *et al.* [2001] (**antibody binding site definition and exposure**, **antibody generation**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1349
MAb ID 1599
HXB2 Location Env
Author Location Env (PR12, BH10)
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
References Gorny & Zolla-Pazner 2004; Jeffs *et al.* 2001
Keywords antibody binding site definition and exposure, antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 1599: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 1599: BH10 was mutated to form the PR12 protein with the first 74 C-terminal amino acids and the V1, V2 and V3 hypervariable loops deleted and a very well exposed CD4 binding domain (CD4bd) – this proteins was used to select three new human CD4BS MAbs 1570, 1595 and 1599 – 1599 was able to bind gp120 only from the B clade from a panel of recombinant proteins from the A, B, C, D, and E subtypes. Jeffs *et al.* [2001] (**antibody binding site definition and exposure**, **antibody generation**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1350
MAb ID 15e (1.5e, 1.5E, 15E)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 CD4BS
Research Contact James Robinson, Tulane University, LA, and David Ho, ADARC, NY, NY

References Vaine *et al.* 2008; Dey *et al.* 2008; Frey *et al.* 2008; Kramer *et al.* 2007; Crooks *et al.* 2007; Yuan *et al.* 2006; Zhou *et al.* 2007; Lin & Nara 2007; Derby *et al.* 2006; Yang *et al.* 2005c; Srivastava *et al.* 2005; Robinson *et al.* 2005; Mc Cann *et al.* 2005; Crooks *et al.* 2005; Nabatov *et al.* 2004; Pantophlet *et al.* 2004; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Raja *et al.* 2003; Pantophlet *et al.* 2003a; Kwong *et al.* 2002; Zhang *et al.* 2002; Xiang *et al.* 2002b; Kolchinsky *et al.* 2001; Park *et al.* 2000; Sullivan *et al.* 1998a; Fouts *et al.* 1998; Trkola *et al.* 1998; Binley *et al.* 1998; Sullivan *et al.* 1998b; Parren *et al.* 1998a; Wyatt *et al.* 1998; Parren *et al.* 1997b; Berman *et al.* 1997; Wyatt *et al.* 1997; Li *et al.* 1997; Fouts *et al.* 1997; Binley *et al.* 1997a; Wisnewski *et al.* 1996; McDougal *et al.* 1996; Trkola *et al.* 1996a; Poignard *et al.* 1996a; Moore & Sodroski 1996; McKeating *et al.* 1996; Lee *et al.* 1995; Sattentau & Moore 1995; Moore *et al.* 1994a; Moore *et al.* 1994b; Cook *et al.* 1994; Thali *et al.* 1994; Bagley *et al.* 1994; Wyatt *et al.* 1993; Watkins *et al.* 1993; Thali *et al.* 1993; Moore & Ho 1993; Takeda *et al.* 1992; Thali *et al.* 1992a; Wyatt *et al.* 1992; Ho *et al.* 1992; Koup *et al.* 1991; Ho *et al.* 1991b; Cordell *et al.* 1991; Thali *et al.* 1991; Robinson *et al.* 1990a

Keywords ADCC, adjuvant comparison, antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, assay development, assay standardization/improvement, binding affinity, brain/CSF, co-receptor, enhancing activity, HAART, ART, kinetics, neutralization, review, structure, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- 15e: UK Medical Research Council AIDS reagent: ARP3016.
- 15e: Five amino acids in the gp41 N-terminal region that promote gp140 trimerization (I535, Q543, S553, K567 and R588) were considered. Their influence on the function and antigenic properties of JR-FL Env expressed on the surfaces of pseudoviruses and Env-transfected cells was studied. Various non-neutralizing antibodies bind less strongly to the Env mutant, but neutralizing antibody binding is unaffected. 15e captured significantly fewer mutant pseudovirions than wild type, and 15e failed to inhibit infection by either pseudovirus. Dey *et al.* [2008] (**binding affinity**)
- 15e: Molecular mechanism of neutralization by MPER antibodies, 2F5 and 4E10, was studied using preparations of trimeric HIV-1 Env protein in the prefusion, the prehairpin intermediate and postfusion conformations. MAb 15e was used to analyze antigenic properties of construct 92UG-gp140-Fd, derived from isolate 92UG037.8 and stabilized by a C-terminal foldon tag. 92UG-gp140-Fd failed to bind 15e, despite high affinity of 15e for 92UG-gp120 core. Frey *et al.* [2008] (**binding affinity**)
- 15e: Sera from gp120 DNA prime-protein boost immunized rabbits competed for binding to 15e while sera from rabbits immunized with protein-only regimen did not, indicating elicitation of 15e-like Abs in animals immunized with DNA prime-protein boost regimen. Competitive virus capture assay also revealed higher titers of 15e Abs in animals immunized with DNA prime-protein boost than in protein-only immunized animals. Vaine *et al.* [2008] (**vaccine antigen design**)
- 15e: Most of the sera from guinea pigs immunized with gp120 protein or with three types of VLPs containing disulfide-shackled functional trimers (SOS-VLP), uncleaved nonfunctional Env (UNC-VLP), naked VLP bearing no Env, weakly or ineffectively inhibited virus capture compared to 15e Ab. Crooks *et al.* [2007] (**neutralization**)
- 15e: This review summarizes 15e Ab epitope, properties and neutralization activity. Kramer *et al.* [2007] (**review**)
- 15e: Molecules designed to eliminate binding by 15e while preserving epitopes of other neutralizing Abs are discussed. Lin & Nara [2007] (**review**)
- 15e: This Ab was used to determine the degree to which fixation of gp120 in its CD4-bound conformation restricts antigenic recognition. 15e was not able to bind well to the stabilized gp120. Zhou *et al.* [2007] (**antibody binding site definition and exposure**, **binding affinity**)
- 15e: Macaques were immunized with SF162gp140, ΔV2gp140, ΔV2ΔV3gp140 and ΔV3gp140 constructs and their antibody responses were compared to the broadly reactive NAb responses in a macaque infected with SHIV SF162P4, and with pooled sera from humans infected with heterologous HIV-1 isolates (HIVIG). 15e-like Abs were generated in the SHIV-infected macaque, and may have been present at very low titers in macaques immunized with ΔV2gp140 and ΔV2ΔV3gp140. No 15e Abs were detected in the sera from F162gp140 immunized animals. Derby *et al.* [2006] (**antibody binding site definition and exposure**, **antibody generation**)
- 15e: Interactions of this Ab with gp120 monomer and two cleavage-defective gp140 trimers were studied. It was shown that 15e recognized the soluble monomer and trimers much more efficiently than the GA-treated (cross-linked) monomers and trimers, indicating that the 15e epitope was affected by cross-linking. This Ab was associated with a large entropy change upon gp120 binding. 15e sucsesfully recognized untreated but not cross-linked proteins expressed on cell surfaces indicating existence of multiple conformational states of gp120 on cell surface. This Ab was shown to have a kinetic disadvantage as it bound to gp120 much slower than the highly neutralizing Abs 2G12 and IgG1b12. Yuan *et al.* [2006] (**antibody binding site definition and exposure**, **antibody interactions**, **kinetics**, **binding affinity**)
- 15e: MAbs were investigated in differnt neutralization formats, including the standard format that measures activity over the entire infection period and several formats that emphasize various stages of infection. 15e did not neutralize in standard format. Crooks *et al.* [2005] (**neutralization**, **assay standardization/improvement**)
- 15e: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mecha-

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nisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **review**)

- 15e: A reverse capture assay was developed to asses what kind of human MAbs were produced in EBV B-cell transformation assays performed on PBMC sampled at different timepoints from three HIV-1 infected patients on HAART. The reverse capture assay was validated by the solid phase MAbs that could not capture biotin-MAbs of the same or overlapping specificity when reacted with patient virus envelope glycoproteins preincubated with or without sCD4. Reverse capture assay showed that the produced Abs from the patients did not block binding of biotin-labeled 15e in early samples from the patients, indicating no detection of CD4bs Abs. CD4bs Abs were only detected in significant numbers in one patient at week 168 after diagnosis. Robinson *et al.* [2005] (**antibody generation**, **assay development**, **HAART, ART**)
- 15e: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **review**)
- 15e: Ab neutralization of viruses with mixtures of neutralization-sensitive and neutralization-resistant envelope glycoproteins was measured. It was concluded that binding of a single Ab molecule is sufficient to inactivate function of an HIV-1 glycoprotein trimer. The inhibitory effect of the Ab was similar for neutralization-resistant and -sensitive viruses indicating that the major determinant of neutralization potency of an Ab is the efficiency with which it binds to the trimer. It was also indicated that each functional trimer on the virus surface supports HIV-1 entry independently, meaning that every trimer on the viral surface must be bound by an Ab for neutralization of the virus to be achieved. Yang *et al.* [2005c] (**neutralization**)
- 15e: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 15e: A set of HIV-1 chimeras that altered V3 net charge and glycosylation patterns in V1V2 and V3, involving inserting V1V2 loops from a late stage primary isolate taken after the R5 to X4 switch, were studied with regard to phenotype, co-receptor usage, and MAb neutralization. The loops were cloned into a HXB2 envelope with a LAI viral backbone. It was observed that the addition of the late-stage isolate V1V2 region and the loss of V3-linked glycosylation site in the context of high positive charge gave an X4 phenotype. R5X4, R5, and X4 viruses were generated, and sCD4, 2G12 and b12 neutralization resistance patterns were modified by addition of the late stage V1V2, glycosylation changes, and charge in concert, while neutralization by 2F5 was unaffected. 15e, 17b, and 48d could not neutralize any of the variants tested. Nabatov *et al.* [2004] (**antibody binding site definition and exposure**, **co-receptor**)
- 15e: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 15e. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- 15e: Alanine scanning mutagenesis was used to compare substitutions that affected anti-CD4BS NAb b12 – rec gp120s were engineered to contain combinations of Alanine substitutions that enhanced b12 binding, and while binding of b12 to these gp120 monomers was generally maintained or increased, binding by five non-neutralizing anti-CD4bs MAbs (b3, b6, F105, 15e, and F91) was reduced or completely abolished. Pantophlet *et al.* [2003a] (**antibody binding site definition and exposure**)
- 15e: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- 15e: This paper shows that binding of CD4BS MAbs to Env blocks the conformational shift that allows co-receptor CCR5 binding and CD4-independent mediated cell fusion. CD4BS MAbs F105, 15e, and IgG1b12 as well as their Fab fragments inhibited CD4-independent binding of the V1/V2 loop-deleted gp120 glycoproteins of R5 HIV-1 isolates ADA, YU2 and JRFL and to CCR5 in a concentration dependent manner. Raja *et al.* [2003] (**co-receptor**)
- 15e: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- 15e: Called 1.5e. Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar.

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Enthalpy and entropy changes were divergent, but compensated. Not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs (17b, 48d, 1.5e, b6, F105 and F91) had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, but the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol, The high values suggest surface burial or protein folding an ordering of amino acids. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)

- 15e: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91 was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b] (**antibody binding site definition and exposure**)
- 15e: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002] (**antibody binding site definition and exposure**)
- 15e: Mutations in two glcosylation sites in the V2 region of HIV-1 ADA at positions 190 and 197 (187 DNTSYRLINCNTS 199) cause the virus to become CD4-independent and able to enter cells through CCR5 alone – these same mutations tended to increase the neutralization sensitivity of the virus, including to 15e. Kolchinsky *et al.* [2001] (**antibody binding site definition and exposure**)
- 15e: Six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000] (**antibody binding site definition and exposure**)
- 15e: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer – CD4BS MAbs 15e, F91 and IgG1b12 bound better to the deleted protein than to wild type. Binley *et al.* [1998] (**antibody binding site definition and exposure**)
- 15e: CD4BS MAbs 15e, 21h, and F91 bind with even lower affinity than 205-43-1 and 205-42-15 to JRFL oligomer. Fouts *et al.* [1998] (**antibody binding site definition and exposure**)
- 15e: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**antibody binding site definition and exposure**)
- 15e: Competes with CG-10 binding, a MAb raised against a gp120 CD4 complex, this was probably due to the disruption of CD4-gp120 by 15e. Sullivan *et al.* [1998b] (**antibody binding site definition and exposure**, **antibody interactions**)
- 15e: Called 1.5e – the HIV-1 virus YU2 entry can be enhanced by MAbs binding to the CD4BS, V3 loop, and CD4i epitopes – the activation for this enhanced entry state could be conferred on HxB2 by introducing the YU2 V3 loop, or the YU2 V3 and V1/V2 loops – a similar effect is observed by sub-neutralizing concentrations of sCD4 and the effect is dependent of CCR5 – 1.5e enhances and does not neutralize YU2 env even at 50 ug/ml. Sullivan *et al.* [1998a] (**antibody binding site definition and exposure**)
- 15e: No detectable neutralizing activity among primary isolates with different co-receptor usage – some neutralization of TCLA strains. Trkola *et al.* [1998] (**variant cross-recognition or cross-neutralization**)
- 15e: Summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAb binding – probable mechanism of neutralization by CD4BS Ab is direct interference with CD4 binding. Wyatt *et al.* [1998] (**structure**)
- 15e: Called 1.5E – Binds to 7/7 isolates from breakthrough cases from a MN gp120 vaccine trial. Berman *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- 15e: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – 15e bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
- 15e: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env – 15e could only achieve 50% neutralization, but could act synergistically with anti-V3 MAb 694/98-D to achieve 90%. Li *et al.* [1997] (**antibody interactions**)
- 15e: Neutralizes TCLA strains, but not primary isolates. Parren *et al.* [1997b]
- 15e: Does not bind to HXBc2 gp120 if the 19 C-term amino acids, in conjunction with C1 positions 31-93, are deleted. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)

- 15e: Neutralizes HIV-1 LAI less potently than V3 specific MAbs. McDougal *et al.* [1996]
- 15e: Called 1.5e – Neutralizes HXB2, but fails to neutralize chimeric virus with gp120 from primary isolates in an HXB2 background. McKeating *et al.* [1996] (**variant cross-recognition or cross-neutralization**)
- 15e: gp120 binding enhanced by anti-V3 MAb 5G11 and anti-V2 MAb G3-136 – binding inhibited by other CD4 binding site MAbs, antibodies that bind to gp120 only when CD4 is bound, and CD4-IgG. Moore & Sodroski [1996] (**antibody interactions**)
- 15e: Anti-CD4BS MAbs 15e, 21h, and IgG1b12 did not cause gp120 dissociation from virus, or exposure of the gp41 epitope of MAb 50-69, in contrast to CD4i MAb 48d and anti-V3 neutralizing MAbs. Poignard *et al.* [1996a] (**antibody interactions**)
- 15e: Inhibits gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a] (**antibody binding site definition and exposure**)
- 15e: 15e is V H4 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996] (**antibody sequence variable domain**)
- 15e: The V4 and V5 domains are essential for 1.5e binding, in contrast to the V1, V2, and V3 loops. Lee *et al.* [1995] (**antibody binding site definition and exposure**)
- 15e: Binds with higher affinity to monomer than to oligomer, moderate association rate. Sattentau & Moore [1995] (**antibody binding site definition and exposure**)
- 15e: Heavy chain is V HIV, V2-1 – light chain is V_kappaI, Hum01/012. Compared to 21h and F105. Bagley *et al.* [1994] (**antibody sequence variable domain**)
- 15e: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – anti-CD4 MAbs moderately inhibit gp120 binding to GalCer, possibly through steric hindrance – binding of GalCer to gp120 inhibited but did not completely block 15e binding. Cook *et al.* [1994] (**antibody binding site definition and exposure**, **brain/CSF**)
- 15e: Cross-reactive with gp120 proteins from clades B and D, less so with A and C, and not reactive with clade E and F. Moore *et al.* [1994b] (**subtype comparisons**)
- 15e: A mutation in gp41, 582 A/T, confers resistance to neutralization (also confers resistance to MAbs F105, 48d, 21h and 17b).. Thali *et al.* [1994] (**antibody binding site definition and exposure**)
- 15e: Conformational, does not bind denatured gp120 – neutralizes IIIB – reactive with SF-2 gp120 – strong inhibition of HIV+ human sera binding to IIIB gp120. Moore & Ho [1993] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 15e: Called 15E – a neutralization escape mutant (HXB2 A281V) was selected by growth of HXB2 in the presence of broadly neutralizing sera – 15E neutralization was not affected by this mutation. Watkins *et al.* [1993] (**antibody binding site definition and exposure**)
- 15e: Binding to Delta V1/2 and Delta V1/2/3 mutant glycoproteins is greater than binding to wildtype gp120. Wyatt *et al.* [1993] (**antibody binding site definition and exposure**)
- 15e: gp120 mutants that affect 15e epitope binding: 113, 257, 368, 370, 421, 427, 475 – four of these coincide with amino acids important for the CD4 binding domain. Ho *et al.* [1992] (**antibody binding site definition and exposure**)
- 15e: Amino acid substitutions in HXB2 that strongly inhibit binding, similar to Ho *et al.* [1992], some additional, 88, 102, 117, 113, 257, 368, 370, 421, 427, 457, 470, 480 Thali *et al.* [1992a]. Ho *et al.* [1992]; Thali *et al.* [1992a] (**antibody binding site definition and exposure**)
- 15e: Called N70-1.5e – does not enhance infection of HIV-1 IIIB and MN. Thali *et al.* [1992a] (**enhancing activity**)
- 15e: Precipitation of Delta 297-329 env glycoprotein, with a deleted V3 loop, is much more efficient that precipitation of wild type. Wyatt *et al.* [1992] (**antibody binding site definition and exposure**)
- 15e: Cross-competes with MAbs ICR 39.13g and ICR 39.3b. Cordell *et al.* [1991] (**antibody interactions**)
- 15e: Broadly neutralizing, binds multiple strains, competes with CD4 for gp120 binding, DTT reduction of env abrogates binding – more potent blocking of gp120-sCD4 binding than MAbs G3-536 and G3-537.. Ho *et al.* [1991b] (**adjuvant comparison**, **variant cross-recognition or cross-neutralization**)
- 15e: Binds to gp120 of HIV-1 IIIB, but not RF – mediates ADCC – deletion of the V3 loop from gp120 does not alter ADCC activity. Koup *et al.* [1991] (**ADCC**, **variant cross-recognition or cross-neutralization**)

No.	1351
MAb ID	21h (2.1H)
HXB2 Location	Env
Author Location	gp120
Epitope	
Neutralizing	L
Immunogen	HIV-1 infection
Species (Isotype)	human (IgG1)
Ab Type	gp120 CD4BS
Research Contact	James Robinson, Tulane University, LA
References	Srivastava *et al.* 2005; Gorny & Zolla-Pazner 2004; Xiang *et al.* 2002b; Fouts *et al.* 1998; Parren *et al.* 1998a; Wyatt *et al.* 1998; Parren *et al.* 1997b; Wyatt *et al.* 1997; Ugolini *et al.* 1997; Li *et al.* 1997; Fouts *et al.* 1997; Binley *et al.* 1997a; McKeating *et al.* 1996; Wisnewski *et al.* 1996; Poignard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; Thali *et al.* 1994; Bagley *et al.* 1994; Moore *et al.* 1994a; Moore *et al.* 1994b; Moore & Ho 1993; Wyatt *et al.* 1993; Ho *et al.* 1992; Thali *et al.* 1992a; Ho *et al.* 1991b
Keywords	acute/early infection, antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, binding affinity, review, structure, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- 21h: UK Medical Research Council AIDS reagent: ARP3017.

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- 21h: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**vaccine antigen design**, **review**)
- 21h: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 21h: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations—375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91) was markedly reduced—IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced—2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope—another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b] (**antibody binding site definition and exposure**)
- 21h: CD4BS MAbs 15e, 21h, and F91 bind with even lower affinity than 205-43-1 and 205-42-15 to JRFL oligomer – conclusions of this paper contrast with Parren *et al.* [1998a] Fouts *et al.* [1998]. Fouts *et al.* [1998]; Parren *et al.* [1998a] (**binding affinity**)
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- 21h: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – 21h bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
- 21h: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env – 50% neutralization could not be achieved at a maximal concentration of 67 mug/ml. Li *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- 21h: Neutralizes TCLA strains, but not primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 21h: Viral binding inhibition by 21h strongly correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5). Ugolini *et al.* [1997] (**antibody binding site definition and exposure**)
- 21h: Binds both gp120 and soluble gp120+gp41 complex efficiently, suggesting its gp120 epitope is not blocked by gp41 binding – major deletions in C1 and C5 and deletions of the V1V2 and V3 loops do not diminish binding. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
- 21h: Called 2.1H – Neutralizes HXB2, but fails to neutralize chimeric virus with gp120 from primary isolates in an HXB2 background. McKeating *et al.* [1996] (**variant cross-recognition or cross-neutralization**)
- 21h: Anti-CD4 binding site MAb – reciprocal inhibition by anti-C1, -C4 and other anti-CD4 binding site antibodies – enhanced by some anti-V2 MAbs and anti-V3 MAb 5G11 – enhances binding of some anti-V3 and -V2 MAbs. Moore & Sodroski [1996] (**antibody interactions**)
- 21h: Anti-CD4BS MAbs 15e, 21h, and IgG1b12 did not cause gp120 dissociation from virus, or exposure of the gp41 epitope of MAb 50-69, in contrast to CD4i MAb 48d and anti-V3 neutralizing MAbs. Poignard *et al.* [1996a] (**antibody binding site definition and exposure**, **antibody interactions**)
- 21h: 21h is V H3 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996] (**antibody sequence variable domain**)
- 21h: Binds with higher affinity to monomer than to oligomer, moderate association rate. Sattentau & Moore [1995] (**antibody binding site definition and exposure**)
- 21h: Heavy chain is V HIII, VDP-35 – light chain is V_lambdaIIIa, Hum318. Compared to 15e and F105. Bagley *et al.* [1994] (**antibody sequence variable domain**)
- 21h: Has strong cross-reactivity with gp120 monomers from most subtypes, A-F, with the least reactivity to clade E. Moore *et al.* [1994b] (**subtype comparisons**)
- 21h: Competition studies with human sera from seroconverting individuals showed that anti-CD4 BS antibodies can arise very early in infection, comparable or prior to anti-V3 antibodies. Moore *et al.* [1994a] (**acute/early infection**)
- 21h: A mutation in gp41, 582 A/T, confers resistance to neutralization (also confers resistance to MAbs F105, 48d, 15e and 17b). Thali *et al.* [1994] (**variant cross-recognition or cross-neutralization**)
- 21h: Conformational, does not bind denatured gp120 – neutralizes IIIB – reactive with SF-2 gp120 – strong inhibition of HIV+ human sera binding to IIIB gp120. Moore & Ho [1993] (**antibody binding site definition and exposure**)
- 21h: Binding to Delta V1/2 and Delta V1/2/3 mutant glycoproteins is greater than binding to wildtype gp120. Wyatt *et al.* [1993] (**antibody binding site definition and exposure**)
- 21h: Amino acid substitutions in HXB2 that inhibit binding, some shared with CD4 binding inhibition, 88, 113, 257, 368, 370, 421, 470, 480. Thali *et al.* [1992a] (**antibody binding site definition and exposure**)

No.	1352
MAb ID	28A11/B1
HXB2 Location	Env
Author Location	gp120 (SF162)
Epitope	
Subtype	B

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Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 CD4BS
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords review, subtype comparisons, variant cross-recognition or cross-neutralization

- 28A11/B1: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 28A11/B1: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—6 anti-CD4BS MAbs competed with anti-CD4BS MAb 5145A, blocked sCD4 binding and were conformationally sensitive—4/6 could neutralize the autologous strain SF162, and were broadly cross-reactive with B clade R5 and X4 strains (not E clade)—28A11/B1 was one of these four MAbs. He *et al.* [2002] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1353
MAb ID 2G6
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 CD4BS
Research Contact Herman Katinger, Inst. Appl. Microbiol. University of Agricultural Science, or Polymun Scientific Inc., Vienna, Austria
References Gorny & Zolla-Pazner 2004; Parren *et al.* 1998a; Fouts *et al.* 1998
Keywords antibody binding site definition and exposure, review, variant cross-recognition or cross-neutralization

- 2G6: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 2G6: Binds to JRFL oligomer with an affinity comparable to IgG1b12, but does not neutralize the virus, so binding of oligomer is not always predictive of neutralization – conclusions of this paper contrast with Parren *et al.* [1998a] – authors propose a model where 205-46-9 and 2G6 may inhibit CD4 binding, but cause a conformational shift which enhances CCR5 binding and thus counteracts the neutralizing effect Fouts *et al.* [1998]. Fouts *et al.* [1998]; Parren *et al.* [1998a] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)

No. 1354
MAb ID 35F3/E2
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 CD4BS
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords review, subtype comparisons, variant cross-recognition or cross-neutralization

- 35F3/E2: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 35F3/E2: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—6 anti-CD4BS MAbs competed with anti-CD4BS MAb 5145A, blocked sCD4 binding and were conformationally sensitive—4/6 could neutralize the autologous strain SF162, and were broadly cross-reactive with B clade R5 and X4 strains (not E clade)—35F3/E2 was one of these four MAbs. He *et al.* [2002] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1355
MAb ID 38G3/A9
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 CD4BS
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Tuen *et al.* 2005; Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords antibody interactions, binding affinity, variant cross-recognition or cross-neutralization

- 38G3/A9: This Ab bound weakly to gp120IIIb and it had a weak inhibitory effect on gp120 antigen presentation by MHC class II. Lysosomal enzyme digestion of gp120 treated with 38G3/A9 yielded fragmentation similar to that of gp120 alone, and digestion rate was intermediate, between the rapid digestion of gp120 alone and the slow digestion of gp120 in complex with high-affinity Ab5145A. It is thus concluded that

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CD4bs Ab 38G3/A9, with low affinity to gp120, does not have a strong inhibitory effect on gp120 processing and presentation. Tuen *et al.* [2005] (**antibody interactions**, **binding affinity**)

- 38G3/A9: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**)
- 38G3/A9: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—6 anti-CD4BS MAbs competed with anti-CD4BS MAb 5145A, blocked sCD4 binding and were conformationally sensitive—4/6 could neutralize the autologous strain SF162, and were broadly cross-reactive with B clade R5 and X4 strains (not E clade)—38G3/A9 was one of these four MAbs. He *et al.* [2002] (**variant cross-recognition or cross-neutralization**)

No. 1356
MAb ID 428
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
References Jeffs *et al.* 1996; Karwowska *et al.* 1992a

- 428: Slight, not significant increased binding when V1/V2 or V1/V2 and V3 were deleted from gp120. Jeffs *et al.* [1996]

No. 1357
MAb ID 448-D (448D)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 CD4BS
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU Med Center, NY, NY
References Kramer *et al.* 2007; Srivastava *et al.* 2005; Mc Cann *et al.* 2005; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Wyatt *et al.* 1998; Li *et al.* 1997; Manca *et al.* 1995a; Forthal *et al.* 1995; Laal *et al.* 1994; Spear *et al.* 1993; McKeating *et al.* 1992c; Karwowska *et al.* 1992a
Keywords ADCC, antibody binding site definition and exposure, antibody interactions, complement, enhancing activity, review, structure, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- 448D: This review summarizes 448D Ab epitope, properties and neutralization activity. Kramer *et al.* [2007] (**review**)
- 448D: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **review**)
- 448D: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**vaccine antigen design**, **review**)
- 448-D: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 448-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 CD4BS MAbs – CD4BS MAbs bound consistently to most isolates of clade D, but poorly to isolates of other clades with the exception of broadly reactive MAb IgG1b12. Nyambi *et al.* [2000] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 448-D: Summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAb binding – probable mechanism of neutralization by CD4BS Ab is direct interference with CD4 binding. Wyatt *et al.* [1998] (**structure**)
- 448-D: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env. Li *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- 448-D: Neutralizing activity, positive ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995] (**ADCC**, **enhancing activity**)
- 448-D: Virions complexed to gp120 Ab facilitate presentation of p66 RT epitopes to Th cells. Manca *et al.* [1995a]
- 448-D: Dissociation constant gp120 IIIB 0.029 – neutralizes IIIB, acts synergistically with anti-V3 MAb 447-52D. Laal *et al.* [1994] (**antibody interactions**)
- 448-D: Did not mediate deposition of complement component C3 on HIV infected cells. Spear *et al.* [1993] (**complement**)
- 448-D: Conformational – reactive with IIIB gp120 in RIP, but not WB assay. Karwowska *et al.* [1992a] (**antibody binding site definition and exposure**)
- 448-D: Called 448D – blocks gp120-CD4 binding – substitutions at gp120 residues 88, 113, 117, 257, 368 and 370 reduce binding – epitope similar to rat MAbs 39.13g and 39.3b.

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McKeating *et al.* [1992c] (**antibody binding site definition and exposure**)

No. 1358
MAb ID 46D2/D5
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 CD4BS
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References He *et al.* 2002

- 44D2/D5: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—6 anti-CD4BS MAbs competed with anti-CD4BS MAb 5145A, blocked sCD4 binding and were conformationally sensitive—4/6 could neutralize the autologous strain SF162, and were broadly cross-reactive with B clade R5 and X4 strains (not E clade)—44D2/D5 could not neutralize autologous SF162, and while it was cross-reactive, it was at lower affinity. He *et al.* [2002]

No. 1359
MAb ID 48-16
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgGκ)
Ab Type gp120 CD4BS
References Gorny & Zolla-Pazner 2004; Fevrier *et al.* 1995
Keywords antibody binding site definition and exposure, binding affinity, review, variant cross-recognition or cross-neutralization

- 48-16: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database. Most neutralize TCLA strains only, 48-16 is one of four that are non-neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
- 48-16: Broadly cross-reactive, reacts outside the CD4 binding site and V3 region—competes with sera from 45 seropositive subjects—binding affinity 2–5 $\times$ 10^{-9} M. Fevrier *et al.* [1995] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **binding affinity**)

No. 1360
MAb ID 50-61A
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgGκ)
Ab Type gp120 CD4BS
References Gorny & Zolla-Pazner 2004; Fevrier *et al.* 1995
Keywords binding affinity, review, variant cross-recognition or cross-neutralization

- 50-61A: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 50-61A: Neutralizes lab strains LAI and SF2 – competes with sera from 45 seropositive subjects – binding affinity 2.4 $\times$ 10^{-10} M. Fevrier *et al.* [1995] (**variant cross-recognition or cross-neutralization**, **binding affinity**)

No. 1361
MAb ID 5145A
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
Ab Type gp120 CD4BS
Research Contact Abraham Pinter, Public Health Research Institute, Newark, NJ, 07103. pinter@phri.org.
References Visciano *et al.* 2008b; Wilkinson *et al.* 2007; Tuen *et al.* 2005; Pinter *et al.* 2005; Pinter *et al.* 2004; Gorny & Zolla-Pazner 2004; He *et al.* 2002; Alsmadi & Tilley 1998; Pincus *et al.* 1996; Warrier *et al.* 1996; Pinter *et al.* 1993a
Keywords ADCC, anti-idiotype, antibody binding site definition and exposure, antibody generation, antibody interactions, binding affinity, immunotoxin, neutralization, rate of progression, variant cross-recognition or cross-neutralization

- 5145A: A significantly higher level of anti-V3 Ab (694/98D) and anti-C1 mAb (EH21) bound to gp120 complexed with 5145A mAb than to gp120 alone or in complex with other non-CD4bs Abs, indicating that binding of 5145A to gp120 increases exposure of specific V3 and C1 mAb epitopes. Visciano *et al.* [2008b]
- 5145A: This Ab was used to select phages from two different peptide libraries. Synthetic peptides corresponding to the selected phage sequences were fused to either phage pIII protein or a small heat shock protein. The constructs were able to inhibit binding of 5145A to gp120, and were able to induce antibodies that bound to recombinant gp120 in immunized rabbits. The induced Abs did not, however, bind to HIV-1 infected cells, nor did they neutralize HIV. Sera from the immunized rabbits did not inhibit binding of 5145A to gp120. Wilkinson *et al.* [2007] (**antibody generation**, **neutralization**)

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- 5145A: This study is about the V2 MAb C108g, that is type-specific and neutralizes BaL and HXB2. JR-FL is a neutralization resistant strain; modification of JRFL at V2 positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potently neutralize the modified JR-FL. The modification in V2 also increased neutralization sensitivity to V3 MABs 4117c, 2219, 2191, and 447-52D, but only had minor effects on neutralization by CD4BS MAb 5145A, and broadly neutralizing MAbs IgG1b12, 2G12, and 2F5. A modification in the NAb sensitive isolate SF162 to introduce the C108g epitope, including the introduction of a glycosylation site (160-161 KV -> NI) and 167-169 NKM -> GKV, decreased neutralization sensitivity to 5145A more than 50-fold. 5145A is a disulfide-dependent epitope in the CD4 binding domain that is lost after reduction; C108g, contrary to earlier reports, was also shown to require disulfide bonds. Pinter *et al.* [2005] (**anti-idiotype**, **antibody binding site definition and exposure**)
- 5145A: This Ab bound with a high affinity to gp120IIIb and it strongly suppressed gp120 antigen presentation by MHC class II. Binding of 5145A to gp120 did not prevent uptake of gp120 by APCs. 5145A did not, however, disassociate from gp120 at acidic pH, suggesting that gp120-5145A complexes remain stable in the APC endolysosomes. Lysosomal enzyme digestion of gp120 in complex with 5145A was slow and yielded limited fragmentation of gp120 with distinct patterns. It is thus concluded that poorly neutralizing high-affinity CD4bs Abs produced by chronically infected patients prevent the stimulation of gp120-specific CD4 T-cell responses by producing gp120-Ab complexes resistant to the proteolytic processing by lysosomal enzymes. Tuen *et al.* [2005] (**antibody interactions**, **binding affinity**, **rate of progression**)
- 5145A: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**)
- 5145A: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neturalization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Three anti-CD4BS MAbs were tested, including IgG1b12, which neutralizes both JRFL and SF162. The affinities for IgG1b12 and 5145A were similar for both JRFL and SF612, but 1125A bound with 2.5 fold higher affinity to SF162. 5145A and 1125H both preferentially neutralize SF162, but not JRFL, and the CD4BS is more sensitive to neutralization in the context of the SF162 V1V2 loop. This was also true for neutralization by sCD4. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 5145A: Transgenic mice carrying human genes allowing production of fully human MAbs were used to rapidly create a panel of anti-HIV gp120 MAb producing hybridomas by immunization with HIV SF162 gp120 – the previously described human MAbs 5145A, 4117C and 697D were used as controls. He *et al.* [2002]
- 5145A: A study of 6 anti-Env MAbs and their ability to bind or direct ADCC against target cells infected with IIIB, MN, SF-2, and RF – bound and directed lysis against all four strains. Alsmadi & Tilley [1998] (**ADCC**)
- 5145A: A panel of immunotoxins were generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but killing was not directly proportional to binding. Pincus *et al.* [1996] (**immunotoxin**)
- 5145A: Synergistic neutralization of HIV-1 when combined with anti-V2 MAb C108G. Warrier *et al.* [1996] (**antibody interactions**)
- 5145A: Potent and broadly cross-reactive neutralization of lab strains. Pinter *et al.* [1993a] (**variant cross-recognition or cross-neutralization**)

No. 1362
MAb ID 558-D
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU Med Center, NY, NY
References Gorny & Zolla-Pazner 2004; Nyambi *et al.* 1998; McKeating *et al.* 1992c
Keywords antibody binding site definition and exposure, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 558-D: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 558-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – CD4BS Abs tended to bind weakly without clade specificity to virions, but bound well to soluble gp120 – 558-D did not bind to any B clade viruses, and weakly bound to clade A, C, and G isolates – 559/64-D, 558-D and 1202-D had similar reactivities. Nyambi *et al.* [1998] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 558-D: Blocks gp120-CD4 binding – binds a panel of mutants all except for 256 S/Y and 262 N/T, which are probably conformationally disruptive. McKeating *et al.* [1992c] (**antibody binding site definition and exposure**)

No. 1363
MAb ID 559/64-D (559, 559-64D)
HXB2 Location Env
Author Location gp120 (LAI)
Epitope
Subtype B
Neutralizing L
Immunogen HIV-1 infection

Species (Isotype) human (IgG1κ)
Ab Type gp120 CD4BS
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU Med Center, NY, NY
References Visciano *et al.* 2008b; Srivastava *et al.* 2005; Gorny & Zolla-Pazner 2004; Zwick *et al.* 2003; York *et al.* 2001; Hioe *et al.* 2001; Nyambi *et al.* 2000; Hioe *et al.* 2000; Gorny *et al.* 2000; Nyambi *et al.* 1998; Hioe *et al.* 1997b; Hioe *et al.* 1997a; Jeffs *et al.* 1996; Forthal *et al.* 1995; Stamatatos & Cheng-Mayer 1995; Spear *et al.* 1993; McKeating *et al.* 1992c; Karwowska *et al.* 1992a
Keywords ADCC, antibody binding site definition and exposure, antibody interactions, assay development, complement, enhancing activity, neutralization, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- 559/64D: A significantly higher level of anti-V3 Ab (694/98D) and anti-C1 mAb (EH21) bound to gp120 complexed with 559/64D mAb than to gp120 alone or in complex with other non-CD4bs Abs, indicating that binding of 559/64D to gp120 increases exposure of specific V3 and C1 mAb epitopes. Immunization of mice with gp120-559/64D complex elicited higher and faster V3-specific Ab responses than immunization with gp120 alone or gp120 in complex with other mAbs, while responses to other gp120 regions was comparable. Abs elicited by immunization with gp120-559/64D complex reacted preferentially with the homologous V3 peptide, and the sera from immunized mice neutralized homologous, but not heterologous, HIV-1 isolates. Visciano *et al.* [2008b] (**neutralization**, **vaccine antigen design**)
- 559/64D: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody interactions**, **neutralization**, **vaccine antigen design**, **review**)
- 559/64D: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 559/64D: called 559-64D: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- 559/64-D: CD4BS MAbs when complexed with gp120, inhibit proliferation of gp120-specific CD4 T-cells and IFNγ production—anti-CD4BS MAbs inhibit gp120 presentation by altering the uptake and/or processing of gp120 by the APCs, not by blocking of gp120 attachment to CD4 on the surface of APCs. Hioe *et al.* [2001]
- 559/64-D: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4 induced or CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAbs alters some step after binding. York *et al.* [2001] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 559/64-D: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – CD4BS MAbs 559/64-D, 654-D, 729-D, 9CL and 1331E bound with a 5-13 fold preference for the oligomer. Gorny *et al.* [2000] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 559/64-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – anti-CD4 binding site MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – CD4BS MAbs 654-D, 559/64-D, 588-D, 830-D, 1027-30-D, and 1202-30D strongly diminished proliferation. Hioe *et al.* [2000]
- 559/64-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 CD4BS MAbs – CD4BS MAbs bound consistently to most isolates of clade D, but poorly to isolates of other clades with the exception of broadly reactive MAb IgG1b12. Nyambi *et al.* [2000] (**subtype comparisons**)
- 559/64-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – CD4BS Abs tended to bind weakly without clade specificity to virions, but bound well to soluble gp120 – 559/64-D did not bind to any B clade viruses, and weakly bound clade A, C, and G isolates – 559/64-D, 558-D and 1202-D had similar reactivities. Nyambi *et al.* [1998] (**antibody binding site definition and exposure**, **subtype comparisons**)
- 559/64-D: Used in the development of resting cell neutralization assay. Hioe *et al.* [1997a] (**assay development**)
- 559/64-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593

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and 91US056 were neutralized by V3 loop (419-D, and 447-52D)and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)

- 559/64-D: Called 559 – slight, not significant increased binding when V1/V2 or V1/V2 and V3 were deleted from gp120. Jeffs *et al.* [1996] (**antibody binding site definition and exposure**)
- 559/64-D: Neutralizing activity, no ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995] (**ADCC**, **enhancing activity**, **variant cross-recognition or cross-neutralization**)
- 559/64-D: Called 559-64D – The binding of conformation-dependent anti-V2, anti-V3, and anti-CD4BS MAbs to monomeric and virion-associated gp120 from HIV-1 isolates with differences in cell tropism was studied – CD4BS loop epitopes are somewhat occluded in the oligomeric gp120 epitopes on the virion surface relative to the gp120 monomer as indicated by an increase in the half-maximal binding values to macrophage-tropic isolates SF162 and SF128a and to T-cell tropic SF2 – binding of anti-CD4BS MAbs to SF2 resulted in a significant amount of dissociation of gp120 from virion surface. Stamatatos & Cheng-Mayer [1995] (**antibody binding site definition and exposure**)
- 559/64-D: Did not mediate deposition of complement component C3 on HIV infected cells. Spear *et al.* [1993] (**complement**)
- 559/64-D: Conformational – reactive with IIIB gp120 in RIP, but not WB assay. Karwowska *et al.* [1992a] (**antibody binding site definition and exposure**)

No. 1364
MAb ID 55D5/F9
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 CD4BS
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords review, variant cross-recognition or cross-neutralization

- 55D5/F9: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database. Most neutralize TCLA strains only, this is one of four that are non-neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
- 55D5/F9: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—6 anti-CD4BS MAbs competed with anti-CD4BS MAb 5145A, blocked sCD4 binding and were conformationally sensitive—4/6 could neutralize the autologous strain SF162, and were broadly cross-reactive with B clade R5 and X4 strains (not E clade)—55D5/F9 was one of these four MAbs. He *et al.* [2002] (**variant cross-recognition or cross-neutralization**)

No. 1365
MAb ID 588-D (588)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 CD4BS
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU Med Center, NY, NY
References Nyambi *et al.* 2000; Hioe *et al.* 2000; Nyambi *et al.* 1998; Jeffs *et al.* 1996; Moore & Ho 1993; Buchbinder *et al.* 1992; Karwowska *et al.* 1992a

- 588-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – anti-CD4 binding site MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – CD4BS MAbs 654-D, 559/64-D, 588-D, 830-D, 1027-30-D, and 1202-30D strongly diminished proliferation. Hioe *et al.* [2000]
- 588-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 CD4BS MAbs – CD4BS MAbs bound consistently to most isolates of clade D, but poorly to isolates of other clades with the exception of broadly reactive MAb IgG1b12. Nyambi *et al.* [2000]
- 588-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – CD4-BS Abs tended to bind weakly without clade specificity to virions, but bound well to soluble gp120 – 588-D did not bind to any B clade viruses, and weakly bound a clade A, C, and G clade isolate – 559/64-D, 558-D and 1202-D reacted had similar reactivities. Nyambi *et al.* [1998]
- 588-D: Called 588 – slight, not significant increased binding when V1/V2 or V1/V2 and V3 were deleted from gp120. Jeffs *et al.* [1996]
- 588-D: Weak neutralization of IIIB – strong inhibition of HIV+ human sera binding to IIIB gp120. Moore & Ho [1993]
- 588-D: 4-fold increase in neutralization potency for 588-D when combined 1:1 with human MAb 447-D. Buchbinder *et al.* [1992]
- 588-D: Conformational – reactive with IIIB gp120 in RIP, but not WB assay. Karwowska *et al.* [1992a]

No. 1366
MAb ID 654-D (654-30D, 654/30D, 654-D100, 654.30D, 654, 654D)
HXB2 Location Env
Author Location gp120 (LAI)

Epitope
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgGκ)
Ab Type gp120 CD4BS
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU Med Center, NY, NY
References Visciano *et al.* 2008a; Visciano *et al.* 2008b; Forsman *et al.* 2008; Holl *et al.* 2006a; Tuen *et al.* 2005; Srivastava *et al.* 2005; Kalia *et al.* 2005; Gorny & Zolla-Pazner 2004; Zwick *et al.* 2003; Gorny *et al.* 2002; Verrier *et al.* 2001; Nyambi *et al.* 2000; Hioe *et al.* 2001; Hioe *et al.* 2000; Gorny *et al.* 2000; Hioe *et al.* 1999; Stamatatos & Cheng-Mayer 1998; Nyambi *et al.* 1998; Schonning *et al.* 1998; Gorny *et al.* 1998; Hioe *et al.* 1997b; Gorny *et al.* 1997; Stamatatos *et al.* 1997; Li *et al.* 1997; Stamatatos & Cheng-Mayer 1995; Gorny *et al.* 1994; Laal *et al.* 1994; Karwowska *et al.* 1993
Keywords antibody binding site definition and exposure, antibody interactions, binding affinity, dendritic cells, enhancing activity, kinetics, neutralization, rate of progression, review, subtype comparisons, vaccine antigen design, vaccine-induced epitopes, variant cross-recognition or cross-neutralization

- 654-D: Variable domains of three heavy chain Abs, the VHH, were characterized. The Abs were isolated from llamas, who produce immunoglobulins devoid of light chains, immunized with HIV-1 CRF07_BC, to gp120. It was hypothesized that the small size of the VHH, in combination with their protruding CDR3 loops, and their preference for cleft recognition and binding into active sites, may allow for recognition of conserved motifs on gp120 that are occluded from conventional Abs. 654-D was found to compete for binding to recombinant gp120 with the three neutralizing VHH Abs, indicating overlapping epitopes or steric hinderance. Forsman *et al.* [2008] (**binding affinity**)
- 654D: A significantly higher level of anti-V3 Abs (694/98D and 447-52D) and anti-C1 mAb (EH21) bound to gp120 complexed with 654D mAb than to gp120 alone or in complex with other non-CD4bs Abs, indicating that binding of 654D to gp120 increases exposure of specific V3 and C1 mAb epitopes. Immunization of mice with gp120-654D complex elicited higher and faster V3-specific Ab responses than immunization with gp120 alone or gp120 in complex with other mAbs, while responses to other gp120 regions was comparable. Abs elicited by immunization with gp120-654D complex reacted preferentially with the homologous V3 peptide, and the sera from immunized mice neutralized homologous, but not heterologous, HIV-1 isolates. Visciano *et al.* [2008b] (**vaccine antigen design**)
- 654: A mouse CD4 T cell clone proliferated well in response to gp120 alone but this response was inhibited by more than 80% when gp120 was complexed with mAb 654. Mice immunized with gp120-654 complex showed lower levels of lymphoproliferation than mice immunized with gp120-670 complex, indicating that anti-CD4bs Abs supress the induction of CD4 T cell responses in vivo. However, mice immunized with gp120/654 Ab displayed faster kinetics and higher levels of gp120-specific serum IgG and IgA, but not IgM, indicating that immunization with gp120 in the presence of anti-CD4 Ab alters the immunogenicity of gp120 such that the immune response is dominated by anti-gp120 IgG. Visciano *et al.* [2008a] (**vaccine-induced epitopes**, **kinetics**)
- 654-D: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 654-30D: Point mutations in the highly conserved structural motif LLP-2 within the intracytoplasmic tail of gp41 resulted in conformational alternations of both gp41 and gp120. The alternations did not affect virus CD4 binding, coreceptor binding site exposure, or infectivity of the virus, but did result in decreased binding and neutralization by certain MAbs and human sera. 654-30D exhibited similar levels of binding to both the LLP-2 mutant and wildtype viruses, indicating that its epitope was not altered by the mutation. Kalia *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)
- 654-D (650-D): This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody interactions**, **vaccine antigen design**, **review**)
- 654D: This Ab bound with a high affinity to gp120IIIb and it strongly suppressed gp120 antigen presentation by MHC class II. Binding of 654D to gp120 did not prevent uptake of gp120 by APCs nor did it inhibit transport of gp120 into the endolysosomes of the APCs. 654D did not, however, disassociate from gp120 at acidic pH, suggesting that gp120-654D complexes remain stable in the APC endolysosomes. Lysosomal enzyme digestion of gp120 in complex with 654D was slow and yielded limited fragmentation of gp120 with distinct patterns. It is thus concluded that poorly neutralizing high-affinity CD4bs Abs produced by chronically infected patients prevent the stimulation of gp120-specific CD4 T-cell responses by producing gp120-Ab complexes resistant to the proteolytic processing by lysosomal enzymes. Tuen *et al.* [2005] (**antibody interactions**, **binding affinity**, **rate of progression**)
- 654-D: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 654-D: Called 654-30D. scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the follow-

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ing regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)

- 654-D: Called 654: Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions and the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control), and MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades) Gorny *et al.* [2002]
- 654-D: CD4BS MAbs when complexed with gp120, inhibit proliferation of gp120-specific CD4 T-cells and IFN gamma production – anti-CD4BS MAbs inhibit gp120 presentation by altering the uptake and/or processing of gp120 by the APCs, not by blocking of gp120 attachment to CD4 on the surface of APCs. Hioe *et al.* [2001]
- 654-D: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6—six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D, while six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281—no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001] (**antibody interactions**, **variant cross-recognition or cross-neutralization**)
- 654-D: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – CD4BS MAbs 559/64-D, 654-D, 729-D, 9CL and 1331E bound with a 5-13 fold preference for the oligomer. Gorny *et al.* [2000] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 654-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – CD4BS MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – MAb 654-D strongly diminished proliferation – there is a discrepancy in isotyping this antibody, previous reports indicated IgG1kappa, while Hioe suggests it is IgG1lambda. Hioe *et al.* [2000]
- 654-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 CD4BS MAbs – CD4BS MAbs bound consistently to most isolates of clade D, but poorly to isolates of other clades with the exception of broadly reactive MAb IgG1b12 – 654-D had the weakest binding among CD4BS MAbs, binding to only 4/26 isolates. Nyambi *et al.* [2000] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 654-D: The presence of leukocyte function-associated molecule 1 (LFA-1) promotes virus infectivity and hinders neutralization, and anti-LFA-1 MAbs can enhance the neutralizing effect of anti-HIV V3 MAb 447-52D and anti-HIV CD4BS MAb IgG1b12 – non-neutralizing anti-HIV CD4BS MAb 654-D did not become neutralizing in the presence of anti-LFA-1 MAbs. Hioe *et al.* [1999]
- 654-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – CD4-BS Abs tended to bind very weakly without clade specificity to virions, but bound well to soluble gp120 – 654-D bound only to JRFL. Nyambi *et al.* [1998] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 654-D: Called 654-D100 – 654-D100 and IgG1b12 neutralized viruses HIV-BRU and a mutated virus that lacks the V3 loop glycan equally effectively – in contrast, sera from guinea pigs immunized with BRU gp120 neutralize viruses more effectively that lack the V3 glycan. Schonning *et al.* [1998] (**variant cross-recognition or cross-neutralization**)
- 654-D: Called 654.30D – deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V2 but not V1 slightly allowed neutralization by CD4BS MAb 654.30D. Stamatatos & Cheng-Mayer [1998] (**antibody binding site definition and exposure**, **subtype comparisons**)
- 654-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D)and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 654-D: Called 654-30D – One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env. Li *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- 654-D: Anti-CD4 BS MAb 654-30D and IgG1b12 have comparable binding affinities, neither mediates gp120-virion dissociation, but IgG1b12 can neutralize SF128A and SF162 and 654-D cannot – 654-D actually enhances infection by both viruses in primary macrophages. Stamatatos *et al.* [1997] (**enhancing activity**, **binding affinity**)
- 654-D: Called 654-30D – The binding of conformation-dependent anti-V2, anti-V3, and anti-CD4BS MAbs to monomeric and virion-associated gp120 from HIV-1 isolates

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with differences in cell tropism was studied – CD4BS loop epitopes are somewhat occluded in the oligomeric gp120 epitopes on the virion surface relative to the gp120 monomer as indicated by an increase in the half-maximal binding values to macrophage-tropic isolates SF162 and SF128a and to T-cell tropic SF2 – binding of anti-CD4BS MAbs to SF2 resulted in a significant amount of dissociation of gp120 from virion surface. Stamatatos & Cheng-Mayer [1995] (**antibody binding site definition and exposure**)

- 654-D: Mild oxidation of carbohydrate moieties inhibits binding. Gorny *et al.* [1994] (**antibody binding site definition and exposure**)
- 654-D: Dissociation constant gp120 IIIB 0.008 – neutralizes IIIB, acts synergistically with anti-V3 MAb 447-52D – reported to be human(IgG1lambda) Laal *et al.* [1994] (**antibody interactions**, **kinetics**)

No. 1367
MAb ID 67G6/C4
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 CD4BS
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Tuen *et al.* 2005; Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords antibody interactions, binding affinity, review, variant cross-recognition or cross-neutralization

- 67G6/C4: This Ab did not bind to gp120IIIb, it did not prevent uptake of gp120 by APCs,and had no inhibitory effect on gp120 antigen presentation by MHC class II. Lysosomal enzyme digestion of gp120 treated with 67G6/C4 yielded digestion rate and fragmentation similar to that of gp120 alone. It is thus concluded that CD4bs Ab 67G6/C4, with low affinity to gp120, does not inhibit gp120 processing and presentation. Tuen *et al.* [2005] (**antibody interactions**, **binding affinity**)
- 67G6/C4: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database. Most neutralize TCLA strains only, this MAb is one of four that are non-neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
- 67G6/C4: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—6 anti-CD4BS MAbs competed with anti-CD4BS MAb 5145A, blocked sCD4 binding and were conformationally sensitive—4/6 could neutralize the autologous strain SF162, and were broadly cross-reactive with B clade R5 and X4 strains (not E clade)—67G6/C4 could not neutralize autologous SF162, and its binding was strain-specific. He *et al.* [2002] (**variant cross-recognition or cross-neutralization**)

No. 1368
MAb ID 729-D (729-30D)
HXB2 Location Env
Author Location gp120 (LAI)
Epitope
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 CD4BS
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU Med Center, NY, NY
References Gorny & Zolla-Pazner 2004; Gorny *et al.* 2000; Parren *et al.* 1997b; Li *et al.* 1997; D'Souza *et al.* 1997; Laal *et al.* 1994
Keywords antibody binding site definition and exposure, antibody interactions, kinetics, review, variant cross-recognition or cross-neutralization

- 729-D: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 729-D: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – CD4BS MAbs 559/64-D, 654-D, 729-D, 9CL and 1331E bound with a 5-13 fold preference for the oligomer. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)
- 729-D: In a multilaboratory blinded study, failed to consistently neutralize any of nine B clade primary isolates – reported here to have a lambda light chain, but originally reported in Laal *et al.* [1994] to be IgG1kappa D'Souza *et al.* [1997]. D'Souza *et al.* [1997]; Laal *et al.* [1994] (**variant cross-recognition or cross-neutralization**)
- 729-D: Called 720-30D – one of 14 human MAbs tested for ability to neutralize chimeric SHIV-vpu+, which expressed HIV-1 IIIB env. Li *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- 729-D: Neutralizes TCLA strains, but not primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 729-D: Dissociation constant gp120 IIIB 0.025 – neutralizes IIIB, acts synergistically with anti-V3 MAb 447-52D. Laal *et al.* [1994] (**antibody interactions**, **kinetics**)

No. 1369
MAb ID 830D (830-D)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen

B Cell

Species (Isotype) human (IgG1κ)
Ab Type gp120 CD4BS
References Srivastava *et al.* 2005; Gorny & Zolla-Pazner 2004; Hioe *et al.* 2000; Wyatt *et al.* 1998; Hioe *et al.* 1997b
Keywords review, structure, vaccine antigen design, variant cross-recognition or cross-neutralization

- 830D: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**vaccine antigen design**, **review**)
- 830D: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 830D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – anti-CD4 binding site MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – CD4BS MAbs 654-D, 559/64-D, 588-D, 830-D, 1027-30-D, and 1202-30D strongly diminished proliferation. Hioe *et al.* [2000]
- 830D: Summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAb binding – probable mechanism of neutralization by CD4BS Ab is direct interference with CD4 binding. Wyatt *et al.* [1998] (**structure**)
- 830D: Called 830-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D)and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)

No. 1370
MAb ID 9CL
HXB2 Location Env
Author Location gp120 (LAI)
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU Med Center, NY, NY
References Gorny & Zolla-Pazner 2004; Gorny *et al.* 2000
Keywords antibody binding site definition and exposure, review

- 9CL: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 9CL: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – CD4BS MAbs 559/64-D, 654-D, 729-D, 9CL and 1331E bound with a 5-13 fold preference for the oligomer. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)

No. 1371
MAb ID BM12
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
References Kessler *et al.* 1995

- BM12: Broad cross-clade neutralization of primary isolates – additive effect in combination with MAb 2F5. Kessler *et al.* [1995]

No. 1372
MAb ID D20
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4BS
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1997; Otteken *et al.* 1996; Richardson *et al.* 1996; Broder *et al.* 1994; Earl *et al.* 1994
Keywords antibody binding site definition and exposure, antibody generation

- D20: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D20 is part of a group of MAbs labeled A1 – all A1 MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, blocked CD4 binding, were sensitive to mutations in gp120 positions 368 and 370 that directly contact CD4. Sugiura *et al.* [1999] (**antibody binding site definition and exposure**)

B Cell

- D20: Used for comparison in a study of gp41 antibodies – D20 binds to a greater extent to cell surface expressed Env than any of 38 conformation dependent anti-gp41 MAbs. Earl *et al.* [1997] (**antibody binding site definition and exposure**)
- D20: Pulse label experiments of 4 MAbs (D20, D27, T20, and T22) binding to noncleavable gp160 revealed that these anti-CD4 MAbs bound with a delay, and that the epitope formed with a t 1/2 of about 10 minutes. Otteken *et al.* [1996]
- D20: Human sera blocked binding in oligomeric ELISA assay to a similar extent for gp41 MAbs D20, D43, D61, and T4. Richardson *et al.* [1996]
- D20: Binding completely blocked by pooled human sera. Broder *et al.* [1994]
- D20: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994] (**antibody generation**)

No. 1373
MAb ID D21
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB
HIV component: oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4BS
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1994

- D21: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D21 is part of a group of MAbs labeled A1 – all A1 MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, blocked CD4 binding, were sensitive to mutations in gp120 positions 368 and 370 that directly contact CD4. Sugiura *et al.* [1999]
- D21: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1374
MAb ID D24
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB
HIV component: oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4BS
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1994

- D24: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D24 is part of a group of MAbs labeled B-I, that had limited cross-reactivity – of seven clade B isolates BH8 and B-al were they only two that consistently reacted with B-I MAbs – B-I MAbs fully blocked CD4 binding. Sugiura *et al.* [1999]
- D24: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1375
MAb ID D25
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB
HIV component: oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4BS
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Wright *et al.* 2008; Huang *et al.* 2005b; Sugiura *et al.* 1999; Earl *et al.* 1994
Keywords isotype switch, mucosal immunity, neutralization

- D25: Several IgG MAbs were isotype switched to IgA and tested for their abilities to generate immune complexes with HIV-1 and be excreted from polarized epithelial cells from the basolateral to the apical surface via polymeric Ig receptor (pIgR) binding. IgA D25 was able to excrete HIV but it had lower level of binding to the virus, and as immune complex to the pIgR, than D10 and D47 MAbs. These results show that IgA Abs have potential to excrete HIV from mucosal lamina propria thus decreasing the viral burden and access to susceptible cells. Wright *et al.* [2008] (**isotype switch**, **mucosal immunity**)
- D25: By isotype switching, IgG and IgA variants of D25 were produced. Both D25 IgA and IgG showed no significant neutralization of virus in conventional neutralization assays nor did they show any capability of intracellular neutralization of HIV-1. Huang *et al.* [2005b] (**isotype switch**, **neutralization**, **mucosal immunity**)
- D25: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D25 is part of a group of MAbs labeled A1 – all A1 MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, blocked CD4 binding, were sensitive to mutations in gp120 positions 368 and 370 that directly contact CD4. Sugiura *et al.* [1999]
- D25: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1376
MAb ID D28
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB
HIV component: oligomeric gp140
Species (Isotype) mouse (IgG)

B Cell

Ab Type gp120 CD4BS
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1994

- D28: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D28 is part of a group of MAbs labeled B-I, that had limited cross-reactivity – of seven clade B isolates BH8 and B-al were they only two that consistently reacted with B-I MAbs – B-I MAbs fully blocked CD4 binding. Sugiura *et al.* [1999]
- D28: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1377
MAb ID D35
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4BS
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1994

- D35: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D35 is part of a group of MAbs labeled B-I, that had limited cross-reactivity – of seven clade B isolates BH8 and B-al were they only two that consistently reacted with B-I MAbs – B-I MAbs fully blocked CD4 binding. Sugiura *et al.* [1999]
- D35: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1378
MAb ID D39
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4BS
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1994

- D39: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D39 is part of a group of MAbs labeled A1 – all A1 MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, blocked CD4 binding, were sensitive to mutations in gp120 positions 368 and 370 that directly contact CD4. Sugiura *et al.* [1999]
- D39: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1379
MAb ID D42
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4BS
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1994

- D42: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D42 is part of a group of MAbs labeled B-I, that had limited cross-reactivity – of seven clade B isolates BH8 and B-al were they only two that consistently reacted with B-I MAbs – B-I MAbs fully blocked CD4 binding. Sugiura *et al.* [1999]
- D42: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1380
MAb ID D52
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4BS
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1994

- D52: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D52 is part of a group of MAbs labeled B-I, that had limited cross-reactivity – of seven clade B isolates BH8 and B-al were they only two that consistently reacted with B-I MAbs – B-I MAbs fully blocked CD4 binding. Sugiura *et al.* [1999]
- D52: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1381
MAb ID D53
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine

B Cell

Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4BS
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1994

- D53: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D53 is part of a group of MAbs labeled B-I, that had limited cross-reactivity – of seven clade B isolates BH8 and B-al were they only two that consistently reacted with B-I MAbs – B-I MAbs fully blocked CD4 binding. Sugiura *et al.* [1999]
- D53: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1382
MAb ID D60
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4BS
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Richardson *et al.* 1996; Earl *et al.* 1994

- D60: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D60 is part of a group of MAbs labeled B-I, that had limited cross-reactivity – of seven clade B isolates BH8 and B-al were they only two that consistently reacted with B-I MAbs – B-I MAbs fully blocked CD4 binding. Sugiura *et al.* [1999]
- D60: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1383
MAb ID DA48
HXB2 Location Env
Author Location gp120 (BRU)
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
References Gorny & Zolla-Pazner 2004; Sullivan *et al.* 1998a; Parren *et al.* 1998a
Keywords antibody binding site definition and exposure, antibody generation, binding affinity, review, variant cross-recognition or cross-neutralization

- DO8i: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- DA48: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**binding affinity**)
- DA48: The HIV-1 virus YU2 entry can be enhanced by MAbs binding to the CD4BS, V3 loop, and CD4i epitopes – the activation for this enhanced entry state could be conferred on HxB2 by introducing the YU2 V3 loop, or the YU2 V3 and V1/V2 loops – a similar effect is observed by sub-neutralizing concentrations of sCD4 and the effect is dependent of CCR5 – Fab Ab fragment DA48 also enhances YU2 entry, ruling out Fc interactions or Env cross-linking as a mechanism – while DA48 enhances YU2, it neutralizes HXBc2 – DA48 was obtained by panning libraries derived from bone marrow from a >15 year long term non-progressor against BRU gp120. Sullivan *et al.* [1998a] (**antibody binding site definition and exposure**, **antibody generation**, **variant cross-recognition or cross-neutralization**)

No. 1384
MAb ID DO8i
HXB2 Location Env
Author Location gp120 (BRU)
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
References Sullivan *et al.* 1998a; Parren *et al.* 1998a

- DO8i: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- DO8i – the HIV-1 virus YU2 entry can be enhanced by MAbs binding to the CD4BS, V3 loop, and CD4i epitopes – the activation for this enhanced entry state could be conferred on HxB2 by introducing the YU2 V3 loop, or the YU2 V3 and V1/V2 loops – a similar effect is observed by sub-neutralizing concentrations of sCD4 and the effect is dependent of CCR5 – Fab fragment DO8i also enhances YU2 entry, ruling out Fc interactions or Env cross-linking as a mechanism, while neutralizing HXBc2 – DO8i was obtained by panning libraries derived from bone marrow from a long term asymptomatic donor against BRU gp120. Sullivan *et al.* [1998a]

B Cell

No. 1385
MAb ID F105 (F-105)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 CD4BS
Research Contact Marshall Posner, Boston MA
References Wu *et al.* 2008; Visciano *et al.* 2008b; Perdomo *et al.* 2008; Pacheco *et al.* 2008; Martin *et al.* 2008; Gopi *et al.* 2008; Yuan *et al.* 2006; Prabakaran *et al.* 2006; Zhou *et al.* 2007; Wilkinson *et al.* 2007; Wang *et al.* 2007a; Phogat *et al.* 2007; McFadden *et al.* 2007; Lin & Nara 2007; Li *et al.* 2007b; Kramer *et al.* 2007; Hong *et al.* 2007; Dunfee *et al.* 2007; Dey *et al.* 2007b; Clayton *et al.* 2007; Holl *et al.* 2006a; Derby *et al.* 2006; Yuan *et al.* 2005; Yang *et al.* 2005c; Wilkinson *et al.* 2005; Teeraputon *et al.* 2005; Srivastava *et al.* 2005; Selvarajah *et al.* 2005; Pancera *et al.* 2005; Pancera & Wyatt 2005; Mc Cann *et al.* 2005; Masiero *et al.* 2005; Martín-García *et al.* 2005; Kang *et al.* 2005; Kalia *et al.* 2005; Dorgham *et al.* 2005; Beddows *et al.* 2005b; Pantophlet *et al.* 2004; Ling *et al.* 2004; Biorn *et al.* 2004; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Ohagen *et al.* 2003; Raja *et al.* 2003; Xiang *et al.* 2003; Poignard *et al.* 2003; Pantophlet *et al.* 2003a; Choe *et al.* 2003; Kwong *et al.* 2002; Ferrantelli *et al.* 2004a; Cavacini *et al.* 2002; Ling *et al.* 2002; Liu *et al.* 2002; Ferrantelli & Ruprecht 2002; Zhang *et al.* 2002; Basmaciogullari *et al.* 2002; Grundner *et al.* 2002; Edwards *et al.* 2002; Xiang *et al.* 2002b; Chakrabarti *et al.* 2002; Xu *et al.* 2002; Yang *et al.* 2002; York *et al.* 2001; Kolchinsky *et al.* 2001; Si *et al.* 2001; Yang *et al.* 2000; Park *et al.* 2000; Fortin *et al.* 2000; Baba *et al.* 2000; Robert-Guroff 2000; Oscherwitz *et al.* 1999a; Cavacini *et al.* 1999; Giraud *et al.* 1999; Sugiura *et al.* 1999; Kropelin *et al.* 1998; Sullivan *et al.* 1998a; Brand *et al.* 1998; Cavacini *et al.* 1998a; Li *et al.* 1998; Cavacini *et al.* 1998b; Wyatt *et al.* 1998; Wyatt *et al.* 1997; Cao *et al.* 1997b; Li *et al.* 1997; D'Souza *et al.* 1997; Parren *et al.* 1997b; Chen *et al.* 1996; Litwin *et al.* 1996; Pincus *et al.* 1996; Wisnewski *et al.* 1996; McDougal *et al.* 1996; Wolfe *et al.* 1996; Jagodzinski *et al.* 1996; Khouri *et al.* 1995; Sullivan *et al.* 1995; Cavacini *et al.* 1995; Posner *et al.* 1995; Turbica *et al.* 1995; Chen *et al.* 1994a; Earl *et al.* 1994; Cavacini *et al.* 1994a; Cavacini *et al.* 1994b; Cook *et al.* 1994; Thali *et al.* 1994; Bagley *et al.* 1994; Marasco *et al.* 1993; Watkins *et al.* 1993; Pincus *et al.* 1993; Klasse *et al.* 1993a; Potts *et al.* 1993; Montefiori *et al.* 1993; Wyatt *et al.* 1993; Cavacini *et al.* 1993b; Cavacini *et al.* 1993a; Posner *et al.* 1993; Moore & Ho 1993; Posner *et al.* 1992a; Posner *et al.* 1992b; Wyatt *et al.* 1992; Marasco *et al.* 1992; Thali *et al.* 1992a; Thali *et al.* 1991; Posner *et al.* 1991
Keywords ADCC, antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, assay development, binding affinity, brain/CSF, co-receptor, complement, dendritic cells, enhancing activity, escape, immunoprophylaxis, immunotherapy, immunotoxin, kinetics, mimics, mother-to-infant transmission, mucosal immunity, neutralization, rate of progression, review, structure, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- F105: No neutralization of primary isolates observed (John Moore, pers comm). (**variant cross-recognition or cross-neutralization**)
- F105: NIH AIDS Research and Reference Reagent Program: 857.
- F105: A series of peptide conjugates were constructed via click reaction of both aryl and alkyl acetylenes with an internally incorporated azidoproline 6 derived from parent peptide RINNIPWSEAMM. Many of these conjugates exhibited increase in both affinity for gp120 and inhibition potencies at both the CD4 and coreceptor binding sites. All high affinity peptides inhibited the interactions of YU2 gp120 with F105 Ab. The aromatic, hydrophobic, and steric features in the residue 6 side-chain were found important for the increased affinity and inhibition of the high-affinity peptides. Gopi *et al.* [2008]
- F105: A new purification method was developed using a high affinity peptide mimicking CD4 as a ligand in affinity chromatography. This allowed the separation in one step of HIV envelope monomer from cell supernatant and capture of pre-purified trimer. Binding of F105 to gp120SF162 purified by the miniCD4 affinity chromatography and a multi-step method was comparable, suggesting that the miniCD4 allows the separation of HIV-1 envelope with an intact F105 epitope. gp140DF162ΔV2 was purified by the miniCD4 method to asses its ability to capture gp140 trimers. Binding of F105 to gp140DF162ΔV2 purified by the miniCD4 affinity chromatography and a multi-step method was comparable, suggesting that the SF162 trimer antigenicity was preserved. Martin *et al.* [2008] (**assay development**, **binding affinity**)
- F105: Two HIV-1 isolates, NL4-3 and KB9, were adapted to replicate in cells using the common marmoset receptors CD4 and CXCR4. The adaptation resulted in a small number of changes of env sequences in both isolates. The adapted NL4-3 variants were generally more sensitive to neutralization by

F105 than the adapted KB9 variants. All of the NL4-3 exhibited similar sensitivity to neutralization by F105 except for the viruses containing the V242I change, which exhibited a slight increase in neutralization sensitivity to F105. Wildtype KB9 is resistant to neutralization by F105 but the changes associated with adaptation to marmoset receptors resulted in variants with increased sensitivity to neutralization by F105. Thus, adaptation to marmoset receptors resulted in an increase in sensitivity to neutralization by F105 for KB9 but not for NL4-3. Pacheco *et al.* [2008] (**neutralization**)

- F105: Neutralization of HIV-1 IIIB LAV isolate by F105 was within the same range as the neutralization of the virus by natural antibodies from human sera against the gal(α1,3)gal disaccaride linked to CD4 gp120-binding peptides, indicating that the activity of natural antibodies can be re-directed to neutralize HIV-1. Perdomo *et al.* [2008] (**neutralization**)
- F105: A significantly higher level of anti-V3 Ab (694/98D) and anti-C1 mAb (EH21) bound to gp120 complexed with F105 mAb than to gp120 alone or in complex with other non-CD4bs Abs, indicating that binding of F105 to gp120 increases exposure of specific V3 and C1 mAb epitopes. Visciano *et al.* [2008b]
- F105: F105 was tested for its ability to induce conformational changes similar to those induced by CD4. Although presence of sCD4 increased neutralization of JRFL by 447-52D and immune sera rich in V3-Abs from guinea pigs, the presence of F105 did not, indicating that F105 does not induce a conformation alternation in Env that exposes the V3 loop to neutralizing Abs. Wu *et al.* [2008]
- F105: F105 bound exclusively to cells expressing gp120 in a co-receptor-independent manner. Although binding and uptake of F105 was increased with increased expression of gp120 on the cell surface, efficient internalization in short amount of time was possible even in cells expressing low levels of gp120. Internalized F105 was localized to the Golgi compartment. Kinetic analyses of F105 binding to gp120 demonstrated a heterogeneous mode of binding that did not trigger a conformational change in the formed complex. Compared to sCD4, F105 had a higher gp120 affinity, due to slower dissociation. Clayton *et al.* [2007] (**co-receptor**, **kinetics**, **binding affinity**)
- F105: gp120 proteins with double mutation T257S+S375W, which alters the cavity at the epicenter of the CD4 binding region, decreased F105 recognition to an undetectable level. The S375W single mutation also disrupted the binding surface of the F105 Ab. Dey *et al.* [2007b] (**binding affinity**)
- F105: A D386N change in the V4 region, which results in restoration of N-glycosylation at this site, did not have any impact on the neutralization of a mutant virus by F105 compared to wildtype. Also, there was no association between increased sensitivity to F105 neutralization and enhanced macrophage tropism. Dunfee *et al.* [2007] (**neutralization**)
- F105: A recombinant gp120-Fc, used in an assay to determine 2G12 epitope contribution to DC-SIGN binding to gp120, bound to F105, indicating it was conformationally intact. Hong *et al.* [2007] (**binding affinity**)
- F105: This review summarizes F105 Ab epitope, properties and neutralization activity. F105 use in passive immunization studies in primates and possible mechanisms explaining protection against infection are discussed. Kramer *et al.* [2007] (**immunotherapy**, **review**)
- F105: 32 human HIV-1 positive sera neutralized most viruses from clades A, B, and C. Two of the sera stood out as particularly potent and broadly reactive. IgG eluted from gp120 wildtype and core protein from the sera were readsorbed with the gp120-D368R mutant protein to remove non-CD4-binding site Abs. Binding of the resulting flow-through core eluate/368ft IgG to gp120 was completely blocked by Fab F105. Fab F105 also blocked most of the binding of the gp120WT eluate/368ft IgG, indicating that these Ab fractions were highly enriched with CD4-binding site Abs. Li *et al.* [2007b] (**neutralization**)
- F105: F105 structure, binding and neutralization are reviewed in detail. Molecules designed to eliminate binding by F105 while preserving epitopes of other neutralizing Abs are discussed. Lin & Nara [2007] (**review**, **structure**)
- F105: A chimeric protein entry inhibitor, L5, was designed consisting of an allosteric peptide inhibitor 12p1 and a carbohydrate-binding protein cyanovirin (CNV) connected via a flexible linker. The L5 chimera inhibited F105-gp120 interaction, but the CNV alone did not, indicating that the chimera has the high affinity binding property of the CNV molecule and the inhibitory property of the 12p1 peptide. McFadden *et al.* [2007]
- F105: This review provides information on the HIV-1 glycoprotein properties that make it challenging to target with neutralizing Abs. F105 neutralization properties and binding to HIV-1 envelope, and current strategies to develop versions of the Env spike with functional trimer properties for elicitation of broadly neutralizing Abs, are discussed. In addition, approaches to target cellular molecules, such as CD4, CCR5, CXCR4, and MHC molecules, with therapeutic Abs are reviewed. Phogat *et al.* [2007] (**review**)
- F105: Compared to the full-length Con-S gp160, chimeric VLPs containing Con-S ΔCFI gp145 with transmembrane (TM) and cytoplasmic tail (CT) sequences derived from the mouse mammary tumor virus (MMTV), showed higher binding capacity to F105. Chimeric VLPs with only CT derived from MMTV also showed higher binding capacity to F105 than the full-length Con-S gp160, however, not as high as the chimeric CT-TM VLPs. Wang *et al.* [2007a] (**binding affinity**)
- F105: This Ab was used to select phages from two different peptide libraries. Synthetic peptides corresponding to the selected phage sequences showed slight inhibition of F105 binding to gp120. F105 did not bind to synthetic peptides to 5145A MAb fused to phage pIII protein. Sera from rabbits immunized with 5145A peptide-phage pIII protein did not inhibit binding of F105 to gp120. Wilkinson *et al.* [2007] (**antibody generation**)
- F105: This Ab was used to determine the degree to which fixation of gp120 in its CD4-bound conformation restricts antigenic recognition. F105 was not able to bind well to the stabilized gp120. Zhou *et al.* [2007]
- F105: Macaques were immunized with SF162gp140, ΔV2gp140, ΔV2ΔV3gp140 and ΔV3gp140 constructs and their antibody responses were compared to the broadly reactive NAb responses in a macaque infected with SHIV

B Cell

SF162P4, and with pooled sera from humans infected with heterologous HIV-1 isolates (HIVIG). F105 bound to SF162gp140 but a deletion of V2 or V3 loops from the gp140 construct reduced the binding. Derby *et al.* [2006] (**antibody binding site definition and exposure**)

- F105: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- F105: The crystal structure of this Ab was compared to the high resolution crystal structure of Fab m18. Although the variable domains of m18 and F105 showed sequence similarity, the H3s of these Abs showed distinct conformations. Similarly, the H2s conformations of these Abs differed. Prabakaran *et al.* [2006] (**antibody binding site definition and exposure**, **mimics**, **antibody sequence variable domain**, **structure**)
- F105: The major infectivity and neutralization differences between a PBMC-derived HIV-1 W61D strain and its T-cell line adapted counterpart were conferred by the interactions of three Env amino acid substitutions, E440G, D457G and H564N. Chimeric Env-pseudotyped virus Ch5, containing all three of the mutations, was more neutralization sensitive to F105 than Ch2, which did not contain any of these mutations. Neutralization sensitivity to F105 by Env-pseudotyped viruses containing D457G mutation alone, or in combination with E440G or H564N, was unaffected compared to mutants lacking this mutation. Binding of F105 to gp120 derived from Env-pseudotyped viruses was unaffected by any of these mutations. Beddows *et al.* [2005b] (**neutralization**, **binding affinity**)
- F105: All clones derived from biopanning using IgG1b12 bound to this Ab but not to the control Ab F105. Dorgham *et al.* [2005] (**antibody binding site definition and exposure**)
- F105: Point mutations in the highly conserved structural motif LLP-2 within the intracytoplasmic tail of gp41 resulted in conformational alternations of both gp41 and gp120. The alternations did not affect virus CD4 binding, coreceptor binding site exposure, or infectivity of the virus, but did result in decreased binding and neutralization by certain MAbs and human sera. F105 exhibited similar levels of binding to both the LLP-2 mutant and wildtype viruses, indicating that its epitope was not altered by the mutation. Kalia *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)
- F105: A series of genetically modified Env proteins were generated and expressed in both insect and animal cells to be monitored for their antigenic characteristics. For F105, modified protein 3G (mutations in 3 glycosylation sites) showed the highest binding to this Ab compared to the other Env proteins. Kang *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)
- F105: The HIV-1 Bori-15 variant was adapted from the Bori isolate for replication microglial cells. Bori-15 had increased replication in microglial cells and a robust syncytium-forming phenotype, ability to use low levels of CD4 for infection, and increased sensitivity to neutralization by sCD4 and 17b. Four amino acid changes in gp120 V1-V2 were responsible for this change. Protein functionality and integrity of soluble, monomeric gp120-molecules derived from parental HIV-1 Bori and microglia-adapted HIV-1 Bori-15 was assessed in ELISA binding assays using CD4BS MAbs F105 and IgG1b12, glycan-specific 2G12, and V3-specific 447-52D, and were unchanged. Association rates of sCD4 and 17b were not changed, but dissociation rates were 3-fold slower for sCD4 and 14-fold slower for 17b. Martín-García *et al.* [2005] (**antibody binding site definition and exposure**)
- F105: A chimeric cell surface receptor (105TCR) was designed consisting of the single chain Fv domain of F105, CD8α hinge and the transmembrane, and the cytoplasmic domains of TCRζ. 105TCR was successfully expressed on the surface of T-cells. It mediated full activation of T-cells leading to cytokine production when bound to gp120 on the surface of an infected cell. It did not bind to soluble gp120. Retrovirally transduced CD8+ cells expressed high levels of 105TCR and were able to lyse HIV-1 envelope expressing cells specifically in an MHC-unrestricted manner. Masiero *et al.* [2005] (**immunotherapy**)
- F105: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **antibody interactions**, **neutralization**, **variant cross-recognition or cross-neutralization**, **immunotherapy**, **review**)
- F105: JR-FL and YU2 HIV-1 strains were not neutralized by F105. F105 and other non-neutralizing Abs only recognized JR-FL cleavage-defective glycoproteins, while the neutralizing Abs (2G12 and IgG1b12) recognized both cleavage competent and cleavage-defective glycoproteins. It is suggested that an inefficient env glycoprotein precursor cleavage exposes non-neutralizing determinants, while only neutralizing regions remain accessible on efficiently cleaved spikes. For YU2, both cleavage-competent and -defective glycoproteins were recognized by both neutralizing and non-neutralizing Abs. F105, along with other Abs able to neutralize lab-adapted isolates, displayed enhanced viral entry at higher Ab concentrations, whereas the Abs that cannot neutralize any virus did not display such enhancement. Pancera & Wyatt [2005] (**antibody binding site definition and exposure**, **enhancing activity**, **neutralization**, **binding affinity**)
- F105: A stable trimerization motif, GCN4, was appended to the C terminus of YU2gp120 to obtain stable gp120 trimers (gp120-GCN4). Each trimer subunit was capable of binding IgG1b12, indicating that they were at least 85% active. D457V mutation in the CD4 binding site resulted in a decreased affinity of the gp120-GCN4 for CD4, but the mutation did not affect binding of F105. F105 was able to bind to both wildtype gp120, gp120-GCN4, and to the respective corresponding mutant molecules D457Vgp120 and D457Vgp120-GCN4. Pancera *et al.* [2005] (**binding affinity**)
- F105: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a

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series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. CD4BS MAbs except Fab b12 (b6, b3, F105) did not bind to either GDMR or mCHO. Selvarajah *et al.* [2005] (**vaccine antigen design**, **vaccine-specific epitope characteristics**)

- F105: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **immunotherapy**, **mother-to-infant transmission**, **review**)
- F105: A T-cell line adapted strain (TCLA) of CRF01_AE primary isolate DA5 (PI) was more neutralization sensitive to F105 than the primary isolate. Mutant virus derived from the CRF01_AE PI strain, that lacked N-linked glycosylation at position 197 in the C2 region of gp120, was significantly more sensitive to neutralization by F105 then the PI strain. Deglycosylated subtype B mutants at positions 197 and 234 were significantly more neutralizable by F105 than the parental strain. Teeraputon *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **subtype comparisons**)
- F105: The crystal structure of the Fab fragment from F105 was solved. It has an extended CDR H3 loop, with a Phe at the apex that may recognize the binding pocket of gp120 used by the Phe-42 residue of CD4. The potent NAB IgG1b12 recognizes an overlapping binding site, the main difference is that F105 extends across the interface of the inner and outer domains of gp120 while b12 does not. IgG1b12 also has undergone extensive affinity maturation (45 mutations) while F105 has not (13 mutations) – an average for gp120 MAbs is 22 mutations. Wilkinson *et al.* [2005] (**antibody sequence variable domain**, **structure**)
- F105: Ab neutralization of viruses with mixtures of neutralization-sensitive and neutralization-resistant envelope glycoproteins was measured. It was concluded that binding of a single Ab molecule is sufficient to inactivate function of an HIV-1 glycoprotein trimer. The inhibitory effect of the Ab was similar for neutralization-resistant and -sensitive viruses indicating that the major determinant of neutralization potency of an Ab is the efficiency with which it binds to the trimer. It was also indicated that each functional trimer on the virus surface supports HIV-1 entry independently, meaning that every trimer on the viral surface must be bound by an Ab for neutralization of the virus to be achieved. Yang *et al.* [2005c] (**neutralization**)
- F105: A substantial fraction of soluble envelope glycoprotein trimers contained inter-subunit disulfide bonds. Reduction of these disulfide bonds had little effect on binding of the F105 to the glycoprotein indicating that the inter-S-S bonds had no impact on the exposure of F105 epitope. Yuan *et al.* [2005] (**antibody binding site definition and exposure**)
- F105: The peptide 12p1 (RINNIPWSEAMM) inhibits direct binding of YU2 gp120 or Env trimer to CD4, CCR5 and MAb 17b in a concentration-dependent allosteric manner. 12p1 is thought to bind to unbound gp120 near the CD4 binding site, with a 1:1 stoichiometry. 12p1 also inhibited MAb F105 binding. presumably because F105 favors an unactivated conformation, but not MAbs 2G12 or b12. The 1:1 stoichiomtry, the fact that the peptide binding site is accessible on the trimer, the non-CD4 like aspect of the binding, and an ability to inhibit viral infection in cell cultures make 12p1 a promising lead for therapeutic design. Biorn *et al.* [2004]
- F105: NAbs against HIV-1 M group isolates were tested for their ability to neutralize 6 randomly selected HIV-1 O group strains. F105 was not particularly effective at neutarlizing HIV-1 group O strains. Ferrantelli *et al.* [2004a] (**variant cross-recognition or cross-neutralization**)
- F105: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- F105: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of CD4BS MAb F105 was decreased by trypsin, but increased by thrombin. Thrombin may increase HIV-induced cell fusion in blood by causing a conformational activating shift in gp120. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- F105: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including F105. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- F105: The ability of F105 to neutralize R5, R5X4 and X4 primary isolates was compared to that of MAbs 17b, E51 and 412d. F105 neutralized the R5 ADA virus more efficiently than 17b, comparable to 412d, however, it neutralized R5X4 isolate 89.6 less efficiently than 412d and E51. F105 was, on the other hand, more efficient in neutralizing the X4 isolate HXBc2 than the other MAbs. Choe *et al.* [2003] (**neutralization**)
- F105: Env genes derived from uncultured brain biopsy samples from four HIV-1 infected patients with late-stage AIDS were compared to env genes from PBMC samples. Brain isolates did not differ in the total number or positions of N-glycosylation sites, patterns of coreceptor usage, or ability to be recognized by gp160 and gp41 MAbs. F105 recognized most variants,some from each of the four individuals by gp120 immunoprecipitation. Ohagen *et al.* [2003] (**brain/CSF**, **variant cross-recognition or cross-neutralization**)

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- F105: Alanine scanning mutagenesis was used to compare substitutions that affected anti-CD4BS NAb b12 – rec gp120s were engineered to contain combinations of Alanine substitutions that enhanced b12 binding, and while binding of b12 to these gp120 monomers was generally maintained or increased, binding by five non-neutralizing anti-CD4bs MAbs (b3, b6, F105, 15e, and F91) was reduced or completely abolished. Pantophlet *et al.* [2003a] (**antibody binding site definition and exposure**)
- F105: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- F105: Virion capture assays are not a good preditor of neutralization, and the presentation of epitopes using this assay seems to be different from that of functional Envelope spikes on primary isolates – F105 and b6 could efficiently block the b12-mediated capture of infectious virions in a virus capture, but did not inhibit b12 neutralization – while b12 was potent at neutralizing the three primary virions JR-CSF, ADA, and 89.6, the Abs F105, 19b, and Fab b6 were overall very poor neutralizers. Poignard *et al.* [2003] (**antibody interactions**)
- F105: This paper shows that binding of CD4BS MAbs to Env blocks the conformational shift that allows co-receptor CCR5 binding and CD4-independent mediated cell fusion. CD4BS MAbs F105, 15e, and IgG1b12 as well as their Fab fragments inhibited CD4-independent binding of the V1/V2 loop-deleted gp120 glycoproteins of R5 HIV-1 isolates ADA, YU2 and JR-FL and to CCR5 in a concentration dependent manner. CD4BS MAbs IgG1b12, F91 and F105 and their Fab counterparts (except for C11, used as a negative control) inhibited CD4-independent JR-FL and YU-2 gp120-CCR5 binding to CCR5-expressing Cf2Th cells and syncytium formation. Raja *et al.* [2003] (**antibody binding site definition and exposure**, **co-receptor**)
- F105: 17b: This paper describes the generation of CD4i MAb E51, that like CD4i MAb 17b, blocks CCR5 binding to sCD4-bound gp120. The substitutions E381R, F383S, R419D I420R, K421D, Q422L, I423S, and Y435S (HXB2 numbering) all severely reduce 17b and E51 binding. All but I423S also diminish CCR5 binding by more than 50%. The mutation F383S also inhibits sCD4 binding and F105 binding, and K421D inhibits F105 binding, but not sCD4. Xiang *et al.* [2003] (**antibody binding site definition and exposure**)
- F105: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- F105: gp120 mutants were used to define the CXCR4 binding site using CXCR4 displayed on paramagnetic proteoliposomes (PMPLs) to reduce non-specific gp120 binding—basic residues in the V3 loop and the β19 strand (RIKQ, positions 419-422) were involved, and deletion of the V1-V2 loops allowed CD4-independent CXCR4 binding—MAbs 17b (CD4i) and F105 (CD4BS) were used to study conformational changes in the mutants—the affinity of ΔV1 and ΔV1-V2 mutants for F105 was comparable to the wildtype—V3 mutants did not affect F105 binding—the K421A mutation in the β19 strand dramatically reduced F105 affinity, consistent with what is known about the F105 epitope. Basmaciogullari *et al.* [2002] (**antibody binding site definition and exposure**)
- F105: This study examined Ab interactions, binding and neutralization with a B clade R5 isolate (92US660) and R5X4 isolate (92HT593). Abs generally bound and neutralized the R5X4 isolate better than the R5 isolate. Anti-gp41 MAb F240 enhanced the binding of CD4BS MAbs IgG1b12 and F105 to both R5X4 and R5 isolates, but had no effect on neutralization. Anti-V3 MAb B4a1 increased CD4BS MAbs IgG1b12 and F105 to R5X4 virions, but only IgG1b12 binding was increased by B4a1 to the R5 isolate, and neutralization was not impacted. Cavacini *et al.* [2002] (**co-receptor**)
- F105: A modified gp140 (gp140deltaCFI), with C-term mutations intended to mimic a fusion intermediate and stabilize trimer formation, retained antigenic conformational determinants as defined by binding to CD4 and to MAbs 2F5, 2G12, F105, and b12, and enhanced humoral immunity without diminishing the CTL response in mice injected with a DNA vaccine. Chakrabarti *et al.* [2002] (**vaccine antigen design**)
- F105: Review of NAbs that notes that F105 binds the CD4BS, in combination with other MAbs it can protect some macaques against SHIV infection, and that it has strong ADCC activity. Ferrantelli & Ruprecht [2002] (**ADCC**, **antibody interactions**, **immunoprophylaxis**, **review**)
- F105: HIV-1 gp160δCT (cytoplasmic tail-deleted) proteoliposomes (PLs) containing native, trimeric envelope glycoproteins from R5 strains YU2 and JRFL, and X4 strain HXBc2, were made in a physiologic membrane setting as candidate immunogens for HIV vaccines—2F5 bound to gp160δCT with a reconstituted membrane ten-fold better than the same protein on beads, while such an affinity difference was not seen with F105 and 2G12—anti-CD4BS MAbs IgG1b12 and F105, A32 (C1-C4), C11 (C1-C5), and 39F (V3) MAbs bound gp160δCT PLs indistinguishably from gp160δCT expressed on the cell surface. Grundner *et al.* [2002] (**antibody binding site definition and exposure**)
- F105: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar. Enthalpy and entropy changes were divergent, but compensated. Not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs (17b, 48d, 1.5e, b6, F105 and F91) had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120

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monomer, but the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. The high values suggest surface burial or protein folding and ordering of amino acids. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)

- F105: A pseudotyping assay showed that an X4 V3 loop peptide could enhance infectivity of X4 virus, R5 and R5X4 V3 loops peptides could enhance infectivity of an R5 virus, and R5X4 peptides could enhance infectivity of an R5X4 virus. Neither R5 nor R5X4 peptides influenced binding of CD4BS MAbs F105 and Ig1Gb12, but did increase binding of CD4i MAb 17b. Ling *et al.* [2002] (**antibody binding site definition and exposure**, **co-receptor**)
- F105: Review of NAbs that discusses mechanisms of neutralization, passive transfer of NAbs and protection in animal studies, and vaccine strategies. Liu *et al.* [2002] (**immunoprophylaxis**)
- F105: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91 was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b] (**antibody binding site definition and exposure**)
- F105: Passive immunization of neonate macaques with a combination of F105+2G12+2F5 conferred complete protection against oral challenge with SHIV-vpu+ or – the combination b12+2G12+2F5 conferred partial protection against SHIV89.6 – such combinations may be useful for prophylaxis at birth and against milk born transmission – the synergistic combination of IgG1b12, 2G12, 2F5, and 4E10 neutralized a collection of HIV clade C primary isolates. Xu *et al.* [2002] (**immunoprophylaxis**, **mother-to-infant transmission**)
- F105: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibritin—stabilized oligomer gp140δ683(-FT) showed strong preferential recognition by NAbs IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAbs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002] (**vaccine antigen design**)
- F105: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002] (**antibody binding site definition and exposure**)
- F105: Mutations in two glcosylation sites in the V2 region of HIV-1 ADA at positions 190 and 197 (187 DNTSYRLINCNTS 199) cause the virus to become CD4-independent and able to enter cells through CCR5 alone – these same mutations tended to increase the neutralization sensitivity of the virus, including to F105. Kolchinsky *et al.* [2001] (**antibody binding site definition and exposure**)
- F105: SHIV-HXBc2 is a neutralization sensitive non-pathogenic virus, and several *in vivo* passages through monkeys yielded highly pathogenic SHIV KU-1—HXBc2 and the KU-1 clone HXBc2P3.2 differ in 12 amino acids in gp160—substitutions in both gp120 and gp41 reduced the ability of sCD4, IgG1b12, F105 and AG1121 to Env achieve saturation and full occupancy, and neutralize KU-1—17b and 2F5 also bound less efficiently to HXBc2P3.2, although 2G12 was able to bind both comparably. Si *et al.* [2001] (**antibody binding site definition and exposure**)
- F105: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAbs alters some step after binding. York *et al.* [2001] (**antibody binding site definition and exposure**)
- F105: A triple combination of 2F5, F105 and 2G12 effectively neutralized perinatal infection of macaque infants when challenged with SHIV-vpu+ – the plasma half-life was 7.2 +/- 2.2 days. Baba *et al.* [2000] (**immunoprophylaxis**, **mother-to-infant transmission**)
- F105: Host encoded intercellular adhesion molecule (ICAM-1) is incorporated by the HIV-1 virion and enhances viral infectivity – ICAM-1 does not modify virus sensitivity to antibodies 0.5beta or 4.8D or sCD4, but neutralizing ability of F105 was diminished in ICAM bearing virions in the presence of lymphocyte function-association antigen-1 (LFA-1) Ab. Fortin *et al.* [2000]
- F105: Six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form, although F105 was an exception and cannot neutralize either form of MN – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000]
- F105: A mini-review of observations of passive administration of IgG NAbs conferring protection against intervenous or

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vaginal SHIV challenge, that considers why IgG MAbs might protect against mucosal challenge. Robert-Guroff [2000] (**immunoprophylaxis**, **mucosal immunity**, **review**)

- F105: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000] (**vaccine antigen design**)
- F105: A comparison of 25 gp120 specific, conformation dependent MAbs was done and F105 was used for competition studies – F105 did cross-compete with multiple CD4BS specific MAbs, however most could not neutralize even the autologous NL4-3 strains. Sugiura *et al.* [1999] (**antibody interactions**)
- F105: Immunoprecipitation of gp120 and gp160 expressed from a rec Semliki Forest virus by F105 and IgG1b12 indicated that the SFV expressed HIV-1 Env was folded appropriately – and SVF-HIV-1 Env vaccine gave the strongest anti-HIV-1 Env response in mice, when compared to an HIV-1 Env DNA vaccine and a rgp160 protein. Brand *et al.* [1998] (**vaccine antigen design**)
- F105: Phase I dose escalation study, single dose of 100 or 500 mg/m2 was given to 4 HIV+ patients – sustained levels, no immune response against F105, no toxicity, infused Ab retained function – there was no evidence of anti-HIV-1 activity and virus was not diminished at day 1 or 7, by culture or plasma RNA. Cavacini *et al.* [1998b] (**kinetics**, **immunotherapy**)
- F105: The MAb F240 binds to the immunodominant region of gp41 and enhances infection in the presence of complement – reactivity of F240 is enhanced by preincubation of cells with sCD4 or anti-CD4BS MAb F105. Cavacini *et al.* [1998a] (**antibody interactions**)
- F105: Anti-C1 region MAb 87-135/9 blocks gp120 interaction with CD4+ cells – blocking activity is additive when combined with antibodies which bind in the C4 region of gp120 (F105, 388/389, and b12). Kropelin *et al.* [1998] (**antibody interactions**)
- F105: Neutralization synergy was observed when the MAbs 694/98-D (V3), 2F5 (gp41), and 2G12 (gp120 discontinuous) were used in combination, and even greater neutralizing potential was seen with the addition of a fourth MAb, F105 (CD4 BS). Li *et al.* [1998] (**antibody interactions**)
- F105: F105 enhances viral entry of viruses carrying the YU2 envelope glycoproteins, but neutralizes HXBc2. Sullivan *et al.* [1998a] (**enhancing activity**)
- F105: Summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAb binding – probable mechanism of neutralization by CD4BS Ab is direct interference with CD4 binding. Wyatt *et al.* [1998] (**antibody binding site definition and exposure**, **structure**)
- F105: Virus with the V1-V2 loop deleted was viable and more susceptible to neutralization by CD4i MAb 17b, and anti-V3 MAbs 1121, 9284, and 110.4, but not to a CD4BS MAb, F105 or sCD4. Cao *et al.* [1997b] (**antibody binding site definition and exposure**)
- F105: In a multilaboratory blinded study, failed to neutralize any of nine B clade primary isolates. D'Souza *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- F105: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env – F105 could only achieve 50% neutralization alone – all Ab combinations tested showed synergistic neutralization – F105 has synergistic response with MAbs 694/98-D (anti-V3), 48d, 2F5, and 2G12, and also with HIVIG. Li *et al.* [1997] (**antibody interactions**, **variant cross-recognition or cross-neutralization**)
- F105: Neutralizes TCLA strains, but not primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- F105: Binds both gp120 and soluble gp120+gp41 complex efficiently, suggesting its gp120 epitope is not blocked by gp41 binding – does not bind to HXBc2 gp120 if the 19 C-term amino acids, in conjunction with C1 positions 31-93, are deleted. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
- F105: Intracellular co-expression of heavy and light chains of the Fab105 fragment MAb F105 was enhanced by inclusion of an internal ribosome entry site (IRES) sequence – the Fab105 IRES expression cassette was cloned into an adeno-associated virus (AAV) shuttle vector, and transduced into human lymphocytes which were able to produce and secrete the Fab105 fragments while maintaining normal growth – several primary HIV-1 patient isolates were effectively blocked. Chen *et al.* [1996] (**immunotherapy**)
- F105: The sulfated polysaccharide curdlan sulfate (CRDS) binds to the Envelope of T-tropic viruses and neutralizes virus – deletion of the V3 loop results in less potent inhibition of F105 binding by CRDS – binding site of F105 described as 256-257 ST, 368-370 DPE, 421 K, and 470-484 PGGGDMRDNWRSELY. Jagodzinski *et al.* [1996] (**antibody binding site definition and exposure**)
- F105: Binding of F105 to oligomeric gp120 occurs despite the fact it cannot neutralize primary isolates. Litwin *et al.* [1996]
- F105: Neutralizes HIV-1 LAI less potently than V3 specific MAbs. McDougal *et al.* [1996]
- F105: A panel of immunotoxins were generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but killing was not directly proportional to binding. Pincus *et al.* [1996] (**immunotoxin**)
- F105: F105 is V H4 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996] (**antibody sequence variable domain**)
- F105: Phase I study – MAb clearance in plasma has a 13 day half-life. Wolfe *et al.* [1996] (**kinetics**, **immunotherapy**)
- F105: Changing heavy chain from IgG1 to IgG3 increased neutralization efficiency. Cavacini *et al.* [1995]
- F105: Biotinylated F105 was used for competition studies with Ab derived from pregnant HIV-1 + women – a correla-

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tion between maternal anti-CD4 BS Abs overlapping the F105 binding site and lack of HIV-1 transmission to infants was noted. Khouri *et al.* [1995] (**mother-to-infant transmission**)

- F105: Eight patient phase Ia trial for use as an immunotherapeutic – no clinical or biochemical side effects observed, plasma levels of 10 ug/ml maintained for 21 days. Posner *et al.* [1995] (**immunotherapy**)
- F105: Efficient neutralization of T-cell adapted lines HXBc2 and MN, no neutralization of primary isolates 89.6, ADA and YU2 – even some enhancement of infection of ADA and YU2 was observed. Sullivan *et al.* [1995] (**enhancing activity**, **variant cross-recognition or cross-neutralization**)
- F105: An immunoassay for titrating CD4BS serum antibody was developed using a gp120-coated solid phase and competition with MAb F105 – 109/110 French HIV-1 + sera and 51/56 HIV-1 + African sera had detectable CD4BS Abs using this assay, demonstrating CD4 binding site conservation among diverse subtypes – CD4BS Abs were detected soon after seroconversion and persisted – 0/21 HIV-2 + sera reacted, indicating that the HIV-1 and HIV-2 CD4BS Abs are not cross-reactive. Turbica *et al.* [1995] (**assay development**, **subtype comparisons**)
- F105: Comparison of MAb F105 sequences with those of MAbs 21h and 15e. Bagley *et al.* [1994] (**antibody sequence variable domain**)
- F105: Administered intravenously to four cynomologus monkeys, plasma pharmacokinetics and biological activity tested. Cavacini *et al.* [1994b] (**kinetics**)
- F105: Fab fragments show reduced capacity to neutralize IIIB, MN, and RF compared to intact IgG1, suggesting bivalent interaction may be important in binding and neutralization. Cavacini *et al.* [1994a] (**variant cross-recognition or cross-neutralization**)
- F105: A human CD4+ T lymphocyte line was transduced to express Fab fragments of F105 – heavy and light chains are joined by an inter-chain linker – in the transduced cells infected with HIV-1, the Fab binds intracellularly to the envelope protein and inhibits HIV-1 production – secreted Fab fragments neutralize cell-free HIV-1– combined intra- and extracellular binding activities of the expressed Fab make transduced cells resistant to HIV-1 infection and also can protect surrounding lymphocytes by secreting neutralizing antibodies. Chen *et al.* [1994a]; Marasco *et al.* [1993] (**variant cross-recognition or cross-neutralization**)
- F105: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – anti-CD4 MAbs moderately inhibit gp120 binding to GalCer, possibly through steric hindrance – binding of GalCer to gp120 inhibited but did not completely block F105 binding. Cook *et al.* [1994] (**brain/CSF**)
- F105: Used as a positive control for CD4 BS antibodies in a study of the influence of oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994] (**antibody binding site definition and exposure**)
- F105: A mutation in gp41, 582 A/T, confers resistance to neutralization (also confers resistance to MAbs 48d, 21h, 15e and 17b). Thali *et al.* [1994] (**antibody binding site definition and exposure**)
- F105: Additive MN or SF2 neutralization when combined with anti-V3 MAbs 447-52D and 257-D. Cavacini *et al.* [1993a] (**antibody interactions**)
- F105: Serum from all asymptomatic HIV-1 positive people tested block F105 binding, but only from 27% of symptomatic individuals. Cavacini *et al.* [1993b] (**rate of progression**)
- F105: The gp41 mutation 582(Ala to Thr) results in conformational changes in gp120 that confer neutralization resistance to a class of conformation sensitive neutralizing MAbs – required >81 fold higher concentrations to neutralize the mutant than wild type. Klasse *et al.* [1993a] (**antibody interactions**)
- F105: Study of synergy between F105 and sera from vaccinated volunteers with V3-loop specific neutralization activity – 2/3 sera demonstrated neutralization synergy, and 3/3 binding/fusion-inhibition synergy. Montefiori *et al.* [1993] (**antibody interactions**)
- F105: Called F-105 – neutralizes IIIB – strong inhibition of HIV+ human sera binding to IIIB gp120. Moore & Ho [1993]
- F105: Ab response in IIIB lab workers was compared to gp160 LAI vaccine recipients – F105 was used as a control – infected lab workers and some of the gp160 vaccinees had a MAb response that could inhibit gp120-CD4 binding, at lower titers than the infected lab workers. Pincus *et al.* [1993] (**vaccine-specific epitope characteristics**)
- F105: F105 binds to and neutralizes selected lab strains and 3/9 HIV-1 primary isolates – synergistic enhancement of neutralization by seropositive sera. Posner *et al.* [1993] (**antibody interactions**, **variant cross-recognition or cross-neutralization**)
- F105: Study of synergy of neutralization and binding comparing F105 and sCD4 with the V3 MAbs: 50.1, 59.1, 83.1, and 58.2 – synergy was observed, and the data suggest that binding of one ligand (F105) can increase the binding of the second (e. g. V3 loop MAbs) due to conformational changes. Potts *et al.* [1993] (**antibody interactions**)
- F105: A neutralization escape mutant (HXB2 A281V) was selected by growth of HXB2 in the presence of broadly neutralizing sera – F105 neutralization was not affected by this mutation. Watkins *et al.* [1993] (**escape**)
- F105: Binding to Delta V1/2 and Delta V1/2/3 mutant glycoproteins is 2.4- and 13-fold greater, respectively, than binding to wildtype gp120. Wyatt *et al.* [1993] (**antibody binding site definition and exposure**)
- F105: MAb cDNA sequence – V H4 V71-4 rearranged with a D H D-D fusion product of dlr4 and da4, and with J H5 – V kappa is from the Humvk325 germline gene joined with Jkappa 2. Marasco *et al.* [1992] (**antibody sequence variable domain**)
- F105: F105 mediates ADCC against SF2 through the CD16+ population of PBMC – does not mediate complement-dependent cytotoxicity. Posner *et al.* [1992b] (**ADCC**, **complement**)
- F105: Significant enhancement of F105 binding to RF infected cells preincubated with V3-specific MAbs V3-2 and V3-1. Posner *et al.* [1992a] (**antibody interactions**)
- F105: Amino acid substitutions that impair F105 neutralization inhibit gp120-CD4 interaction. Thali *et al.* [1992a] (**antibody binding site definition and exposure**)

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- F105: Precipitation of Delta 297-329 env glycoprotein, which has a deleted V3 loop, is much more efficient than precipitation of wild type. Wyatt *et al.* [1992] (**antibody binding site definition and exposure**)
- F105: First description of F105, binds topographically near the CD4-binding site – inhibits binding of free, infectious virions to uninfected HT-H9 cells, but does not react with virus adsorbed to uninfected HT-H9 cells – soluble rCD4 prebound to infected cells inhibits F105 binding – F105 inhibits infection of HT-H9 cells in standard neutralization assays with HIV-1 and MN strains. Posner *et al.* [1991] (**antibody binding site definition and exposure**, **antibody generation**)
- F105: F105 neutralization escape mutants result from changes in amino acids in discontinuous regions: C2, 256-262 and C3, 386-370. Thali *et al.* [1991] (**antibody binding site definition and exposure**)

No.	1386
MAb ID	F91 (F-91)
HXB2 Location	Env
Author Location	gp120
Epitope	
Neutralizing	no
Immunogen	
Species (Isotype)	
Ab Type	gp120 CD4BS
Research Contact	James Robinson, University of Connecticut, Storrs
References	Zhou *et al.* 2007; Lin & Nara 2007; Yuan *et al.* 2005; Yang *et al.* 2005c; Srivastava *et al.* 2005; Pantophlet *et al.* 2004; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Raja *et al.* 2003; Pantophlet *et al.* 2003a; Kwong *et al.* 2002; Xiang *et al.* 2002b; Yang *et al.* 2002; Yang *et al.* 2000; Fouts *et al.* 1998; Binley *et al.* 1998; Parren *et al.* 1998a; Mondor *et al.* 1998; Fouts *et al.* 1997; Moore & Sodroski 1996; Moore *et al.* 1994b; Moore & Ho 1993
Keywords	antibody binding site definition and exposure, antibody interactions, binding affinity, co-receptor, neutralization, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- F91: Molecules designed to eliminate binding by F91 while preserving epitopes of other neutralizing Abs are discussed. Lin & Nara [2007] (**review**)
- F91: This Ab was used to determine the degree to which fixation of gp120 in its CD4-bound conformation restricts antigenic recognition. F91 was not able to bind well to the stabilized gp120. Zhou *et al.* [2007] (**antibody binding site definition and exposure**, **binding affinity**)
- F91: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **review**)
- F91: Ab neutralization of viruses with mixtures of neutralization-sensitive and neutralization-resistant envelope glycoproteins was measured. It was concluded that binding of a single Ab molecule is sufficient to inactivate function of an HIV-1 glycoprotein trimer. The inhibitory effect of the Ab was similar for neutralization-resistant and -sensitive viruses indicating that the major determinant of neutralization potency of an Ab is the efficiency with which it binds to the trimer. It was also indicated that each functional trimer on the virus surface supports HIV-1 entry independently, meaning that every trimer on the viral surface must be bound by an Ab for neutralization of the virus to be achieved. Yang *et al.* [2005c] (**neutralization**)
- F91: A substantial fraction of soluble envelope glycoprotein trimers contained inter-subunit disulfide bonds. Reduction of these disulfide bonds had little effect on binding of the F91 to the glycoprotein indicating that the inter-S-S bonds had no impact on the exposure of F91 epitope. Yuan *et al.* [2005] (**antibody binding site definition and exposure**)
- F91: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- F91: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including F91. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- F91: Alanine scanning mutagenesis was used to compare substitutions that affected anti-CD4BS NAb b12 – rec gp120s were engineered to contain combinations of Alanine substitutions that enhanced b12 binding, and while binding of b12 to these gp120 monomers was generally maintained or increased, binding by five non-neutralizing anti-CD4bs MAbs (b3, b6, F105, 15e, and F91) was reduced or completely abolished. Pantophlet *et al.* [2003a] (**antibody binding site definition and exposure**)
- F91: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- F91: This paper shows that binding of CD4BS MAbs to Env blocks the conformational shift that allows co-receptor CCR5 binding and CD4-independent mediated cell fusion. CD4BS MAbs F105, 15e, and IgG1b12 as well as their Fab fragments inhibited CD4-independent binding of the V1/V2 loop-deleted

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gp120 glycoproteins of R5 HIV-1 isolates ADA, YU2 and JR-FL and to CCR5 in a concentration dependent manner. CD4BS MAbs IgG1b12, F91 and F105 and their Fab counterparts (except for C11, used as a negative control) inhibited CD4-independent JR-FL and YU-2 gp120-CCR5 binding to CCR5-expressing Cf2Th cells and syncytium formation. Raja *et al.* [2003] (**co-receptor**)

- F91: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- F91:Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar. Enthalpy and entropy changes were divergent, but compensated. Not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs (17b, 48d, 1.5e, b6, F105 and F91) had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, but the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. The high values suggest surface burial or protein folding an ordering of amino acids. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- F91: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91 was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b] (**antibody binding site definition and exposure**)
- F91: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibritin – stabilized oligomer gp140 delta683(-FT) showed strong preferential recognition by NAbs IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAbs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002] (**antibody binding site definition and exposure**)
- F91: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000] (**antibody binding site definition and exposure**)
- F91: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer – CD4BS MAbs 15e, F91 and IgG1b12 bound better to the deleted protein than to wild type. Binley *et al.* [1998] (**antibody binding site definition and exposure**)
- F91: CD4BS MAbs 15e, 21h, and F91 bind with even lower affinity than 205-43-1 and 205-42-15 to JRFL oligomer – conclusions of this paper contrast with Parren *et al.* [1998a] Fouts *et al.* [1998]. Fouts *et al.* [1998]; Parren *et al.* [1998a] (**antibody binding site definition and exposure**)
- F91: Weak inhibition of binding of Hx10 to CD4 positive or negative cells, weakly neutralizing. Mondor *et al.* [1998]
- F91: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**antibody binding site definition and exposure**)
- F91: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – F91 bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
- F91: Unusual pattern of reciprocal enhancement with several anti-V2 and V3 directed MAbs – reciprocal inhibition of other CD4BS MAbs. Moore & Sodroski [1996] (**antibody binding site definition and exposure**, **antibody interactions**)
- F91: Has strong cross-reactivity with gp120 monomers from most subtypes, A-F. Moore *et al.* [1994b] (**subtype comparisons**)
- F91: Called F-91 – neutralizes IIIB – reactive with SF-2 gp120 – strong inhibition of HIV+ human sera binding to IIIB gp120. Moore & Ho [1993] (**variant cross-recognition or cross-neutralization**)

No.	1387
MAb ID	FG39
HXB2 Location	Env
Author Location	gp120

Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
References Zwick *et al.* 2003
Keywords antibody interactions

- FG39: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This is a novel CD4BS Fab first used in this study. Zwick *et al.* [2003] (**antibody interactions**)

No. 1388
MAb ID Fbb14
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
References Zwick *et al.* 2003
Keywords antibody interactions

- Fbb14: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This is a novel CD4BS Fab first used in this study. Fbb14 was unusual among CDBS Abs in that it didn't enhance 4KG5's binding, like b12, but it did not inhibit it either as the other 13 CD4BS Abs did, it remained neutral. Zwick *et al.* [2003] (**antibody interactions**)

No. 1389
MAb ID GP13 (ARP3054)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
Ab Type gp120 CD4BS
References Gorny & Zolla-Pazner 2004; Vella *et al.* 2002; Schutten *et al.* 1997; Schutten *et al.* 1996; Wisnewski *et al.* 1996; Bolmstedt *et al.* 1996; Schutten *et al.* 1995b; Schutten *et al.* 1995a; Bagley *et al.* 1994; Back *et al.* 1993; Schutten *et al.* 1993
Keywords antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, assay development, binding affinity, enhancing activity, escape, review, subtype comparisons, variant cross-recognition or cross-neutralization

- GP13: UK Medical Research council AIDS reagent: ARP3054.
- GP13: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- GP13: Called ARP3054: Herpesvirus saimiri-immortalized CD4+ T lymphocytes (HVS T cells) were used to isolate virus and perform HIV-1 neutralization assays, and compared with a standard PBMC protocol – neutralization sensitivities to a panel of MAbs and to homologous or heterologous plasma/sera were similar for HVS T cells (CN-2 cells) and PBMCs. Vella *et al.* [2002] (**assay development**)
- GP13: Neutralized (50%) an SI-env chimeric virus and enhanced (>5 fold) an NSI-env chimeric virus. Schutten *et al.* [1997] (**enhancing activity**, **variant cross-recognition or cross-neutralization**)
- GP13: Sera were obtained from guinea pigs vaccinated either with gp160, or with gp160 lacking N-linked glycans at N406, N448, and N463 – these sera could block equally well both the CD4 BS MAb GP13 and the V3 MAb F58/H3. Bolmstedt *et al.* [1996] (**antibody interactions**)
- GP13: IIIB neutralizing MAbs *in vitro* fail to neutralize in a mouse model *in vivo*. Schutten *et al.* [1996]
- GP13: GP13 is V H5 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996] (**antibody sequence variable domain**)
- GP13: Neutralizes IIIB – only slight inhibition of SI phenotype, and strong enhancement of NSI phenotype chimeric viruses, that incorporated different envs from the same donor. Schutten *et al.* [1995a] (**enhancing activity**, **variant cross-recognition or cross-neutralization**)
- GP13: Neutralizes T-cell adapted viruses but not the SI strain 16.2, despite high binding affinity. Schutten *et al.* [1995b] (**variant cross-recognition or cross-neutralization**, **binding affinity**)
- GP13: Mutations in a neutralization resistant isolate obtained by passage of the IIIB isolate in chimpanzees reduced neutralization, but the escape was not as clear as seen with anti-V3 MAbs. Back *et al.* [1993] (**escape**)
- GP13: Neutralized a broad range of HIV-1 strains from phylogenetically different subfamilies – the following gp120 amino acid substitutions strongly inhibit binding: 256(S/Y), 257(T/G), 262(N/T), 368(D/R or K), 370(E/R or Q or D), 384(Y/E). Schutten *et al.* [1993] (**antibody binding site definition and exposure**, **subtype comparisons**)

No. 1390
MAb ID GP44
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
Ab Type gp120 CD4BS
References Gorny & Zolla-Pazner 2004; Wisnewski *et al.* 1996; Bagley *et al.* 1994; Schutten *et al.* 1993
Keywords antibody binding site definition and exposure, antibody sequence variable domain, review, variant cross-recognition or cross-neutralization

- GP44: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- GP44: GP44 is V H1 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996] (**antibody sequence variable domain**)
- GP44: Exhibited a more restricted pattern of neutralizing activity than GP13 and GP68 – the following gp120 amino acid substitutions strongly inhibit binding: 256(S/Y), 257(T/G), 262(N/T), 368(D/R or K), 370(E/R or Q or D) Schutten *et al.* [1993] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)

No. 1391
MAb ID GP68
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
Ab Type gp120 CD4BS
References Forsman *et al.* 2008; Holl *et al.* 2006a; Gorny & Zolla-Pazner 2004; Guillon *et al.* 2002b; Wisnewski *et al.* 1996; Schutten *et al.* 1995a; Bagley *et al.* 1994; Klasse *et al.* 1993a; Schutten *et al.* 1993
Keywords antibody binding site definition and exposure, antibody sequence variable domain, binding affinity, dendritic cells, enhancing activity, neutralization, review, variant cross-recognition or cross-neutralization

- GP68: UK Medical Research Council AIDS reagent: ARP3055.
- GP68: Variable domains of three heavy chain Abs, the VHH, were characterized. The Abs were isolated from llamas, who produce immunoglobulins devoid of light chains, immunized with HIV-1 CRF07_BC, to gp120. It was hypothesized that the small size of the VHH, in combination with their protruding CDR3 loops, and their preference for cleft recognition and binding into active sites, may allow for recognition of conserved motifs on gp120 that are occluded from conventional Abs. GP68 was found to compete for binding to recombinant gp120 with the three neutralizing VHH Abs, indicating overlapping epitopes or steric hinderance. Forsman *et al.* [2008] (**binding affinity**)
- GP68: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- GP68: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- GP68: The affect of Ab binding on infectivity was studied by pseudotyping three related envs with different phenotypes – R5 viruses were preferentially enhanced, not X4 – the V3 region was the main determinant of Ab-mediated enhancement and modulation of the interaction between CCR5 and gp120 is critical – tests with MAbs anti-V3 391/95-D and CD4BS-specific GP68 indicate that Ab specificity did not determine whether or not infectivity was enhanced or neutralized, rather the phenotype was determined by Envelope conformation. Guillon *et al.* [2002b] (**enhancing activity**, **variant cross-recognition or cross-neutralization**)
- GP68: GP68 is V H1 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996] (**antibody sequence variable domain**)
- GP68: Neutralizes IIIB – only slight inhibition of SI phenotype, and strong enhancement of NSI phenotype chimeric viruses, that incorporated different envs from the same donor. Schutten *et al.* [1995a] (**variant cross-recognition or cross-neutralization**)
- GP68: The gp41 mutation 582(Ala to Thr) results in conformational changes in gp120 that confer neutralization resistance to a class of conformation sensitive neutralizing MAbs – GP68 required markedly higher concentrations to neutralize the mutant than wild type. Klasse *et al.* [1993a] (**antibody binding site definition and exposure**)
- GP68: Neutralized a broad range of HIV-1 lab strains from phylogenetically different subfamilies – the following gp120 amino acid substitutions strongly inhibit binding: 117(K/W), 256(S/Y), 257(T/G), 262(N/T), 368(D/R or K), 370(E/R or Q), 384(Y/E), 435(Y/H) Schutten *et al.* [1993] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)

No. 1392
MAb ID HF1.7
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen anti-idiotype
Species (Isotype) mouse (IgM)
Ab Type gp120 CD4BS
References Chanh *et al.* 1987

- HF1.7: An anti-Id antibody stimulated by anti-CD4 MAb Leu-3a binds to recombinant gp160, suggesting HF1.7 mimics CD4. Chanh *et al.* [1987]

No. 1393

MAb ID HT5 (205-43-1)
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing L (weak)
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
Research Contact Ciba-Geigy AG (Basel, Switzerland), and Tanox Biosystems, Houston, Texas
References Srivastava *et al.* 2005; Pugach *et al.* 2004; Gorny & Zolla-Pazner 2004; Herrera *et al.* 2003; Grovit-Ferbas *et al.* 2000; Parren *et al.* 1998a; Fouts *et al.* 1998; Fouts *et al.* 1997; Moore *et al.* 1995a; Moore *et al.* 1994b
Keywords antibody binding site definition and exposure, antibody interactions, binding affinity, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization, viral fitness and reversion

- 205-43-1 (204-43-4): This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **antibody interactions**, **review**)
- HT5: Also called 205-43-1. This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- HT5: Called 205-43-1: A primary isolate, CC1/85, was passaged 19 times in PBMC and gradually acquired increased sensitivity to FAb b12 and sCD4 that was attributed to changes in the the V1V2 loop region, in particular the loss of a potential glycosylation site. The affinity for sCD4 was unchanged in the monomer, suggesting that the structural impact of the change was manifested at the level of the trimer. The passaged virus, CCcon19, retained an R5 phenotype and its neutralization susceptibility to other Abs was essentially the same as CC1/85. Three CD4BS MAbs, 205-46-9, 205-42-15, and 205-43-1, did not neutralize either the primary or passaged variant. Pugach *et al.* [2004] (**variant cross-recognition or cross-neutralization**, **viral fitness and reversion**)
- HT5: Called 205-43-1 – CD4BS MAbs b12 (neutralizing) and 205-42-15, 204-43-1, 205-46-9 (nonneutralizing) all cross-competed for binding to monomeric gp120, indicating the topological proximity of their epitopes, however, the nonneutralizing CD4BS MAbs did not interfere with the neutralization activity of MAb b12 – the nonneutralizing MAbs partially competed with b12 for Env binding of the surface of Env-transfected cells – this suggests Env has two categories of binding site for CD4BS MAbs, one recognized by both b12 and nonneutralizing CD4BS MAbs, the other is recognized by only b12 – Ab-gp120 interactions based on the use of monomeric gp120 or Env-transfected cells do not predict the outcome of HIV-1 neutralization assays, and they should be interpreted with caution. Herrera *et al.* [2003] (**antibody binding site definition and exposure**, **antibody interactions**)
- HT5: Called 205-43-1: To determine the antigenicity of virus killed by thermal and chemical inactivation, retention of conformation-dependent neutralization epitopes was examined, and exposure of CD4BS epitopes was found to be enhanced (MAbs IgG1b12, 205-46-9, and 205-43-1) – binding to 2G12 and 447-52D epitopes was essentially unaltered – the 17b CD4i epitope was also exposed. Grovit-Ferbas *et al.* [2000] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- HT5: HT5, HT6, and HT7 are also known as 205-43-1, 205-42-15, and 205-46-9, respectively. Rank order of CD4BS antibodies oligomer binding is IgG1b12 = 2G6 = 205-46-9 > 205-43-1 = 205-42-15 > 15e = 21h = F91, and the only thing notably distinguishing about neutralizing IgG1b12 is that it depends on residues in V2. Fouts *et al.* [1998] (**binding affinity**)
- HT5: HT5 and HT6 bind JRSF oligomer but with low affinity, and are not neutralizing – conclusions of this paper contrast with Parren *et al.* [1998a] Fouts *et al.* [1998]. Fouts *et al.* [1998]; Parren *et al.* [1998a] (**antibody binding site definition and exposure**)
- HT5: MAbs IgG1b12, HT5, HT6, and HT7 cross-compete for binding to monomeric gp120, bind equally well, inhibit gp120-sCD4 interactions, but only IgG1b12 neutralizes JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**, **antibody interactions**)
- HT5: Despite highly cross-reactive binding to many primary and T-cell adapted viral strains, only weakly neutralizes IIIB and MN. Moore *et al.* [1995a] (**variant cross-recognition or cross-neutralization**)
- HT5: 205-46-9 was cross-reactive across clades A-F, 205-43-1 very cross-reactive but not quite as extensive 205-46-9. Moore *et al.* [1994b] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1394
MAb ID HT6 (205-42-15)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L (weak)
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
Research Contact Ciba-Geigy AG Basel, Switzerland, and Tanox Biosystems, Houston, Texas
References Srivastava *et al.* 2005; Pugach *et al.* 2004; Gorny & Zolla-Pazner 2004; Herrera *et al.* 2003; Parren *et al.* 1998a; Fouts *et al.* 1998; Fouts *et al.* 1997; Moore *et al.* 1995a; Moore *et al.* 1994b
Keywords antibody binding site definition and exposure, antibody interactions, review, subtype comparisons, variant cross-recognition or cross-neutralization, viral fitness and reversion

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- 205-42-15: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **antibody interactions**, **review**)
- HT6: Called 205-42-15: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- HT6: Called 205-42-15: A primary isolate, CC1/85, was passaged 19 times in PBMC and gradually acquired increased sensitivity to FAb b12 and sCD4 that was attributed to changes in the the V1V2 loop region, in particular the loss of a potential glycosylation site. The affinity for sCD4 was unchanged in the monomer, suggesting that the structural impact of the change was manifested at the level of the trimer. The passaged virus, CCcon19, retained an R5 phenotype and its neutralization susceptibility to other Abs was essentially the same as CC1/85. Three CD4BS MAbs, 205-46-9, 205-42-15, and 205-43-1, did not neutralize either the primary or passaged variant. Pugach *et al.* [2004] (**variant cross-recognition or cross-neutralization**, **viral fitness and reversion**)
- HT6: Called 205-42-15: CD4BS MAbs b12 (neutralizing) and 205-42-15, 204-43-1, 205-46-9 (nonneutralizing) all cross-competed for binding to monomeric gp120, indicating the topological proximity of their epitopes, however, the nonneutralizing CD4BS MAbs did not interfere with the neutralization activity of MAb b12 – the nonneutralizing MAbs partially competed with b12 for Env binding of the surface of Env-transfected cells – this suggests Env has two categories of binding site for CD4BS MAbs, one recognized by both b12 and nonneutralizing CD4BS MAbs, the other is recognized by only b12 – Ab-gp120 interactions based on the use of monomeric gp120 or Env-transfected cells do not predict the outcome of HIV-1 neutralization assays, and they should be interpreted with caution. Herrera *et al.* [2003] (**antibody binding site definition and exposure**, **antibody interactions**)
- HT6: HT5, HT6, and HT7 are also known as 205-43-1 , 205-42-15, and 205-46-9, respectively. Fouts *et al.* [1998]
- HT6: HT5 and HT6 bind JRSF oligomer but with low affinity, and are not neutralizing – conclusions of this paper contrast with Parren *et al.* [1998a] Fouts *et al.* [1998]. Fouts *et al.* [1998]; Parren *et al.* [1998a] (**antibody binding site definition and exposure**)
- HT6: MAbs IgG1b12, HT5, HT6, and HT7 cross-compete for binding to monomeric gp120, bind equally well, inhibit gp120-sCD4 interactions, but only IgG1b12 neutralizes JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**, **antibody interactions**)
- HT6: Despite highly cross-reactive binding to many primary and T-cell adapted viral strains, only weakly neutralizes IIIB and MN. Moore *et al.* [1995a] (**variant cross-recognition or cross-neutralization**)
- HT6: 205-46-9 was cross-reactive across clades A-F, 205-43-1 was not quite as extensively cross-reactive. Moore *et al.* [1994b] (**subtype comparisons**)

No.	1395
MAb ID	HT7 (205-46-9)
HXB2 Location	Env
Author Location	gp120
Epitope	
Neutralizing	L (IIIB)
Immunogen	HIV-1 infection
Species (Isotype)	human
Ab Type	gp120 CD4BS
Research Contact	Ciba-Geigy AG (Basel, Switzerland), and Tanox Biosystems, Houston, Texas
References	Srivastava *et al.* 2005; Herrera *et al.* 2005; Beddows *et al.* 2005b; Pugach *et al.* 2004; Gorny & Zolla-Pazner 2004; Herrera *et al.* 2003; Grovit-Ferbas *et al.* 2000; Parren *et al.* 1998a; Fouts *et al.* 1998; Fouts *et al.* 1997; Moore *et al.* 1995a; Moore *et al.* 1994b
Keywords	antibody binding site definition and exposure, antibody interactions, assay standardization/improvement, binding affinity, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization, viral fitness and reversion

- 205-46-9: The major infectivity and neutralization differences between a PBMC-derived HIV-1 W61D strain and its T-cell line adapted counterpart were conferred by the interactions of three Env amino acid substitutions, E440G, D457G and H564N. Chimeric Env-pseudotyped virus Ch5, containing all three of the mutations, was more neutralization sensitive to 205-46-9 than Ch2, which did not contain any of these mutations. Neutralization sensitivity to 205-46-9 was somewhat increased in Env-pseudotyped viruses containing individual D457G, E440G, and H564N, or in combinations, compared to viruses lacking these mutations. Binding of 205-46-9 to gp120 derived from Env-pseudotyped viruses was, however, unaffected by any of these mutations. Beddows *et al.* [2005b] (**neutralization**, **binding affinity**)
- 205-46-9: 205-46-9 bound with a similar maximal mean fluorescence intensity (MFI) to Env protein on the surface of cells producing gp140Δct-pseudotyped neutralization sensitive HXBc2 or neutralization resistant 3.2P viruses. Neutralization assays with the pseudotyped viruses showed that HXBc2 was more sensitive to neutralization by 205-46-9 than 3.2P. Furin co-transfection did not have an effect on the reactivity of pseudoviruses with 205-46-9 or on their neutralization sensitivity. Presence or absence of sialic acid residues did not affect Env reactivity with 205-46-9. A cleavage-competent form of 3.2P reacted poorly with 205-46-9, while its cleavage-defective counterpart showed higher level of MAb reactivity. Both cleavage-competent and cleavage-defective HXBc2 showed higher levels of reactivity to 205-46-9. Herrera *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- 205-46-9: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and

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importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **antibody interactions**, **review**)

- HT7: Also called 205-46-9. This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- HT7: Called 205-46-9: A primary isolate, CC1/85, was passaged 19 times in PBMC and gradually acquired increased sensitivity to FAb b12 and sCD4 that was attributed to changes in the V1V2 loop region, in particular the loss of a potential glycosylation site. The affinity for sCD4 was unchanged in the monomer, suggesting that the structural impact of the change was manifested at the level of the trimer. The passaged virus, CCcon19, retained an R5 phenotype and its neutralization susceptibility to other Abs was essentially the same as CC1/85. Three CD4BS MAbs, 205-46-9, 205-42-15, and 205-43-1, did not neutralize either the primary or passaged variant. Pugach *et al.* [2004] (**variant cross-recognition or cross-neutralization**, **viral fitness and reversion**)
- HT7: Called 205-46-9 – CD4BS MAbs b12 (neutralizing) and 205-42-15, 204-43-1, 205-46-9 (nonneutralizing) all cross-competed for binding to monomeric gp120, indicating the topological proximity of their epitopes, however, the nonneutralizing CD4BS MAbs did not interfere with the neutralization activity of MAb b12 – the nonneutralizing MAbs partially competed with b12 for Env binding of the surface of Env-transfected cells – this suggests Env has two categories of binding site for CD4BS MAbs, one recognized by both b12 and nonneutralizing CD4BS MAbs, the other is recognized by only b12 – Ab-gp120 interactions based on the use of monomeric gp120 or Env-transfected cells do not predict the outcome of HIV-1 neutralization assays, and they should be interpreted with caution. Herrera *et al.* [2003] (**antibody binding site definition and exposure**)
- HT7: Called 205-46-9. To determine the antigenicity of virus killed by thermal and chemical inactivation, retention of conformation-dependent neutralization epitopes was examined, and exposure of CD4BS epitopes was found to be enhanced (MAbs IgG1b12, 205-46-9, and 205-43-1) – binding to 2G12 and 447-52D epitopes was essentially unaltered – the 17b CD4i epitope was also exposed. Grovit-Ferbas *et al.* [2000] (**antibody binding site definition and exposure**)
- HT7: Called 205-46-9. HT5, HT6, and HT7 are also known as 205-43-1 , 205-42-15, and 205-46-9, respectively. Binds JRSF oligomer with high affinity as does IgG1b12, but IgG1b12 is neutralizing, 205-46-9 is not – conclusions of this paper contrast with Parren98 – authors propose a model where 205-46-9 and 2G6 may inhibit CD4 binding, but cause a conformational shift which enhances CCR5 binding and thus counteracts the neutralizing effect – rank order of CD4BS antibodies oligomer binding is IgG1b12 = 2G6 = 205-46-9 > 205-43-1 = 205-42-15 > 15e = 21h = F91, and the only thing notably distinguishing about neutralizing IgG1b12 is that it depends on residues in V2. Fouts *et al.* [1998] (**assay standardization/improvement**)
- HT7: Binds JRSF oligomer with high affinity, at least as high as IgG1b12, but IgG1b12 is neutralizing, H7 is not – conclusions of this paper contrast with Parren *et al.* [1998a] – authors propose a model where H7 may inhibit CD4 binding, but cause a conformational shift which enhances CCR5 binding and thus counteracts the neutralizing effect Fouts *et al.* [1998]. Fouts *et al.* [1998]; Parren *et al.* [1998a] (**antibody binding site definition and exposure**)
- HT7: MAbs IgG1b12, HT5, HT6, and HT7 cross-compete for binding to monomeric gp120, bind equally well, inhibit gp120-sCD4 interactions, but only IgG1b12 neutralizes JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
- HT7: Despite highly cross-reactive binding to many primary and T-cell adapted viral strains, only neutralizes IIIB well, with sporadic weak neutralization of other isolates. Moore *et al.* [1995a] (**variant cross-recognition or cross-neutralization**)
- HT7: 205-46-9 was cross-reactive across clades A-F, 205-43-1 was cross-reactive, but not quite as extensive. Moore *et al.* [1994b] (**subtype comparisons**)

No. 1396
MAb ID ICR 39.13g (ICR39.13g, 39.13g, ICR39.13)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10
HIV component: gp120
Species (Isotype) rat (IgG2b)
Ab Type gp120 CD4BS
Research Contact Jackie Cordell and C. Dean
References Holl *et al.* 2006a; Vella *et al.* 2002; Peet *et al.* 1998; Klasse & Sattentau 1996; Armstrong & Dimmock 1996; McKeating *et al.* 1996; Beretta & Dalgleish 1994; McLain & Dimmock 1994; Klasse *et al.* 1993a; Thali *et al.* 1993; Moore & Ho 1993; McKeating *et al.* 1993b; McKeating *et al.* 1992c; McKeating *et al.* 1992a; Cordell *et al.* 1991
Keywords dendritic cells, neutralization

- ICR 39.13g: UK Medical Research Council AIDS reagent: ARP390.
- ICR39.13: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- ICR 39.13g: Called ARP390/391, but no such entry was found at the UK Medical Research Council AIDS reagent web site: Herpesvirus saimiri-immortalized CD4+ T lymphocytes (HVS T cells) were used to isolate virus and perform HIV-1 neutralization assays, and compared with a standard PBMC protocol – neutralization sensitivities to a panel of MAbs and to homologous or heterologous plasma/sera were similar for HVS T cells (CN-2 cells) and PBMCs. Vella *et al.* [2002]
- ICR 39.13g: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind – ICR

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39.13g was not affected by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]

- ICR 39.13g: Post-attachment neutralization mechanism, in contrast to MAb 39.3b. Armstrong & Dimmock [1996]
- ICR 39.13g: Variants of LAI have differing neutralization susceptibility to 39.13g. Klasse & Sattentau [1996]
- ICR 39.13g: Called 39.13g Neutralizes HXB2, but fails to neutralize chimeric virus with gp120 from primary isolates in an HXB2 background. McKeating *et al.* [1996]
- ICR 39.13g: Kinetics of neutralization studied – no lag for 39.3b, while ICR 39.13g and ICR 41.1i have lags of 5 and 15 min respectively – mediates neutralization with 2.3 molecules of IgG. McLain & Dimmock [1994]
- ICR 39.13g: The gp41 mutation 582(Ala to Thr) results in conformational changes in gp120 that confer neutralization resistance to a class of conformation sensitive neutralizing MAbs – ICR 39.13g required moderately higher concentrations to neutralize the mutant than wild type. Klasse *et al.* [1993a]
- ICR 39.13g: Neutralization activity against HXB10, RF, SF-2 and MN strains of HIV-1. McKeating *et al.* [1993b]
- ICR 39.13g: Conformational, does not bind denatured gp120 – weak neutralization of IIIB – strong inhibition of HIV+ human sera binding to IIIB gp120. Moore & Ho [1993]
- ICR 39.13g: Strongly inhibits CD4 inducible MAb 48d. Thali *et al.* [1993]
- ICR 39.13g: Binds to a conformational epitope involved in CD4 binding – exerts a synergistic effect in combination with V3 directed MAbs. McKeating *et al.* [1992a]
- ICR 39.13g: Cross-competes with MAbs ICR 39.3b and 15e. Cordell *et al.* [1991]

No. 1397
MAb ID ICR 39.3b (39.3, 39.3b, ICR39.3b)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10
HIV component: gp120
Species (Isotype) rat (IgG2b)
Ab Type gp120 CD4BS
Research Contact J. Cordell and C. Dean
References Srivastava *et al.* 2005; Wyatt *et al.* 1998; Jeffs *et al.* 1996; Armstrong & Dimmock 1996; McLain & Dimmock 1994; Moore *et al.* 1993b; Moore & Ho 1993; McKeating *et al.* 1992c; Cordell *et al.* 1991
Keywords review, vaccine antigen design

- ICR 39.3b: UK Medical Research Council AIDS reagent: ARP391.
- 39.3: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**vaccine antigen design**, **review**)
- ICR 39.3b: Called 39.3 – summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAb binding – probable mechanism of neutralization by CD4BS Ab is direct interference with CD4 binding. Wyatt *et al.* [1998]
- ICR 39.3b: Neutralizes only if the antibody is added prior to the attachment of the virus to the cell, in contrast to 39.13g. Armstrong & Dimmock [1996]
- ICR 39.3b: Called 39.3b – increased binding when V1/V2 or V1/V2 and V3 were deleted from gp120. Jeffs *et al.* [1996]
- ICR 39.3b: Kinetics of neutralization studied – no lag for 39.3b, while ICR 39.13g and ICR 41.1i have lags of 5 and 15 min respectively. McLain & Dimmock [1994]
- ICR 39.3b: Conformational, does not bind to denatured IIIB. Moore & Ho [1993]
- ICR 39.3b: Cross-competes with MAbs ICR 39.13g and 15e. Cordell *et al.* [1991]

No. 1398
MAb ID Ia3
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
References Zwick *et al.* 2003
Keywords antibody interactions

- Ia3: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This is a novel CD4BS Fab first used in this study. Zwick *et al.* [2003] (**antibody interactions**)

No. 1399
MAb ID Ia7
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
References Zwick *et al.* 2003
Keywords antibody interactions

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- Ia7: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This is a novel CD4BS Fab first used in this study. Zwick *et al.* [2003] (**antibody interactions**)

No. 1400
MAb ID IgG1b12 (Fab b12, Fab 3B3, MAb IgG1b12, IgG1-b12, IgG1 b12, IgGB12, b4/12, Ib12)
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing L P
Immunogen HIV-1 infection
Species (Isotype) goat (IgG1κ)
Ab Type gp120 CD4BS
Research Contact D. Burton, Scripps Research Institute, La Jolla, CA, also J. Geltowsky and J. Pyati, R. W. Johnson Pharmaceutical Resear
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Keywords acute/early infection, antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, assay development, assay standardization/improvement, autologous responses, binding affinity, brain/CSF, co-receptor, complement, dendritic cells, drug resistance, enhancing activity, escape, genital and mucosal immunity, HAART, ART, immunoprophylaxis, immunotherapy, isotype switch, kinetics, mimics, mimotopes, mother-to-infant transmission, mucosal immunity, neutralization, responses in children, review, structure, subtype comparisons, supervised treatment interruptions (STI), therapeutic vaccine, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- IgG1b12 database comment: Fab b12 was derived from IgG1b12, Fab 3B3 was derived from Fab b12 by random mutagenesis and selected for increased affinity to sgp120. (**antibody generation**)
- IgG1b12: UK Medical Research Council AIDS reagent: ARP3065.
- IgG1b12: NIH AIDS Research and Reference Reagent Program: 2640.
- b12: Neutralization sensitivity of maternal and infant viruses to b12 close to transmission timepoint was shown to be somewhat better than for 2G12 Ab. The range of sensitivity of maternal viruses to b12 was greater than that of infant viruses. (**neutralization**, **mother-to-infant transmission**)
- IgG1b12: The neutralization activity of this Ab was tested for HIV-1 isolates 92HT593B and NLHX-ADA and compared to the neutralization activity of anti-IgG collected from sera of healthy HIV-uninfected individuals, based on their reactivity with human IgG. For 92HT593B, the neutralization efficacy of IgG1b12 was comparable to that of anti-IgG. (**neutralization**)
- b12: Neutralization susceptibility of CRF01_AE Env-recombinant viruses, derived from blood samples of Thai HIV-1 infected patients in 2006, was tested to b12. Most of the 35 viruses tested replicated efficiently in the presence of b12, indicating that CRF01_AE is not susceptible to neutralization by b12. One of the viruses was highly susceptible to neutralization by b12, and it was shown that the N-terminal regions of gp120, including C1, V1, V2, C2, V3 and most of C3 regions, were responsible for the high susceptibility of this virus to b12. Utachee *et al.* [2009] (**neutralization**, **subtype comparisons**)
- b12: Dose dependent inhibition studies of HIV-1 subtypes A, B, C and D with polyclonal human sera with Abs to gp120, HLA class I or II, and 70kDa heat shock protein (HSP70) showed that combination of three antisera resulted in highest maximum inhibition. The triple Ab HLA-II+HIVgp120+HSP70 combination yielded highest maximum inhibition of subtype B HIV-1 replication of 96.7%, followed by triple HLA-I+gp120+HSP70 combination (92.8% inhibition). Inhibition with mAb b12 was slightly more effective than the inhibition with the polyclonal serum Abs. Babaahmady *et al.* [2008] (**neutralization**)
- b12: 24 broadly neutralizing plasmas from HIV-1 subtype B an C infected individuals were investigated using a series of mapping methods to identify viral epitopes targeted by NAbs. Mutant versions of JR-FL trimers were designed to selectively eliminate neutralization epitopes. Many subtype B plasmas, and few subtype C plasmas, bound more efficiently to the wildtype than to the b12-eliminated mutant, indicating presence of CD4bs NAbs in the plasmas. Binley *et al.* [2008] (**binding affinity**)
- IgG1b12: This study explored features of Env that would enhance exposure of conserved HIV-1 epitopes. The changes in neutralization susceptibility, mediated by two mutations, T569A (in the HR1) and I675V (in the MPER), were unparal-

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leled in their magnitude and breadth on diverse HIV-1 Env proteins. The variant with both TA and IV mutations was >360-fold more susceptible to 2F5, >180-fold more susceptible to 4E10, 780-fold more susceptible to sCD4 and resulted in 18-fold enhanced susceptibility to autologous plasma and >35-fold enhanced susceptibility to the plasma pool. It was also 2.8-fold more susceptible to b12 but mutants with only one mutations were not neutralized by b12. Blish *et al.* [2008] (**antibody binding site definition and exposure**)

- b12: Three constructs of the outer domain (OD) of gp120 of subtype C, fused with Fc, were generated for immunization of mice: OD(DL3)-Fc (has 29 residues from the centre of the V3 loop removed), OD(2F5)-Fc (has the same deletion reconstructed to contain the sequence of 2F5 epitope), and the parental OD-Fc molecule. Binding of b12 to each of the constructs was found to be negligible. b12 failed to neutralize subtype C CN54 isolate, and was less effective at neutralization of 93MW965.26 isolate than the newly identified OD-specific MAb 2B7, derived by screening of the immunized mice sera. Chen *et al.* [2008a] (**neutralization**, **binding affinity**)
- IgG1b12: The study explores how the V1 loop of Env influences the neutralization susceptibilities of heterologous viruses to antibodies elicited by the SF162gp140 immunogen. All viruses expressing the WT Envs were susceptible to neutralization by IgG1b12. Replacement of the V1 loops by that of SF162 did not alter the neutralization susceptibilities of the viruses, with the exception of one virus, which became more susceptible. Ching *et al.* [2008] (**neutralization**)
- IgG1b12: The goal of the study was to measure NAb responses in patients infected with HIV-1 prevalent subtypes in China. gp160 genes from plasma samples were used to establish a pseudovirus-based neutralization assay. IgG1b12 neutralized 12 of 27 Env-pseudotyped viruses. Chong *et al.* [2008] (**neutralization**, **subtype comparisons**)
- b12: The study compared Ab neutralization against the JR-FL primary isolate and trimer binding affinities judged by native PAGE. There was direct quantitative relationship between monovalent Fab-trimer binding and neutralization, implying that neutralization begins as each trimer is occupied by one Ab. In BN-PAGE, neutralizing Fabs, b12 in particular, and sCD4 were able to shift JR-FL trimers, In contrast, most non-neutralizing Fabs bound to monomer, but their epitopes were conformationally occluded on trimers, confirming the exclusive relationship of trimer binding and neutralization. Crooks *et al.* [2008] (**neutralization**, **binding affinity**)
- b12: Five amino acids in the gp41 N-terminal region that promote gp140 trimerization (I535, Q543, S553, K567 and R588) were considered. Their influence on the function and antigenic properties of JR-FL Env expressed on the surfaces of pseudoviruses and Env-transfected cells was studied. Various non-neutralizing antibodies bind less strongly to the Env mutant, but neutralizing antibody binding is unaffected. There was no difference in b12 binding to wild type and mutant JR-FL, and b12 inhibited infection of the two pseudoviruses with comparable potencies. Dey *et al.* [2008] (**binding affinity**)
- IgG1b12: Envelope determinants that confer natural resistance to b12 were studied. Envelopes from brain tissue (sensitive to b12) and lymph node tissue (resistant to b12) of the same patient were studied. Sensitivity to b12 can be completely modulated by the presence of a glycan at residue 386, although resistance required the presence of an arginine at residue 373. Together, R373 and the N386 glycan may sterically prevent the benzene ring of b12 W100 from penetrating a pocket proximal to these two residues. Nevertheless, b12 bound to monomeric, detergent-solubilized gp120 that carried R373/N386, indicating that the envelope trimer may also play a role in the protection of this epitope. The introduction of R373 into b12-sensitive envelopes rendered both resistant to b12, confirming that this mechanism of b12 resistance transfers to unrelated envelopes. Duenas-Decamp *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **escape**, **structure**)
- b12: Variable domains of three heavy chain Abs, the VHH, were characterized. The Abs were isolated from llamas, who produce immunoglobulins devoid of light chains, immunized with HIV-1 CRF07_BC, to gp120. It was hypothesized that the small size of the VHH, in combination with their protruding CDR3 loops, and their preference for cleft recognition and binding into active sites, may allow for recognition of conserved motifs on gp120 that are occluded from conventional Abs. b12 neutralization and binding activities were compared to the three neutralizing VHH Abs. b12 neutralized 54% of viruses tested, including subtypes B, C, and CRF07_BC, but did not neutralize subtype A, A/G, or D viruses. b12 competed for binding to recombinant gp120 with the three VHH Abs, and inhibited VHH Ab binding to IIIB gp120. Forsman *et al.* [2008] (**neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)
- IgG1b12: Molecular mechanism of neutralization by MPER antibodies, 2F5 and 4E10, was studied using preparations of trimeric HIV-1 Env protein in the prefusion, the prehairpin intermediate and postfusion conformations. MAb IgG1b12 was used to analyze antigenic properties of construct 92UG-gp140-Fd, derived from isolate 92UG037.8 and stabilized by a C-terminal foldon tag. 92UG-gp140-Fd failed to bind IgG1b12 consistent with the resistance of the isolate to neutralization by that MAb, but monomeric gp120 derived from 92UG037 did bind IgG1b12. Frey *et al.* [2008] (**variant cross-recognition or cross-neutralization**, **binding affinity**)
- b12: A series of peptide conjugates were constructed via click reaction of both aryl and alkyl acetylenes with an internally incorporated azidoproline 6 derived from parent peptide RIN-NIPWSEAMM. Many of these conjugates exhibited increase in both affinity for gp120 and inhibition potencies at both the CD4 and coreceptor binding sites. All high affinity peptides inhibited the interactions of YU2 gp120 with b12 Ab. The aromatic, hydrophobic, and steric features in the residue 6 side-chain were found important for the increased affinity and inhibition of the high-affinity peptides. Gopi *et al.* [2008]
- 1b12: This review summarizes the obstacles that stand in the way of making a successful preventive HIV-1 vaccine, such as masked or transiently expressed Ab epitopes, polyclonal B-cell class switching, and inefficient, late, and not sufficiently robust mucosal IgA and IgG responses. Possible reasons why HIV-1 envelope constructs expressing b12 epitope fail to induce broadly neutralizing Abs are discussed. Haynes & Shattock [2008] (**vaccine antigen design**, **review**)
- b12: A mathematical model was developed and used to derive

transmitted or founder Env sequences from individuals with acute HIV-1 subtype B infection. All of the transmitted or early founder Envs were sensitive to neutralization by b12. Keele *et al.* [2008] (**neutralization**, **acute/early infection**)

- b12: Three-dimensional structures of trimeric Env displayed on native HIV-1 in the unligated state and in complex with b12 were compared, using cryo-electron tomography combined with three-dimensional image classification and averaging. Binding of b12 resulted in opening of the trimeric spike, with rotation of each monomer by 20-25 degrees around an axis perpendicular to the viral membrane. Binding of b12 appeared to lock gp120 and trimeric Env in a state that prevents further conformational changes, such as exposure of V3, or rearrangement of gp41. Liu *et al.* [2008] (**antibody binding site definition and exposure**, **structure**)
- b12: A new purification method was developed using a high affinity peptide mimicking CD4 as a ligand in affinity chromatography. This allowed the separation in one step of HIV envelope monomer from cell supernatant and capture of pre-purified trimer. Binding of b12 to gp120SF162 purified by the miniCD4 affinity chromatography and a multistep method was comparable, suggesting that the miniCD4 allows the separation of HIV-1 envelope with intact b12 epitope. gp140DF162ΔV2 was purified by the miniCD4 method to asses its ability to capture gp140 trimers. Purified gp140DF162ΔV2 was recognized by b12, and the k-off value for b12 was reduced compared to gp120SF162 monomer, consistent with the gp140DF162ΔV2 trimeric conformation. Binding of b12 to gp140DF162ΔV2 purified by the miniCD4 affinity chromatography and a multi-step method was comparable, suggesting that the SF162 trimer antigenicity was preserved. Martin *et al.* [2008] (**assay development**, **kinetics**, **binding affinity**)
- b12: Transmission of HIV-1 by immature and mature DCs to CD4+ T lymphocytes was significantly higher for CXCR4- than for CCR5-tropic strains. In contrast to other Abs tested, which lost the capacity to neutralize HIV-1 during capture and transmission by DC-SIGN to T lymphocytes, and which helped in a more efficient transmission of X4 HIV-1 than R5 HIV-1, only b12 efficiently blocked transmission of both virus strains. This indicates that b12, unlike other Abs, cannot be dissociated from HIV-1 following the interaction with DCs. van Montfort *et al.* [2008] (**co-receptor**, **neutralization**, **dendritic cells**)
- IgG b12: Immobilized b12 was able to capture infectious HIV-1 whole virions in a standard virus capture assay, unlike mAbs 8K8 and D5. Addition of soluble CD4 diminished virion capture by b12. Nelson *et al.* [2008]
- IgG1b12: Two HIV-1 isolates, NL4-3 and KB9, were adapted to replicate in cells using the common marmoset receptors CD4 and CXCR4. The adaptation resulted in a small number of changes of env sequences in both isolates. The adapted NL4-3 variants were generally more sensitive to neutralization by b12 than the adapted KB9 variants. All of the NL4-3 exhibited similar sensitivity to neutralization by b12. Wildtype KB9 is resistant to neutralization by b12 but the changes associated with adaptation to marmoset receptors resulted in variants with increased sensitivity to neutralization by b12. Thus, adaptation to marmoset receptors resulted in an increase in sensitivity to neutralization by b12 for KB9 but not for NL4-3. Pacheco *et al.* [2008] (**neutralization**)
- G1b12: Neutralization of HIV-1 IIIB LAV isolate by b12 was within the same range as the neutralization of the virus by natural antibodies from human sera against the gal(α1,3)gal disaccaride linked to CD4 gp120-binding peptides, indicating that the activity of natural antibodies can be re-directed to neutralize HIV-1. Perdomo *et al.* [2008] (**neutralization**)
- b12: The sensitivity of R5 envelopes derived from several patients and sevaral tissue sites, including brain tissue, lymph nodes, blood, and semen, was tested to a range of inhibitors and Abs targeting CD4, CCR5, and various sites on the HIV envelope. All but one envelopes from brain tissue were macrophage-tropic while none of the envelopes from the lymph nodes were macrophage-tropic. Macrophage-tropic envelopes were also less frequent in blood and semen. All but one macrophage-tropic envelopes were sensitive to b12 neutralization, and there was a relationship between increasing macrophage-tropism and increased sensitivity to b12. Peters *et al.* [2008b] (**neutralization**)
- b12: This minireview summarizes data on differences in neutralizing activities of MAbs and pooled human sera using a traditional primary cell neutralization assay and the more standardized TZM-bl reporter cell line assay. Also, suggestions are made on how to improve and standardize neutralization assays for comparable use in different laboratories. b12 neutralization has been shown to correlate well in the two assays (84%), supporting the notion of b12 inhibition of early viral entry steps. In total, however, the assay discordances were shown to be bi-directional and not attributable to assay sensitivity. Polonis *et al.* [2008] (**neutralization**, **review**, **assay standardization/improvement**)
- b12: In order to assess whether small molecule CCR5 inhibitor resistant viruses were more sensitive to neutralization by NAbs, two escape mutant viruses, CC101.19 and D1/85.16, were tested for their sensitivity to neutralization by b12, compared to the sensitivity of CC1/85 parental isolate and the CCcon.19 control isolate. The CC101.19 escape mutant has 4 sequence changes in V3 while the D1/85.16 has no sequence changes in V3 and relies on other sequence changes for its resistance. The two escape mutant viruses were moderately more sensitive to the b12 neutralization than the parental isolate, but not compared to the CCcon.19. Binding of b12 to each of the gp120 proteins was comparable, thus the neutralization sensitivity of the escape mutants may be because alternations in the exposure of the CD4bs on the Env trimer. Overall, the study suggests that CCR5 inhibitor-resistant viruses are likely to be somewhat more sensitive to neutralization than their parental viruses. Pugach *et al.* [2008] (**co-receptor**, **neutralization**, **escape**, **binding affinity**)
- b12: Trimeric envelope glycoproteins with a partial deletion of the V2 loop derived from subtype B SF162 and subtype C TV1 were compared. b12 efficiently recognized subtype B trimers but had negligible reactivity for subtype C trimers. 5 out of 15 amino acid residues involved in b12 binding were shown to differ between the two subtypes. Subtype C trimer had many biophysical, biochemical, and immunological characteristics similar to subtype B trimer, except for a difference in the three binding sites for CD4, which showed cooperativity of CD4

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binding in subtype C but not in subtype B. Srivastava *et al.* [2008] (**binding affinity**, **subtype comparisons**)

- IgG1b12: The neutralization profile of early R5, intermediate R5X4, and late X4 viruses from a rhesus macaque infected with SHIV-SF162P3N was assessed. The parental R5 virus was resistant to neutralization by IgG1b12, while the R5X4 was neutralization sensitive, and the late X4 virus was the most sensitive to neutralization by IgG1b12 of all. The enhanced neutralization susceptibility of the dual-tropic and the X4 viruses to IgG1b12 suggests adoption of an increasingly open conformation of the Env gp120 over time, with exposure of both the CD4 and co-receptor binding sites. Tasca *et al.* [2008] (**antibody binding site definition and exposure**, **co-receptor**, **neutralization**)
- Ib12: To investigate B-cell responses immediately following HIV-1 transmission, env-specific Ab responses to autologous and consensus Envs in plasma donors were determined. Broadly neutralizing Abs with specificity similar to Ib12 did not appear during the first 40 days after plasma virus detection. Tomaras *et al.* [2008] (**antibody generation**, **acute/early infection**)
- b12: Sera from gp120 DNA prime-protein boost immunized rabbits competed for binding to b12 while sera from rabbits immunized with protein-only regimen did not, indicating elicitation of b12-like Abs in animals immunized with DNA prime-protein boost regimen. Competitive virus capture assay also revealed higher titers of b12 Abs in animals immunized with DNA prime-protein boost than in protein-only immunized animals. Vaine *et al.* [2008] (**vaccine antigen design**)
- b12: A significantly higher level of anti-V3 Ab (694/98D) and anti-C1 mAb (EH21) bound to gp120 complexed with b12 mAb than to gp120 alone or in complex with other non-CD4bs Abs, indicating that binding of b12 to gp120 increases exposure of specific V3 and C1 mAb epitopes. Visciano *et al.* [2008b]
- b12: The membrane-disruptive requirements of the MPER region were investigated using a panel of tryptophan-rich, membrane-disrupting mutants that replace most of the MPER region. The mutants were processed, transported, and expressed on the cell surface, the expression measured by staining of the transfected cells with b12, and being at the levels similar to wildtype, except for the mutants which had truncated cytoplasmic tail and showed elevated levels of staining (>350% of wildtype). Study findings show that the MPER region can accommodate large substitutions and retain fusion activity, and that the MPER conformation is more complex and flexible than simply a stable α-helix, which is important for its insertion into the cell membrane and affects the potency of neutralizing Abs that target this region. However, the sequence modifications in the MPER region resulted in reduced incorporation of Envs into virions, and reduced Env stability. Vishwanathan & Hunter [2008]
- b12: The various effects that neutralizing and non-neutralizing anti-envelope Abs have on HIV infection are reviewed, such as Ab-mediated complement activation and Fc-receptor mediated activities, that both can, through various mechanisms, increase and decrease the infectivity of the virus. The importance of these mechanisms in vaccine design is discussed. The unusual features of the b12 MAb are described, including the importance of its FcR-binding site in protective activity. Willey & Aasa-Chapman [2008] (**review**)
- b12: b12 was tested for its ability to induce conformational changes similar to those induced by CD4. Although presence of sCD4 increased neutralization of JRFL by 447-52D and by immune sera rich in V3-Abs from guinea pigs, the presence of b12 did not, indicating that b12 does not induce a conformation alternation in Env that exposes the V3 loop to neutralizing Abs. Wu *et al.* [2008]
- b12: Current insights into CTLs and NAbs, and their possible protective mechanisms against establishment of persistent HIV/SIV infection are discussed. Pre- and post-infection sterile and non-sterile protection of NAbs against viral challenge, and potential role of NAbs in antibody-mediated antigen presentation in modification of cellular immunity, are reviewed. Use of b12 in immunization experiments and its in vivo antiviral activity in suppression of viral rebound in HIV-1 infected humans undergoing structured treatment interruptions are described. Yamamoto & Matano [2008] (**immunotherapy**, **supervised treatment interruptions (STI)**, **review**)
- b12: The newly detected mAb m44 was shown to neutralize a subtype C SHIV strain more potently than b12. In binding assays, b12 bound to Env at the same levels as m44 but it did not compete with m44 for binding. Zhang *et al.* [2008] (**neutralization**, **binding affinity**)
- b12: HIV-1 neutralization by b12 is briefly reviewed. Albert *et al.* [2007] (**neutralization**)
- b12: Sera from rabbits immunized with either monomeric gp120, trimeric cleavage-defective gp140 or disulfide-stabilized soluble trimeric gp140 were incubated with bead-immobilized gp120 and cyclic V3 where gp120 peptide-beads were previously shown to be able to deplete this Ab from test serum. The HIV-1 JR-FL neutralizing activity of sera from rabbits immunized with the disulfide-stabilized protein was substantially but incompletely reduced, showing that most of the Abs were directed to gp120. Beddows *et al.* [2007] (**neutralization**, **vaccine antigen design**)
- IgG1b12: This Ab was found to be able to bind to a highly stable trimeric rgp140 derived from a HIV-1 subtype D isolate containing intermonomer V3-derived disulfide bonds and lacking gp120/gp41 cleavage. Billington *et al.* [2007]
- b12: Pseudoviruses derived from gp120 env variants that evolved in multiple macaques infected with SHIV 89.6P displayed a range of degrees of virion-associated Env cleavage. Pseudoviruses with higher amount of cleaved Env were more resistant to neutralization by b12. Blay *et al.* [2007] (**neutralization**)
- IgG1b12: Only 1/15 subtype A HIV-1 envelopes from samples taken early in infection was neutralized by b12; the SF162 Env control was neutralized as expected. Blish *et al.* [2007] (**neutralization**, **acute/early infection**, **subtype comparisons**)
- IgG1b12: Yeast display was compared to phage display and shown to select all the scFv identified by phage display and additional novel antibodies. This MAb was used in a competition assays to determine the binding region of the MAbs selected from the yeast displayed antibody library. Bowley *et al.* [2007]

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- IgG1b12: (R5)X4 viruses obtained early after X4 emergence showed an increased sensitivity to IgG1b12 compared to their coexisting R5 variants. For 3 patients, (R5)X4 viruses obtained late after X4 emergence also showed significantly higher sensitivities to neutralization by IgG1b12 than their co-existing R5 variants. For 2 patients, the differential sensitivity among late viruses was lost due to increased susceptibility of the R5 viruses to IgG1b12. Bunnik *et al.* [2007] (**co-receptor**, **neutralization**)
- IgG1b12: Spread of HIV-1 through formation of virological synapses (VS) between infected and uninfected T-cells was shown to require Env-CD4 receptor interactions. Treatment of the cells with IgG1b12 inhibited 50% of VS-mediated transfer. Chen *et al.* [2007b] (**neutralization**)
- b12: 2 glycosylation site additions to the clade C gp120 backbone (gp120CN54+) were used to reconstruct the 2G12 epitope. Both gp120CN54+ and an Fc tagged gp120CN54 bound to b12 with equal efficiency, suggesting that the Fc tag had no effect on the primary receptor binding conformation. Fc tagged outer domain of gp120CN54+ (ODCN54+-Fc) bound to b12 poorly in spite of the fact that the b12 epitope was shown to lie within the B clade OD. Chen *et al.* [2007a] (**antibody binding site definition and exposure**, **binding affinity**)
- IgG1b12: This MAb was used in a binding competitive assay to approximately localize epitopes for neutralizing MAbs m22, m24 and m46. It competed against m22 and m24 but not m46. Choudhry *et al.* [2007] (**antibody interactions**)
- b12: Most of the sera from guinea pigs immunized with gp120 protein or with three types of VLPs containing disulfide-shackled functional trimers (SOS-VLP), uncleaved nonfunctional Env (UNC-VLP), naked VLP bearing no Env, weakly or ineffectively inhibited virus capture compared to b12 Ab. Sera that contained Abs that enhanced infection, or that were responsible for nonspecific neutralization, did not reverse neutralization by b12. Crooks *et al.* [2007] (**neutralization**)
- b12: b12 had higher affinities for SF162gp140 and ΔV2gp140 than any of the anti-gp41 MAbs detected in this study. Also, b12 bound with faster on-rates, and slower off-rates than the anti-gp41MAbs to these proteins. Differences in neutralization potency could not, however, be explained by the differing kinetics. Derby *et al.* [2007] (**kinetics**, **binding affinity**)
- b12: gp120 proteins with double mutation T257S+S375W, which alters the cavity at the epicenter of the CD4 binding region, bound to b12 slightly less efficiently than wildtype gp120, while the S375W single mutation adversely affected b12 recognition. Viruses harboring the S375W single mutation were threefold less sensitive to neutralization by b12 than viruses with the double mutation T257S+S375W. The ability of rabbit sera to affect binding of CD4 to unmodified gp120 proteins was tested. CD4 binding to gp120 was efficiently blocked by b12. Dey *et al.* [2007b] (**neutralization**, **binding affinity**)
- IgG1b12: SOSIP Env proteins are modified by the introduction of a disulfide bond between gp120 and gp41 (SOS), and an I559P (IP) substitution in gp41, and form trimers. The KNH1144 subtype A virus formed more stable trimers than did the prototype subtype B SOSIP Env, JRFL. The stability of gp140 trimers was increased for JR-FL and Ba-L SOSIP proteins by substituting the five amino acid residues in the N-terminal region of gp41 with corresponding residues from KNH1144 virus. b12, 2G12, 2F5, 4E10 and CD4-IgG2 all bound similarly to the WT and to the stabilized JRFL SOSIP timers, suggesting that the trimer-stabilizing substitutions do not impair the overall antigenic structure of gp140 trimers. Dey *et al.* [2007a] (**therapeutic vaccine**)
- IgG1b12: Polyclonal IgGs from broadly neutralizing sera from two clade B and one clade A infected asymptomatic individuals were able to efficiently inhibit binding of b12 to the WT gp120 but not to the hyperglycosylated mutant gp120, which does not bind conventional nonneutralizing CD4BS Abs but retains binding of b12. This suggests that any CD4BS Abs present in the sera from the three patients responsible for broad neutralization must recognize the CD4BS somewhat differently than b12. This Ab was used to help define the antigenic profile of envelopes used in serum depletion experiments to attempt to define the neutralizing specificities of broadly cross-reactive neutralizing serum; it bound to JR-FL and JR-CSF gp120 monomers and to a lesser extent to core JR-CSF gp120 monomer used in the same experiments. Dhillon *et al.* [2007] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- IgG1b12: Inhibition kinetics experiments with this Ab showed that after 60 min of incubation of virus and cells, with b12 there was nearly 100% infection, indicating that all of the Envs had escaped inhibition by b12 by attaching to CD4 molecules. This was about 20 min earlier then escape of inhibition by 2F5 and 4E10. Dimitrov *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **kinetics**)
- b12: A D386N change in the V4 region, which results in restoration of N-glycosylation at this site, resulted in 8-fold increase in resistance of a mutant virus to neutralization by b12 compared to wildtype. Molecular modeling with the HXB2 gp120-b12 crystal indicated that the loss of the glycan at position 386 increases exposure of the CD4 and b12 binding sites. There was a significant association between increased sensitivity to b12 neutralization and enhanced macrophage tropism. Most of the viruses without glycosylation at 386 were sensitive to b12 neutralization, while viruses with glycosylation at this site had variable sensitivity to b12 neutralization. This suggests that increased exposure of b12 epitope is associated with enhanced tropism of HIV for macrophages. Dunfee *et al.* [2007] (**antibody binding site definition and exposure**, **brain/CSF**, **neutralization**)
- IgG1b12: Newborn macaques were challenged orally with the highly pathogenic SHIV89.6P and then treated intravenously with a combination of IgG1b12, 2G12, 2F5 and 4E10 one and 12 hours post-virus exposure. All control animals became highly viremic and developed AIDS. In the group treated with mAbs 1 hour post-virus exposure, 3/4 animals were protected from persistent systemic infection and one was protected from disease. In the group treated with mAbs 12 hour post-virus exposure, one animal was protected from persistent systemic infection and disease was prevented or delayed in two animals. IgG1b12, 2G12, and 4E10 were also given 24 hours after exposure in a separate study; 4/4 treated animals become viremic, but with delayed and lower peak viremia relative to controls. 3/4 treated animals did not get AIDS during the fol-

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low up period, and 1 showed a delayed progression to AIDS , while the 4 untreated animals died of AIDS. Thus the success of passive immunization with NAbs depends on the time window between virus exposure and the start of immunoprophylaxis. Ferrantelli *et al.* [2007] (**immunoprophylaxis**)

- b12: A synthetic scaffold peptide was designed that mimicked the CD4 binding site of HIV-1 gp120. The peptide was specifically recognized by b12 and competed with gp120 for binding to b12. Anti-sera from rabbits immunized with the peptide competed with b12 for binding to gp120. Franke *et al.* [2007] (**vaccine antigen design**, **binding affinity**)
- 1b12: This review summarizes data on the development of HIV-1 centralized genes (consensus and ancestral) for induction of neutralizing antibody responses. Functionality and conformation of native epitopes in proteins based on the centralized genes was tested and confirmed by binding to 1b12 and other MAbs. Antibodies induced by immunization with these centralized proteins did not, however, have the breadth and potency compared to that of 1b12 and other broadly neutralizing MAbs. 1b12 physical characteristics of autoantibodies as a possible reason for lack of 1b12 broad production is also discussed. Gao *et al.* [2007] (**antibody binding site definition and exposure**, **neutralization**, **review**)
- IgG1b12: Addition of a glycosylation site at position V295N in three different subtype C envelope clones did not have any impact on binding of IgG1b12 to gp120, indicating that the mutation did not cause a substantial conformational change. There were also no significant differences in neutralization by IgG1b12 between the corresponding mutant and the wildtype viruses. Deletion of the glycan at position 386 resulted in >10-fold increase in neutralization sensitivity to IgG1b12 but had no effect on IgG1b12 binding to gp120. Gray *et al.* [2007b] (**neutralization**, **binding affinity**)
- IgG1b12: The binding of b12, 2F5 and 2G12 to the cell-free virus interferes with a step of infection subsequent to cell attachment. HIV escape from b12 ocurred 30 and 10 min before escape from 2F5 for IIIB infection of HeLa cells and JRFL infection of Cf2Th-CD4/CCR5 cells, respectivelly, indicating that neutralization efficiency is determined by the time frames during which Ab can bind to the receptor-activated envelope proteins during the entry phase. b12 cell-free virus neutralization was initiated immediately after expose to the antibody. Haim *et al.* [2007] (**kinetics**)
- Ib12: A recombinant gp120-Fc, used in an assay to determine 2G12 epitope contribution to DC-SIGN binding to gp120, bound to Ib12, indicating it was conformationally intact. Hong *et al.* [2007] (**binding affinity**)
- IgG1b12: The neutralizing activity of this antibody for the JR-FL Env variant with the N160K/E160K mutations was measured in comparison with the neutralizing activity of 2909, which was found to be higher. Honnen *et al.* [2007] (**neutralization**)
- b12: HIV-1 env clones resistant to cyanovirin (CV-N), a carbohydrate binding agent, showed amino acid changes that resulted in deglycosylation of high-mannose type residues in the C2-C4 region of gp120. Compared to their parental virus HIV-1 IIIB, these resistant viruses maintained similar sensitivity to b12, as the glycan at position 301 in the V3 loop was intact. Hu *et al.* [2007] (**neutralization**, **escape**)
- IgG1b12: Binding of IgG1b12 to envelope glycoprotein was significantly increased in the presence of a small molecule HIV-1 entry inhibitor, IC9564, suggesting that the inhibitor changed the conformation of gp120 so that that reacted better with IgG1b12. IC9564 also induces conformational change of gp120 to allow the CD4i antibody 17b to bind, but inhibits CD4-induced gp41 conformational changes. Huang *et al.* [2007b] (**antibody binding site definition and exposure**)
- IgG1b12: This review summarizes current knowledge on the various functional properties of antibodies in HIV-1 infection, including IgG1b12 mAb, in vivo and in vitro activity of neutralizing Abs, the importance and downfalls of non-neutralizing Abs and antibodies that mediate antibody-dependent cellular cytotoxicity and the complement system, and summarizes data on areas tht need future investigation on Ab-mediated immune control. Huber & Trkola [2007] (**review**)
- IgG1b12: IgG1b12: Four consensus B Env constructs: full length gp160, uncleaved gp160, truncated gp145, and N-linked glycosylation-site deleted (gp160-201N/S) were compared. All were packaged into virions, and all but the fusion defective uncleaved version mediated infection using the CCR5 co-receptor. These constructs were sensitive to neutralization by a panel of patient plasma and neutralizing MAbs. The B consensus envelopes were sensitive to neutralization by IgG1b12 except the one with the removed glycosylation site at the base of the V1V2 loop, and an Env derived from a patient during early infection. In contrast, truncation of the gp41 cytoplasmic domain (gp145) yielded the Env that was the most sensitive to IgG1b12. Kothe *et al.* [2007] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**)
- IgG1b12: Viruses from 304 days and at 643 days (time of death) post-infection of a macaque infected with SHIV SF162P4 were resistant to contemporaneous serum that had broadly reactive NAbs. SF162 was sensitive to neutralization by b12, but the viral isolates evolved to become increasingly resistant. Kraft *et al.* [2007] (**neutralization**, **escape**)
- IgG1b12: This review summarizes b12 Ab epitope, properties and neutralization activity. b12 use in passive immunization studies in primates and possible mechanisms explaining protection against infection are discussed. Also, b12 autoreactivity and its implications for active immunizations are discussed. Kramer *et al.* [2007] (**immunotherapy**, **review**)
- b12: V3 loop deletions were introduced into three different primary HIV-1 strains: R3A, DH12, and TYBE. The deletions included: ΔV3(12,12) containing the first and the last 12 residues of the V3 loop, ΔV3(9,9) containing first and last 9 residues, and ΔV3(6,6) ontaining first and last 6 residues. Only HIV-1 R3A ΔV3(9,9) was able to support cell fusion. Passaging of this virus resulted in a virus strain (TA1) that replicated with wildtype kinetics, and that acquired several adaptive changes in gp120 and gp41 while retaining the V3 loop truncation. TA1 was neutralized by b12 100-fold more efficiently than R3A, ΔV1/V2 virus, and LAI. Laakso *et al.* [2007] (**neutralization**)
- b12: 32 human HIV-1 positive sera neutralized most viruses from clades A, B, and C. Two of the sera stood out as particularly potent and broadly reactive. Two CD4-binding site defective mutant Env proteins were generated to evaluate

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whether Abs to the CD4-binding site are involved in the neutralizing activity of the two sera. The integrity of the wild-type and mutant proteins was tested to their reactivity to b12. Clade A RW20 and clade B PVO viruses were highly resistant to neutralization by b12, while they were neutralized by IgG eluted from the two patient sera, indicating that novel Abs to the CD4-binding site are elicited in some HIV-1 infected individuals. Li *et al.* [2007b] (**neutralization**, **binding affinity**)

- b12: b12 structure, binding, neutralization, and strategies that can be used for vaccine antigen design to elicit b12-like Abs, are reviewed in detail. Lin & Nara [2007] (**vaccine antigen design**, **review**, **structure**)
- b12: Recombinant monomeric, dimeric and polymeric human monoclonal IgA2 Abs carrying the V regions of MAb b12 were constructed. All three forms of IgA2 reacted with gp120 in a dose-dependent manner with binding affinity, avidity, and reactivity similar to that of IgG1 b12. All three forms of IgA2 inhibited HIVBaL and HIVIIIB infection in PBMCs similarly to IgG1 b12. In T-cell assays, monomeric IgA2 b12 was less effective at neutralizing HIV-1 JR-FL than other b12 forms. All forms of IgA2 b12 were poor at neutralizing HIV-1 JR-CSF, but were slightly more effective in neutralizing HIV-1 HxB2 than IgG1 b12. IgA2 b12 in complex with human secretory component (SC) showed enhanced capacity to block HIV-1 infection of T-cells. Both IgA2 and IgG b12 blocked viral attachment to epithelial cells, and epithelial-PBMC transfer, at similar concentrations. Mantis *et al.* [2007] (**genital and mucosal immunity**, **isotype switch**, **neutralization**, **binding affinity**)
- IgG1b12: This review summarizes data on possible vaccine targets for elicitation of neutralizing Abs and discusses whether it is more practical to design a clade-specific than a clade-generic HIV-1 vaccine. Development of a neutralizing Ab response in HIV-1 infected individuals is reviewed, including data that show no apparent division of different HIV-1 subtypes into clade-related neutralization groups. Also, a summary of the neutralizing activity of mAb IgG1b12 in different HIV-1 clades is provided. McKnight & Aasa-Chapman [2007] (**variant cross-recognition or cross-neutralization**, **review**)
- b12: b12 was able to neutralize the majority of tier 1 and 2 clade B isolates, and two clade C tier 2 isolates. Clade A tier 2 isolates were not neutralized by this Ab. PNGase F treatment, which removes all types of N-linked glycosylation, did not affect binding of b12 to recombinant gp120, nor did it affect neutralizing activity of this Ab. Miranda *et al.* [2007] (**neutralization**)
- b12: Transfer of captured b12-neutralized HIV-1 from Raji-DC-SIGN or immature monocyte-derived DCs (iMDDCs) completely blocked CD4+ T lymphocyte infection. This indicated that unlike other NAbs, such as 2F5 and 4E10, b12-HIV-1 complex is not disassembled upon capture on DC-SIGN-cells. van Montfort *et al.* [2007] (**neutralization**, **dendritic cells**)
- b12: Four different co-receptor switch mutants were generated from ADA and BaL wildtype Envs (ADA-1, ADA-3, BaL-1B, and BaL2A) and the intermediate transition mutations were studied on either CCR5 or CXCR4 expressing cells for their sensitivity to b12 compared to wiltype. Most of the ADA-1 mutants were more sensitive to b12 on CCR5 cells, while the sensitivity varied on CXCR4 cells. Mutations P313R and A221T plus P313R increased resistance to b12. Mutations N197D plus S306R rendered virus highly sensitive to b12 on CCR5 cells but not on CXCR4 cells. The sensitivity of ADA-3 mutants to b12 varied, with mutations N160K, V181, and E322K showing the greatest increase in resistance to b12. BaL-1B mutants were highly sensitive to entry inhibition by b12 on CCR5 cells, which further increased on CXCR4 cells. BaL-2A mutants were also more sensitive to b12 inhibition than the wiltdype virus. Pastore *et al.* [2007] (**co-receptor**, **neutralization**)
- IgG1b12: This review provides information on the HIV-1 glycoprotein properties that make it challenging to target with neutralizing Abs. b12 structure and binding to HIV-1 envelope and current strategies to develop versions of the Env spike with functional trimer properties for elicitation of broadly neutralizing Abs, such as b12, are discussed. In addition, approaches to target cellular molecules, such as CD4, CCR5, CXCR4, and MHC molecules, with therapeutic Abs are reviewed. Phogat *et al.* [2007] (**review**)
- b12: The ability of b12 to neutralize recently transmitted viruses was examined in four homosexual and two parenteral transmission couples. The vast majority of recently transmitted viruses from homosexual recipients were resistant to neutralization by b12, although viruses isolated later in the course of infection showed increased sensitivity to b12 in some of the patients. In the parenteral transmission, both recipient viruses were sensitive to b12 neutralization. The neutralization sensitivity patterns of recipient viruses to b12 did not correlate to the neutralization sensitivity patterns of their donors in the homosexual couples, while the HIV-1 variants from the one of the two parenteral pairs were equally sensitive to neutralization by b12. Quakkelaar *et al.* [2007b] (**neutralization**, **acute/early infection**, **mother-to-infant transmission**)
- b12: The crystal structure of a complex of b12 and B2.1 was determined. This revealed that three contiguos residues mediate critical contacts of B2.1 with b12, and that these are unlikely to mimic the discontinuous key binding residues involved in the full b12 epitope for gp120. This was supported by immunization studies, where immunizations of mice with B2.1 failed to produce gp120 cross-reactive sera. Saphire *et al.* [2007] (**mimotopes**)
- b12: A reference panel of recently transmitted Tier 2 HIV-1 subtype B envelope viruses was developed representing a broad spectrum of genetic diversity and neutralization sensitivity. The panel includes viruses derived from male-to-male, female-to-male, and male-to-female sexual transmissions, and CCR5 as well as CXCR4 using viruses. The envelopes displayed varying degrees of neutralization sensitivity to b12, with 8 of 19 enevlopes sensitive to neutralization by this Ab. The panel was overall less sensitive to neutralization by b12 than previously characterized subtype B envelopes. Schweighardt *et al.* [2007] (**neutralization**, **assay standardization/improvement**)
- b12: Pre-treatment of gp120 with b12 did not inhibit induction of IL-10, indicating that gp120-CD4 interaction is not responsible for IL-10 induction. Shan *et al.* [2007]
- IgG1b12: This Ab was used in the analysis of clade C gp140 (97CN54) antigenicity and was shown to bind with relaively

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high avidity to the molecule and to dissociate substantially within 420 s. Binding of this Ab to its epitope was not affected significantly by N3C5 or N03B11 Abs. Sheppard *et al.* [2007b] (**antibody interactions**, **binding affinity**)

- b12: Compared to the full-length Con-S gp160, chimeric VLPs containing Con-S ΔCFI gp145 with transmembrane (TM) and cytoplasmic tail (CT) sequences derived from the mouse mammary tumor virus (MMTV), showed higher binding capacity to b12. Chimeric VLPs with only CT derived from MMTV also showed higher binding capacity to b12 than the full-length Con-S gp160, however, not as high as the chimeric CT-TM VLPs. Wang *et al.* [2007a] (**binding affinity**)
- b12: 5145A MAb was used to select phages from two different peptide libraries. Synthetic peptides corresponding to the selected phage sequences fused to phage pIII protein did not bind to b12. Sera from rabbits immunized with 5145A peptide-phage pIII did not inhibit binding of b12 to gp120. Wilkinson *et al.* [2007] (**antibody generation**)
- IgG1b12: Novel approaches based on sequential (SAP) and competitive (CAP) antigen panning methodiologies, and use of antigens with increased exposure of conserved epitopes, for enhanced identification of broadly cross-reactive neutralizing Abs are reviewed. Previously known broadly neutralizing human mAbs are compared to Abs identified by these methods. Zhang & Dimitrov [2007] (**review**)
- b12: This Ab was found to be able to bind well to a form of gp120 stabilized in a CD4-bound state. The structure and interaction of of Ab-gp120 and CD4-gp120 complexes was determined. It was found that the outer domain of gp120 does not require a conformational change for the initial contact with CD4, however, the conformational change is required to lock CD4 into place once contact has been made. In contrast, b12 is able to lock on to gp120 on the outer domain with high affinity without any requirement of conformational change. Only the heavy chain of b12 was found to interact with gp120 outer domain. Zhou *et al.* [2007] (**antibody binding site definition and exposure**, **binding affinity**, **antibody sequence variable domain**, **structure**)
- Fab b12: Fab b12 inhibited binding of Fc-gp120 to cellular CD4. b12 neutralized virus effectively in the standard neutralization assay, however, it was approximately 2.5-fold less active when the virus was pre-incubated with sCD4. Attachment of Fc-gp120 to MDDCs and PBLs was partially inhibited by 2G12, while b12 and sCD4 did not inhibit binding to MDDCs but did inhibit binding to PBLs. The results indicate that Env attachment is mediated through DC-SIGN and other receptors on MDDCs while it is predominantly mediated by CD4 and CCR5 on PBLs. Binley *et al.* [2006] (**neutralization**, **binding affinity**)
- gG1b12: Inhibition of b12 binding to gp120 by b12-like Abs in sera from long-term non-progressors (LTNP) was determined. It was shown that large amounts of b12-like Abs were present in all sera from LTNPs, however, no statistically significant correlation was found for the specificity of this Ab comparing sera able to neutralize all four HIV-1 strains and sera that could not. Braibant *et al.* [2006] (**enhancing activity**, **neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- IgG1b12: Cloned Envs (clades A, B, C, D, F1, CRF01_AE, CRF02_AG, CRF06_cpx and CRF11_cpx) derived from donors either with or without broadly cross-reactive neutralizing antibodies were shown to be of comparable susceptibility to neutralization by IgG1b12. Cham *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- IgG1b12: Neutralization of HIV-1 primary isolates of different HIV-1 clades (A, B, C, D, E) by b12 was determined in cells expressing high or low surface concentrations of CD4 and CCR5 receptors. CD4 and CCR5 cell surface concentration had no significant effect on the inhibitory activity of this Ab. Choudhry *et al.* [2006] (**co-receptor**, **neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- IgG1b12: Neutralization rates and rate constants for the neutralization of clade B primary isolates SF33, SF162 and 89.6 by this Ab were determined. All isolates were neutralized but with different kinetics. It was shown that neutralization sensitivity is not associated with neutralization of cell-associated or free virus. Davis *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **kinetics**)
- b12: Macaques were immunized with SF162gp140, ΔV2gp140, ΔV2ΔV3gp140 and ΔV3gp140 constructs and their antibody responses were compared to the broadly reactive NAb responses in a macaque infected with SHIV SF162P4, and with pooled sera from humans infected with heterologous HIV-1 isolates (HIVIG). b12 bound to SF162gp140 but a deletion of V2 or V3 loops from the gp140 construct reduced the binding. b12 was found to equally neutralize SF162 and Δ2F5.4E10, which is a virus with mutations in the 2F5 and 4E10 epitopes and is resistant to neutralization by 2F5 and 4E10. Sera from the SHIV-infected macaque and HIVIG, that were absorbed with peptides spanning 2F5 and 4E10 epitopes, did not diminish neutralization by IgG1b12. b12-like Abs were not detected in any of the gp140 sera nor in the sera from the infected macaque confirming that b12 epitope exposure does not correlate well with b12 epitope immunogenicity. Derby *et al.* [2006] (**antibody binding site definition and exposure**, **antibody generation**, **neutralization**)
- b12: Inhibition of gp120 interaction with this Ab by a synthesized scaffolded peptide containing three fragments making up the binding site of gp120 for CD4 was determined. The inhibition activity of the three fragments separately was also determined. It was shown that none of the individual peptides were able to inhibit the b12-gp120 interaction but the scaffolded peptide did, indicating a synergistic effect of combining all three fragments in one molecule. Franke *et al.* [2006] (**mimics**)
- IgGb12: This MAb was used as a positive control in the neutralization assays. It neutralized 5 of 5 subtype B and 4 of 6 non-B primary isolates. Gorny *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- gG1b12: Env-pseudotyped viruses were constructed from the gp160 envelope genes from seven children infected with subtype C HIV-1. IgG1b12 neutralized four of the seven viruses and the clade B control. When this Ab was mixed with 2G12

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and 2F5, the neutralization was similar as to IgGb12 alone, indicating that the majority of the pool activity was due to this Ab. When 4E10 was added to this mix, all isolates were neutralized. Gray *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **responses in children**, **mother-to-infant transmission**)

- IgG1b12: This review describes the effectiveness of the current HIV-1 immunogens in eliciting neutralizing antibody responses to different clades of HIV-1. It also summarizes different evasion and antibody escape mechanisms, as well as the most potent neutralizing MAbs and their properties. MAbs reviewed in this article are: 2G12, IgG1b12, 2F5, 4E10, A32, 447-52D and, briefly, D50. Novel immunogen design strategies are also discussed. Haynes & Montefiori [2006] (**antibody binding site definition and exposure**, **enhancing activity**)
- IgG1b12: Viruses with cleavage-competent 2G12-knockout Env and cleavage-defective Env able to bind 2G12 were constructed. Env pseudotyped virions bearing either Wt3.2P(+)gp140δct Env or a mixture of the wildtype and cleavage-defective Env had similar sensitivities to neutralization by b12. The neutralization by b12 was unaffected by 2G12 binding to uncleaved Env suggesting that only binding to cleavage-competent homotrimers is relevant to neutralization. Herrera *et al.* [2006] (**neutralization**, **binding affinity**)
- IgG1b12: Inhibition of R5 HIV replication by monoclonal and polyclonal IgGs and IgAs in immature monocyte-derived dendritic cells (iMDDCs) was evaluated. It was shown that HIV neutralizing activity of IgG1b12 was more potent in iMDDCs than in PBLs and PHA-stimulated PBMCs using both HIV-1 Bx08 and BaL. Holl *et al.* [2006b] (**neutralization**, **dendritic cells**)
- IgG1b12: The ability of this Ab to inhibit viral growth was increased when macrophages and immature dendritic cells (iDCs) were used as target cells instead of PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication by this Ab for macrophages and iDCs can occur by two distinct mechanisms, neutralization of infectivity involving only the Fab part of the IgG, and, an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**dendritic cells**)
- b12: b12 was shown to interact with cells transiently transfected by VSV-gp120 expressing vector and stained with sera from mice immunized once intranasally with VSV vector expressing HIV-1 HXB2 gp120 indicating that VSV-HXB2 immunization produced anti-HIV-1 Abs. Jiang *et al.* [2006] (**vaccine antigen design**)
- IgG1b12: This Ab neutralized 10 of 17 subtype C env-pseudotyped clones derived from individuals in acute/early stage of HIV-1 infection with subtype C. The sensitivity of clones to a mix of Abs IgG1b12, 2G12 and 2F5 was tracked to IgG1b12. Li *et al.* [2006c] (**neutralization**, **variant cross-recognition or cross-neutralization**, **acute/early infection**, **subtype comparisons**)
- IgG1b12: The gp140δCFI protein of CON-S M group consensus protein and gp140CFI and gp140CF proteins of CON6 and WT viruses from HIV-1 subtypes A, B and C were expressed in recombinant vaccinia viruses and tested as immunogens in guinea pigs. IgG1b12 was shown to bind specifically to CON-S, showing that its conformational epitope was intact. Liao *et al.* [2006] (**antibody binding site definition and exposure**, **vaccine antigen design**, **subtype comparisons**)
- IgG1b12: gp41 and p15E of the porcine endogenous retrovirus (PERV) share structural and functional similarities, and epitopes in the membrane proximal region of p15E are able to elicit NAbs upon immunization with soluble p15E. Rabbits immunized with a VSV recombinant expressing an HIV-1 membrane-proximal external region (MPER) fused to PERV p15E, with a fusion p15E-HIV MPER protein boost, elicited HIV specific NAbs. The IgG1b12 MAb was used as a positive control for neutralization in this study. Luo *et al.* [2006] (**vaccine antigen design**)
- b12: In addition to gp120-gp41 trimers, HIV-1 particles were shown to bear nonfunctional gp120-gp41 monomers and gp120-depleted gp41 stumps on their surface. b12 was found to bind to both nonfunctional monomers and to gp120-gp41 trimers. Binding of b12 to trimers correlated with its neutralization of wildtype virus particles. Monomer binding did not correlate with neutralization, but it did correlate with virus capture. It is hypothesized that the nonfunctional monomers on the HIV-1 surface serve to divert the Ab response, helping the virus to avoid neutralization. Moore *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- IgG1b12: SHIV SF162p4 virus used as challenge in ISCOM vaccinated macaques was shown to be highly sensitive to neutralization by this Ab. Pahar *et al.* [2006] (**neutralization**)
- b12: The neutralizing capacity and binding of this Ab to gp120, as well as strategies for directing Ab responses to the b12 epitope are reviewed. Pantophlet & Burton [2006] (**antibody binding site definition and exposure**, **neutralization**, **review**, **structure**)
- b12: The crystal structure of this Ab was compared to the high resolution crystal structure of Fab m18. The variable domains sequence similarity of Vh and Vl chains was 46% and 63% respectively, while the hypervariable regions differed significantly. The constant regions were identical. Although the variable regions showed sequence similarity, the H3s of these Abs showed distinct conformations. Prabakaran *et al.* [2006] (**antibody binding site definition and exposure**, **mimics**, **antibody sequence variable domain**, **structure**)
- 12: Binding of b12 to wt gp120 and two constructs with 5 and 9 residues deleted in the middle of the beta3-beta5 loop in the C2 region of gp120 was examined. It was shown that the deletions of the loop residues did not affect the conformation of b12 epitope as b12 Ab binding and kinetics were identical for the wt gp120 and both constructs. Rits-Volloch *et al.* [2006] (**antibody binding site definition and exposure**, **kinetics**, **binding affinity**)
- b12: gp120 (monomer), gp120deltaV2 (trimer), gp140 (monomer) and gp140deltaV2 (trimer) from subtype B SF162 were expressed in cells and their affinity for b12 was assessed. While all four Envs bound to b12, the monomers had at least 3-fold weaker affinity for this Ab than trimers. Sharma *et al.* [2006] (**antibody binding site definition and exposure**)
- 1b12: A fusion protein (FLSC R/T-IgG1) that targets CCR5 was expressed from a synthetic gene linking a single chain gp120-CD4 complex containing an R5 gp120 sequence with

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the hinge-Ch2-Ch3 portion of human IgG1. The fusion protein did not activate the co-receptor by binding. In PBMC assays, FLSC R/T-IgG1 neutralized primary R5 HIV-1 isolates more potently than 1b12, while in cell-line based assays the neutralization by FLSC R/T-IgG1 was less potent than by 1b12. Vu *et al.* [2006] (**neutralization**)

- IgG1b12: Viruses with wild-type HIV-1JR-FL Envs and HIV-1 hXBc2 Envs were neutralized by this Ab at much lower concentrations than HIV-1 YU2 Env viruses. Viruses bearing inserted artificial epitopes of FLAG in the V4 region were as sensitive to neutralization by this Ab as the parental viruses. A clear relationship between neutralization potency and the affinity of the anti-FLAG antibody for its cognate epitope was observed. Yang *et al.* [2006] (**neutralization**, **binding affinity**)
- IgG1b12: Interactions of this Ab with gp120 monomer and two cleavage-defective gp140 trimers were studied. It was shown that IgG1b12 recognized the soluble monomer less efficiently than the soluble trimers and that treatment of the proteins with GA (cross-linking) minimally decreased their interactions with this Ab, indicating that the IgG1b12 epitope was maintained after cross-linking. This Ab was associated with a small entropy change upon gp120 binding. IgG1b12 also sucsesfully recognized both untreated and cross-linked proteins expressed on cell surfaces indicating existence of multiple conformational states of gp120 on cell surface. This Ab was shown to have a kinetic advantage as it bound to gp120 faster than other less neutralizing Abs. Yuan *et al.* [2006] (**antibody binding site definition and exposure**, **antibody interactions**, **kinetics**, **binding affinity**)
- b12: The major infectivity and neutralization differences between a PBMC-derived HIV-1 W61D strain and its T-cell line adapted counterpart were conferred by the interactions of three Env amino acid substitutions, E440G, D457G and H564N. Chimeric Env-pseudotyped virus Ch5, containing all three of the mutations, was equally neutralization sensitive to b12 as Ch2, which did not contain any of these mutations. Env-pseudotyped viruses containing D457G mutation were markedly resistant to neutralization by b12. Also, binding of b12 to any gp120 that contained this mutation was severely disrupted. Beddows *et al.* [2005b] (**neutralization**, **binding affinity**)
- IgG1b12: A panel of 60 HIV-1 isolates, with complete genome sequences available, was formed for neutralization assay standardization. It comprises of 10 isolates from each of the subtypes A, B, C, D, CRF01_AE and CRF02AG, with majority of the viruses being of R5 phenotype and few of X4 phenotype. Neutralization profile of each isolate was assessed by measuring neutralization by sCD4, a cocktail of MAbs including 2G12, 2F5 and IgG1b12, and a large pool of sera collected from HIV-1 positive patients. The MAb cocktail neutralized with >50% a large portion of the isolates (51/60) including: 10 subtype A isolates, 8 subtype B isolates, 8 subtype C isolates, 9 subtype D isolates, 7 CRF-01_AE isolates, and 9 CRF_02AG isolates. Brown *et al.* [2005] (**neutralization**, **subtype comparisons**, **assay standardization/improvement**)
- b12: Four primary isolates (PIs), Bx08, Bx17, 11105C and Kon, were tested for binding and neutralization by b12. b12 was able to neutralize Bx08, Bx17 and 11105C with various efficiencies, but bound poorly to all four PIs with similar efficiencies. There was no direct correlation between binding and neutralization of the four PIs by b12. Burrer *et al.* [2005] (**neutralization**, **binding affinity**)
- b12: The structure of the b12 MAb, particularly its long CDRH3 region, is reviewed. Also, the mechanism of its binding to the CD4 binding site of gp120 is compared to other CD4bs MAbs with no neutralizing activity. Engineering of Abs based on revealed structures of broadly neutralizing MAbs is discussed. Burton *et al.* [2005] (**antibody binding site definition and exposure**, **review**, **structure**)
- IgG1b12: The lack of glycosylation sites at residues Asn 295 and Thy 394 within C-clade gp120s generally causes the loss of 2G12 recognition. Introduction of glycans in the subtype C strain HIV-1CN54 at these positions restored 2G12 binding, and addition of just a single glycan partially restored binding (V295N + A394T » V295N > A395T). 2G12 epitope recovery decreased b12 binding. Chen *et al.* [2005]
- b12: b12 was investigated in differnt neutralization formats, including the standard format that measures activity over the entire infection period and several formats that emphasize various stages of infection. The neutralization by b12 was most potent in the standard format and somewhat less potent in the post-CD4 format and the pre-attachment format. The post-CD4/CCR5 neutralization format strongly disfavored b12 neutralization. This suggests that the optimum target for b12 is the native unliganded trimer. HIV-1 + human plasma mediated high-levels of post-CD4 neutralization indicating presence of b12 and 2G12 -like Abs. Crooks *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **assay standardization/improvement**)
- IgG1b12: A phage peptide library was panned on immobilized IgG1b12 which lead to identification of a mimotope consensus sequence for IgG1b12 binding. Second and third generation libraries were used to identify a refined consensus sequence (GLLVWSDEL). The IgG1b12 mimotopes competed with gp160 for the IgG1b12 antigen-binding site. Mice immunized with mimotopes from all three phage library generations developed weak immune responses towards gp160, however, mice vaccinated with the clone from the third library generation exhibited on average stronger gp160-specific Ab response than mice vaccinated with first and second generation clones. Sera of immunized mice were reactive against five different unrelated HIV-1 strains. Dorgham *et al.* [2005] (**mimotopes**, **vaccine antigen design**, **binding affinity**)
- IgG1b12: rSFV-gp140(-GCN4) was constructed for analysis of its immunogenic properties in animal models. Both gp120 and gp140(-GCN4) secreted from rSFV-infected cells were recognized by IgG1b12, suggesting that the proteins retained their native folding. Forsell *et al.* [2005] (**antibody binding site definition and exposure**)
- IgG1b12: Monomeric gp120 and trimeric gp140CF proteins synthesized from an artificial group M consensus Env gene (CON6) bound well to IgG1b12, indicating correct exposure of the IgG1b12 epitope. Gao *et al.* [2005a] (**antibody binding site definition and exposure**)
- IgG1b12: 2909 is a human anti-Env NAb that was selected by neutralization assay and binds to the quaternary structure on

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the intact virion. ELISA-based competition assays and subsequent mutational analysis determined that the CD4BS and V2 and V3 loops contribute to the 2909 epitope: 2909 binding was inhibited by MAbs 447-52d (anti-V3), 830A (anti-V2), and IgG1b12 (anti-CD4BS) and sCD4. 2909 was not inhibited by MAbs 670, 1418, nor 2G12. Gorny *et al.* [2005]

- IgG1b12: IgG1b12, like the other anti-Env broadly neutralizing MAbs 2F5 and 4E10, binds to auto-antigens and has characteristics of polyspecific autoreactive antibodies. Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. IgG1B12 reacted with ribonucleoprotein, dsDNA, centromere B, and histones, as well as nucleolar and cytoplasmic reactivity in HEp-2 cells. Haynes *et al.* [2005a]
- IgG1b12: This review summarizes data on the polyspecific reactivities to host antigens by the broadly neutralizing MAbs IgG1b12, 2G12, 2F5 and 4E10. It also hypothesizes that some broadly reactive Abs might not be routinely made because they are derived from B cell populations that frequently make polyspecific Abs and are thus subjected to B cell negative selection. Haynes *et al.* [2005b] (**antibody generation**, **antibody interactions**, **review**)
- IgG1b12: b12 and the gp41 C-terminal binding MAb SAR1 inhibit HIV-1 infected cell fusion with target cells at comparable levels. Heap *et al.* [2005a]
- b12: b12 bound with a higher maximal mean fluorescence intensity (MFI) to Env protein on the surface of cells producing gp140Δct-pseudotyped neutralization resistant 3.2P strain, than to the Env of pseudotyped neutralization sensitive HXBc2. Neutralization assays with the pseudotyped viruses showed that HXBc2 was more sensitive to neutralization by b12 than 3.2P. Furin co-transfection did not have an effect on the reactivity of pseudoviruses with b12 or on their neutralization sensitivity. Presence or absence of sialic acid residues did not affect Env reactivity with b12. A cleavage-competent form of 3.2P reacted poorly with b12, while its cleavage-defective counterpart showed higher level of MAb reactivity. Both cleavage-competent and cleavage-defective HXBc2 showed higher levels of reactivity to b12. Herrera *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- igG1b12: Point mutations in the highly conserved structural motif LLP-2 within the intracytoplasmic tail of gp41 resulted in conformational alternations of both gp41 and gp120. The alternations did not affect virus CD4 binding, coreceptor binding site exposure, or infectivity of the virus, but did result in increased relative neutralization resistance of the LLP-2 mutant virus to IgG1b12, compared with wildtype virus. The increased neutralization resistance of LLP-2 virus was associated with decreased IgG1b12 binding to its epitope. Kalia *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- b12: A series of genetically modified Env proteins were generated and expressed in both insect and animal cells to be monitored for their antigenic characteristics. For b12, three of the modified proteins expressed in insect cells, including 3G mutant (mutations in 3 glycosylation sites), dV1V2 mutant (V1V2 deletions), and 3G-dV2-1G mutant (1G being a mutation near the TM domain), showed higher binding than the wildtype. Only one of those modified proteins, 3G, now expressed in animal cells, showed higher binding to b12 than the wildtype, indicating that neutralizing epitopes may be more highly exposed in this Env structure. 3G-dV2-1G highly increased binding of b12 compared to 3G-dV2, indicating that glycans in gp41 play a role in the Env antigenicity. Kang *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)
- IgG1b12: A trimeric recombinant gp140 construct was developed for immunization studies. Its structural integrity was assessed by a panel of MAbs. The trimeric gp140 was recognized by IgG1b12 in a manner comparable to monomeric gp120, suggesting that IgG1b12 epitope was well presented on the construct. Kim *et al.* [2005] (**antibody binding site definition and exposure**)
- IgG1b12: Sera from subtype A infected individuals from Cameroon have antibodies that react strongly with subtype A and subtype B V3 loops in fusion proteins, and neutralize SF162 pseudotypes, while sera from 47 subtype B infected individuals reacted only with subtype B V3s. Sera from Cameroon did not neutralize primary A or B isolates, due to indirect masking by the V1/V2 domain rather than due to loss of the target epitope. Neutralization by Cameroonian sera MAbs was blocked by Clade A and B V3 loop fusion proteins, while NAbs to non-V3 epitopes, 2F5, 2G12, and b12, were not blocked. Krachmarov *et al.* [2005]
- IgG1b12: Full-length gp160 clones were derived from acute and early human HIV-1 infections and used as env-pseudotyped viruses in neutralization assays for their characterization as neutralization reference agents. The broadest neutralization sensitivity was observed for IgG1b12, where 12 out of 19 pseudoviruses were neutralized. The sensitivity was however even higher for MN, SF162.LS and IIIB strains. A mixture of IgG1b12, 2F5 and 2G12 (TriMab) exhibited potent neutralizing activity against all Env-pseudotyped viruses except one. 6 out of 12 Env-pseudotyped viruses were more sensitive to neutralization by IgG1b12 than their uncloned parental PBMC-grown viruses. Li *et al.* [2005a] (**neutralization**, **assay standardization/improvement**)
- b12: Pseudoviruses expressing HIV-1 envelope glycoproteins from BL01, BR07 and 89.6 strains were compared in neutralization assays to replication competent clone derived from transfection of 293T cells (IMC-293T) and to the IMC-293T derived from a single passage through PBMC (IMC-PBMC). The neutralization responses of pseudoviruses and corresponding IMC-293T to b12 were similar, while a significant decrease in viral neutralization sensitivity to b12 was observed for the BL01 and 89.6 IMC-PBMC viruses. The decrease was associated with an increase in average virion envelope glycoprotein content on the PBMC-derved virus. Louder *et al.* [2005] (**neutralization**, **assay standardization/improvement**)
- IgG1b12: Called IgG1 b12. The HIV-1 Bori-15 variant was adapted from the Bori isolate for replication microglial cells. Bori-15 had increased replication in microglial cells and a robust syncytium-forming phenotype, ability to use low levels

of CD4 for infection, and increased sensitivity to neutralization by sCD4 and 17b. Four amino acid changes in gp120 V1-V2 were responsible for this change. Protein functionality and integrity of soluble, monomeric gp120-molecules derived from parental HIV-1 Bori and microglia-adapted HIV-1 Bori-15 was assessed in ELISA binding assays using CD4BS MAbs F105 and IgG1b12, glycan-specific 2G12, and V3-specific 447-52D, and were unchanged. Association rates of sCD4 and 17b were not changed, but dissociation rates were 3-fold slower for sCD4 and 14-fold slower for 17b. Martín-García *et al.* [2005]

- IgG1b12: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **immunotherapy**, **review**, **structure**)
- IgG1b12: Viruses containing substitutions at either L568 or K574 of the gp41 hydrophobic pocket were resistant to D5-IgG1 but were as sensitive to IgG1b12 as the wildtype virus. IgG1b12 neutralized more isolates than D5-IgG1 and was shown to be more potent. IgG1b12 did not, however, neutralize some of the isolates neutralized by D5-IgG1. Miller *et al.* [2005] (**neutralization**)
- IgG1b12: This short review summarizes recent findings of the role of neutralizing Abs in controlling HIV-1 infection. Certain neutralizing MAbs and their potential role in immunotherapy and vaccination, as well as the reasons for their poor immunogenicity, are discussed. Montefiori [2005] (**antibody binding site definition and exposure**, **therapeutic vaccine**, **immunotherapy**)
- IgG1b12: IgG1b12 neutralized both JR-FL and YU2 HIV-1 strains. IgGb12 and other neutralizing mAbs recognized JR-FL cleavage-competent and cleavage-defective env glycoproteins, while non-neutralizing Abs only recognized JR-FL cleavage-defective glycoproteins. It is suggested that an inefficient env glycoprotein precursor cleavage exposes non-neutralizing determinants, while only neutralizing regions remain accessible on efficiently cleaved spikes. For YU2, both cleavage-competent and -defective glycoproteins were recognized by both neutralizing and non-neutralizing Abs. Pancera & Wyatt [2005] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- IgG1b12: A stable trimerization motif, GCN4, was appended to the C terminus of YU2gp120 to obtain stable gp120 trimers (gp120-GCN4). Each trimer subunit was capable of binding IgG1b12, indicating that they were at least 85% active. D457V mutation in the CD4 binding site resulted in a decreased affinity of the gp120-GCN4 for CD4, but the mutation did not affect binding of IgG1b12. IgG1b12 was able to bind to both wildtype gp120, gp120-GCN4, and to the respective corresponding mutant molecules D457Vgp120 and D457Vgp120-GCN4. Electron microscopy images showed three, two and one IgG1b12 molecules bound per gp120-GCN4 trimer, with the predominant form being three IgG1b12 per trimer. Pancera *et al.* [2005] (**binding affinity**, **structure**)
- IgG1b12: This study is about the V2 MAb C108g, that is type-specific and neutralizes BaL and HXB2. JR-FL is a neutralization resistant strain; modification of JRFL at V2 positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potently neutralize the modified JR-FL. The modification in V2 also increased neutralization sensitivity to V3 MABs 4117c, 2219, 2191, and 447-52D, but only had minor effects on neutralization by CD4BS MAb 5145A, and broadly neutralizing MAbs IgG1b12, 2G12, and 2F5. gp120 binding to CD4 was inhibited by b12, but not by C108g. Pinter *et al.* [2005]
- IgG1b12: Retrovirus inactivation for vaccine antigen delivery was explored through lipid modification by hydrophobic photoinduced alkylating probe 1.5 iodonaphthylazide (INA). The viral proteins were shown to be structurally intact in the treated non-infectious virus, through the preservation of antibody binding sites for polyclonal anti-gp120 serum, and for broadly neutralizing MAbs 2G12, b12 and 4E10, although the modifications of the lipid disabled viral infection. Raviv *et al.* [2005] (**vaccine antigen design**)
- IgG1b12: Escape mutations in HR1 of gp41 that confer resistance to Enfuvirtide reduced infection and fusion efficiency and also delayed fusion kinetics of HIV-1. The mutations also conferred increased neutralization sensitivity of virus to IgG1b12. Enhanced neutralization correlated with reduced fusion kinetics, indicating that the mutations result in Env proteins remaining in the CD4-triggered state for a longer period of time. Reeves *et al.* [2005] (**antibody binding site definition and exposure**, **drug resistance**, **neutralization**, **escape**, **HAART, ART**)
- IgG1b12: The antibody M2 is specific for a peptide flag inserted into the V4 loop of YU-2, a neutralization resistant variant with a short V4 loop. IgG1b12 and 2F5 could neutralize both the WT YU-2 and the modified variant. The high diversity of V4 suggests it does not play a direct role in receptor binding or viral entry, yet M2, specific for the peptide insert tag, can neutralize the modified virus, demonstrating that neutralizing activity doesn't have to block functionality of the virus. Ren *et al.* [2005] (**neutralization**)
- IgG1b12: 24 out of 58 virus isolates from acutely and chronically HIV-1 infected patients were not inhibited by IgG1b12. There was, however, no difference between the acute and chronic patient viruses in their sensitivity to this Ab. There was no correlation between sensitivities to IgG1b12 and CCR5 inhibitors. Rusert *et al.* [2005] (**autologous responses**, **neutralization**, **acute/early infection**)
- IgG1b12: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies in vaccinated rabbits, but GDMR elicited anti-V3 NAbs. Both antigens successfully dampened other responses that were intended to be

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dampened while not obscuring b12 binding. CD4BS MAbs except Fab b12 (b6, b3, F105) did not bind to either GDMR or mCHO. CD4i MAbs (48d, 17b) did not bind even with sCD4. 2G12 had diminished binding to both. V3 MAbs (447-52D, 19b, F245-B4e8 and 39F) bound to the GDMR antigen, but either did not bind or had diminished binding to mCHO. V2 MAb 697-D did not bind to mCHO and had diminished binding to GDMR, while V2 MAb 8.22.2 bound to GDMR but not mCHO. V1/V2/V3 MAb 4KG2, C1-C4 MAb A32, C1-C5 MAb C11, and HIVIG all either did not bind or had significantly diminished binding to both antigen constructs. Selvarajah *et al.* [2005] (**vaccine antigen design**, **vaccine-specific epitope characteristics**)

- b12: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **binding affinity**, **immunotherapy**, **review**)
- b12: This review summarizes data on 447-52D and 2219 crystallographic structures when bound to V3 peptides and their corresponding neutralization capabilities. b12, like 447-52D and like other HIV-1 neutralizing Abs, was shown to have long CDR H3 loop, which is suggested to help Abs access recessed binding sites on the virus. Stanfield & Wilson [2005] (**antibody binding site definition and exposure**, **review**, **structure**)
- IgG1b12: This Ab bound with high affinity to gp120IIIb but it only weakly suppressed gp120 antigen presentation by MHC class II. Binding of b12 to gp120 did not prevent uptake of gp120 by APCs. b12 showed intermediate disassociation from gp120 at acidic pH. Lysosomal enzyme digestion of gp120 in complex with b12 yielded limited fragmentation similar to that of gp120 alone. It is suggested that neutralizing high-affinity CD4bs Abs, such as b12, provide effective anti-viral protection without strong supressive effects on presentation of gp120. Tuen *et al.* [2005] (**antibody interactions**, **binding affinity**)
- IgG1b12: The crystal structure of the Fab fragment from F105 was solved. It has an extended CDR H3 loop, with a Phe at the apex that may recognize the binding pocket of gp120 used by the Phe-42 residue of CD4. The potent NAB IgG1b12 recognizes an overlapping binding site, the main difference is that F105 extends across the interface of the inner and outer domains of gp120 while b12 does not. IgG1b12 also has undergone extensive affinity maturation (45 mutations) while F105 has not (13 mutations) – an average for gp120 MAbs is 22 mutations. Wilkinson *et al.* [2005] (**antibody sequence variable domain**, **structure**)
- b12: Ab neutralization of viruses with mixtures of neutralization-sensitive and neutralization-resistant envelope glycoproteins was measured. It was concluded that binding of a single Ab molecule is sufficient to inactivate function of an HIV-1 glycoprotein trimer. The inhibitory effect of the Ab was similar for neutralization-resistant and -sensitive viruses indicating that the major determinant of neutralization potency of an Ab is the efficiency with which it binds to the trimer. It was also indicated that each functional trimer on the virus surface supports HIV-1 entry independently, meaning that every trimer on the viral surface must be bound by an Ab for neutralization of the virus to be achieved. Yang *et al.* [2005c] (**neutralization**)
- IgG1b12: A substantial fraction of soluble envelope glycoprotein trimers contained inter-subunit disulfide bonds. Reduction of these disulfide bonds had little effect on binding of the IgG1b12 to the glycoprotein indicating that the inter-S-S bonds had no impact on the exposure of IgG1b12 epitope. Yuan *et al.* [2005] (**antibody binding site definition and exposure**)
- IgG1b12: HIV-1 fusion complexes were prepared from cell lines expressing R5 HIV-1 gp120/gp41 and CD4-CCR5. Neutralizing Abs were raised against both R5 (strain BaL) and X4 (strain 213) viruses. IgG1b12 was used to detect gp120/gp41. Zipeto *et al.* [2005] (**vaccine antigen design**)
- IgG1b12: This review summarizes data that indicate that the V3 region of HIV-1 may be an epitope to target for the induction of protective Abs. Data shows that the V3 region can induce broadly-reactive, cross-neutralizing Abs, that it is partially exposed during various stages of the infectious process, and that it is immunogenic. IgG1b12 is the only neutralizing anti-CD4bs MAb, suggesting that the CD4bs is not an epitope that preferentially induces protective Abs in spite of it being highly immunogenic. Zolla-Pazner [2005] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **review**)
- IgG1b12: 93 viruses from different clades were tested for their neutralization cross-reactivity using a panel of HIV antibodies. IgG1b12 neutralized a fraction of viruses from almost every clade, and was more potent that 2F5 and 4E10, particularly against a subset of B clade viruses. Binley *et al.* [2004] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- IgG1b12: Called b12. The peptide 12p1 (RINNIPWSEAMM) inhibits direct binding of YU2 gp120 or Env trimer to CD4, CCR5 and MAb 17b in a concentration-dependent allosteric manner. 12p1 is thought to bind to unbound gp120 near the CD4 binding site, with a 1:1 stoichiometry. 12p1 also inhibited MAb F105 binding. presumably because F105 favors an unactivated conformation, but not 2G12 or b12. The 1:1 stoichiomtry, the fact that the peptide binding site is accessible on the trimer, the non-CD4 like aspect of the binding, and an ability to inhibit viral infection in cell cultures make it a promising lead for therapeutic design. Biorn *et al.* [2004] (**antibody binding site definition and exposure**)
- IgG1b12: Env sequences were derived from 4 men at primary infection and 4 years later; the antigenicity in terms of the ability to bind to 2G12, 2F5 and IgG1b12 was determined. 2G12 bound primarily to late clones in 3 of the 4 patients, and to both early and late in the other patient. Neither 2F5 nor IgG1b12 showed a difference in binding affinity to early or late envelopes. Dacheux *et al.* [2004]
- IgG1b12: Nabs against HIV-1 M group isolates were tested for their ability to neutralize 6 randomly selected HIV-1 O group strains. IgG1b12 could neutralize some O group strains

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when used on its own, and quadruple combination of b12, 2F5, 2G12, and 4E10, could neutralize the six Group O viruses tested between 62-97%. Ferrantelli *et al.* [2004a]

- IgG1b12: Called b12. A set of oligomeric envelope proteins were made from six primary isolates for potenial use as vaccine antigens: 92/UG/037 (clade A), HAN2/2 (clade B), 92/BR25/025 (clade C), 92/UG/021 (clade D), 93/BR/029 (clade F) and MVP5180 (clade O). This was one of a panel of MAbs used to explore folding and exposure of well characterized epitopes. The clade C isolate BR25 is apparently misfolded, as conformation-dependent antibodies did not bind to it. b12 bound to clade A, B, D and F HIV-1 primary isolates. Polyclonal sera raised in rabbits against these antigens cross-bound the other antigens, but none of the sera had neutralizing activity. Jeffs *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- IgG1b12: Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The loss of the any of the five glycans, within the V3 loop (GM299 V3), C2 (GM292 C2), C3 (GM329 C3), C4 (GM438 C4), or V5 (GM454 V5) made SF162 become more sensitive to IgG1b12 neutralization. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure**)
- IgG1b12: Fab b12. A set of HIV-1 chimeras that altered V3 net charge and glycosylation patterns in V1V2 and V3, involving inserting V1V2 loops from a late stage primary isolate taken after the R5 to X4 switch, were studied with regard to phenotype, co-receptor usage, and MAb neutralization. The loops were cloned into a HXB2 envelope with a LAI viral backbone. It was observed that the addition of the late-stage isolate V1V2 region and the loss of V3-linked glycosylation site in the context of high positive charge gave an X4 phenotype. R5X4 viruses were more sCD4 and 2G12 neutralization resistant than either R5 or X4, but the opposite pattern was observed for b12. Addition of the late stage V1V2 altered neutralization for both MAbs, but this alteration was reversed with the loss of the V3 glycan. Nabatov *et al.* [2004] (**co-receptor**)
- IgG1b12: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it binds to the neutralizing MAb 2G12. It masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120. Pantophlet *et al.* [2004]
- IgG1b12: Called IgG-b12. V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neturalization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12 which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Three anti-CD4BS MAbs were tested, including IgG1b12 which neutralizes both JRFL and SF162. The affinities for IgG1b12 and 5145A were similar for both JRFL and SF612, but 1125A bound with 2.5 fold higher affinity to SF162. 5145A and 1125H both preferentially neutralize SF162, but not JRFL, and the CD4BS is more sensitive to neutralization in the context of the SF162 V1V2 loop. This was also true for neutralization by sCD4. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- IgG1b12: Called b12. A primary isolate, CC1/85, was passaged 19 times in PBMC and gradually acquired increased sensitivity to FAb b12 and sCD4 that was attributed to changes in the V1V2 loop region, in particular the loss of a potential glycosylation site. The affinity for sCD4 was unchanged in the monomer, suggesting that the structural impact of the change was manifested at the level of the trimer. The passaged virus, CCcon19, retained an R5 phenotype and its neutralization susceptibility to other Abs was essentially the same as CC1/85. CCcon19 (IC50 0.3) was significantly more senstivie to neutralization by b12 than was CC1/85 (IC50 6.0). Pugach *et al.* [2004]
- IgG1b12: This review discusses research presented at the Ghent Workshop of prevention of breast milk transmission and immunoprophylaxis for HIV-1 in pediatrics (Seattle, Oct. 2002), and makes the case for developing passive or active immunoprophylaxis in neonates to prevent mother-to-infant transmission. Macaque studies have shown that passive transfer of NAb combinations (for example, IgG1b12, 2G12, 2F5, and 4E10) can confer partial or complete protection to infant macaques from subsequent oral SHIV challenge. Safrit *et al.* [2004]
- IgG1b12: Called IgG1 b12. This paper is a study of the 2F5 NAb complexed to peptide ELDKWAS; the peptide was found to interact with amino acids near the base of the very long (22 residue) CDR 3H region of the Ab, although a Phe at the apex of the loop was also important. The authors suggest that particularly long CDR H3 regions may be a common feature of HIV-1 neuturalizing antibodies – there are 22 residues in 2F5's H3, 18 in IgG1b12's H3, and 22 residues in X5's H3. They express concern that because small animals like mice are unable to elicit Ab responses with such long H3s, they may be poor model systems for HIV vaccine studies. Zwick *et al.* [2004] (**antibody sequence variable domain**)
- IgG1b12: The SOS mutant envelope protein introduces a covalent disulfide bond between gp120 surface and gp41 transmembrane proteins into the R5 isolate JR-FL by adding cysteines at residues 501 and 605. Pseudovirions bearing this protein bind to CD4 and co-receptor bearing cells, but do not fuse until treatment with a reducing agent, and are arrested prior to fusion after CD4 and co-receptor engagement. IgG1b12 neutralized SOS and WT proteins comparably, and neither IgG1b12 nor the Fab b12 could neutralize well post-attachment, consistent with the notion that theb12 binding site would be blocked upon cellular binding. Binley *et al.* [2003]

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- IgG1b12: Called 1b12. The MAb B4e8 binds to the base of the V3 loop, neutralizes multiple primary isolates and was studied for interaction with other MAbs. CD4BS MAb IgG1b12 had no effect on B4e8 binding. Cavacini *et al.* [2003]
- IgG1b12: A sCD4-17b single chain chimera was made that can bind to the CD4 binding site, then bind and block co-receptor interaction. This chimeric protein is a very potent neutralizing agent, more potent than IgG1b12, 2G12 or 2F5 against Ba-L infection of CCR5-MAGI cells. It has potential for prophylaxis or therapy. Dey *et al.* [2003]
- IgG1b12: Four newborn macaques were challenged with pathogenic SHIV 89.6 and given post exposure prophylaxis using a combination of NAbs 2F5, 2G12, 4E10 and IgG1b12. 2/4 treated animals did not show signs of infection, and 2/4 macaques maintained normal CD4+ T cell counts and had a lower delayed peak viremia compared to the controls. Ferrantelli *et al.* [2003] (**immunoprophylaxis**)
- IgG1b12: Called b12 – CD4BS MAbs b12 (neutralizing) and 205-42-15, 204-43-1, 205-46-9 (nonneutralizing) all cross-competed for binding to monomeric gp120, indicating the topological proximity of their epitopes, however, the nonneutralizing CD4BS MAbs did not interfere with the neutralization activity of MAb b12 – the nonneutralizing MAbs partially competed with b12 for Env binding of the surface of Env-transfected cells – this suggests Env has two categories of binding site for CD4BS MAbs, one recognized by both b12 and nonneutralizing CD4BS MAbs, the other is recognized by only b12 – Ab-gp120 interactions based on the use of monomeric gp120 or Env-transfected cells do not predict the outcome of HIV-1 neutralization assays, and they should be interpreted with caution. Herrera *et al.* [2003] (**antibody binding site definition and exposure**)
- IgG1b12: MAbs IgG1b12, 2G12, 2F5 and 4E10 were tested for their ability to neutralize two primary HIV-1 clade A isolates (UG/92/031 and UG/92/037) and two primary HIV-1 clade D isolates (UG/92/001 and UG/92/005). 4E10 demonstrated the most potent cross-neutralization activity. Quadruple administration of MAbs IgG1b12, 2G12, 2F5, and 4E10 induced strong synergistic neutralization of 4 clade A isolates (UG/92/031, UG/92/037, RW/92/020 and RW/92/025) as well as 5 clade D isolates (UG/92/001,UG/9/005, /93/086/RUG/94/108, UG/94/114). The authors note this combination of 4 MAbs neutralizes primary HIV A, B, C, and D isolates. Kitabwalla *et al.* [2003] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- IgG1b12: This review dicusses the importance and function of protective antibody responses in animal model studies in the context of effective vaccine development. SHIV models have shown protection using high levels of MAbs can prevent infection, and partial protection that can influence disease course can be obtained from modest levels of NAbs. SHIV challenges studies conducted with infusions of combinations of MAbs b12, 2G12, and 2F5 are reviewed. Mascola [2003] (**review**)
- IgG1b12: AC10 is a subject who was given treatment early after infection, and had a viral rebound after cessation of therapy, which then declined to a low level. The polyclonal sera from AC10 could potently neutralize the rebound virus, and NAb escape followed with a neutralizing response against the escape variant and subsequent escape from that response. Viral loads remained low in this subject despite escape. The rebound isolate that was potently neutralized by autologous sera was not particularly neutralization sensitive, as it resisted neutralization by sCD4 and MAbs IgG1b12, 2G12 and 2F5, and was only moderately sensitive to sera from other HIV+ individuals that had high titers of NAbs to TCLA strains. Montefiori *et al.* [2003]
- IgG1b12: Called b12 – Alanine scanning mutagenesis was used to compare substitutions that affected anti-CD4BS NAb b12 binding to those that affect binding of sCD4 and two non-neutralizing anti-CD4BS Abs b3 and b6 – while the epitope maps overlapped, there were some differences observed – binding of CD4 was never enhanced, indicating it had evolved to be optimal – rec gp120s were engineered to contain combinations of Alanine substitutions that enhanced b12 binding, and while binding of b12 to these gp120 monomers was generally maintained or increased, binding by five non-neutralizing anti-CD4bs MAbs (b3, b6, F105, 15e, and F91) was reduced or completely abolished – 2G12 binding was largely unperturbed, indicating these proteins were not grossly misfolded – for twelve mutants, b12 neutralization sensitivity and affinity correlated, but for five mutants neutralization efficiency was maintained or increased despite a decrease in affinity suggesting that the subsitutions that influence b12 binding to the monomer are different than those that impact neutralization sensitivity to the trimer. Pantophlet *et al.* [2003a] (**antibody binding site definition and exposure**)
- IgG1b12: This paper describes an attempt to engineer a gp120 molecule that would focus the immune response onto the IgG1b12 epitope. Four Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with seven N-linked glycosylation site sequons and this combination minimized the binding of non-neutralizing MAbs. b12 affinity was lowered, and binding of non-neutralizing MAbs was knocked out. C1 and C5 regions were then removed to eliminate the epitopes for MAbs against these regions, but these also diminished IgG1b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- IgG1b12: Virion capture assays are not a good predictor of neutralization, and the presentation of epitopes using this assay seems to be different from that of functional Envelope spikes on primary isolates – F105 and b6 could efficiently block the b12-mediated capture of infectious virions in a virus capture, but did not inhibit b12 neutralization – b12 was potent at neutralizing the three primary virions JR-CSF, ADA, and 89.6, but anti-V3 Abs 447-52D and 19b, which did not neutralize JR-CSF and ADA captured amounts of p24 equal to or higher than the amounts captured by the neutralizing Ab b12. Poignard *et al.* [2003] (**neutralization**)
- IgG1b12: This paper shows that binding of CD4BS MAbs to Env blocks the conformational shift that allows co-receptor CCR5 binding and CD4-independent mediated cell fusion. CD4BS MAbs F105, 15e, and IgG1b12 as well as their Fab fragments inhibited CD4-independent binding of the V1/V2 loop-deleted gp120 glycoproteins of R5 HIV-1 isolates ADA, YU2 and JR-FL and to CCR5 in a concentration dependent manner. CD4BS MAbs IgG1b12, F91 and F105 and their Fab

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counterparts (except for C11, used as a negative control) inhibited CD4-independent JR-FL and YU-2 gp120-CCR5 binding to CCR5-expressing Cf2Th cells and syncytium formation. Raja *et al.* [2003] (**antibody binding site definition and exposure**)

- IgG1b12: Called b12. The NAb b12 was administered locally to the vagina in macaques and could protect against subsequent vaginal infection with SHIV-162P4. This NAb model of a topical microbicide was dose dependence, and was effective for up to 2 hours after administration. Veazey *et al.* [2003] (**immunoprophylaxis**)
- IgG1b12: Called b12. Review of current neutralizing antibody-based HIV vaccine candidates and strategies of vaccine design. Strategies for targeting of the epitopes for NAbs 2F5, 2G12, 4E10, b12, and Z13 are described. Wang [2003] (**review**)
- IgG1b12: Called b12. The Fab m18 was selected from a human phage display library by a new method called sequential antigen panning (SAP), using a series of antigens to screen the library to pick broadly cross-reactive isolates. The ability to block cell mediated fusion by m17 was compared to Fabs X5 and b12 for a clade A, CRF01 EA, G, and 6 clade B isolates, and the inhibitory activity of m18 was slightly lower but comparable to neutralizing Fabs b12 and X5. Zhang *et al.* [2003]
- IgG1b12: The HIV-1 primary isolate DH012 has preserved the epitopes for the MAbs IgG1b12, 2G12, 17b, however natural DH012 infection in chimpanzees and DH012 gp120 vaccination in guinea pigs does not give rise to Abs against these epitopes. Zhu *et al.* [2003] (**vaccine antigen design**)
- IgG1b12: 4KG5, a single-chain Fv (scFv), reacts with a conformational epitope that is formed by the V1, V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Denaturation of gp120 abolished binding of 4KG5 and Fab b12. Addtionally, binding of 4KG5 was abrogated when any of the V1, V2 or V3 loops were deleted. Of a panel of Abs tested, only NAb b12 enhanced 4KG5 binding to gp120 JR-FL. MAbs to the following regions diminished or abroated binding: V2 loop MAbs (G3-4, G3-136), V3 loop MAbs (19b, 447-52D, hNM01, AH48, loop2, F425 B4e8, 694-88D), V3-C4 (G3-299, G3-42, G3-519, G3-537), CD4BS (b6, b3, F91, F105, 15e, L33, 1008-D, 654-30D, 559-64D, 1027-30D, Ia3, Ia7, FG39, Fbb14). MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1, V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. 4KG5 did not enhance IgG1b12 neutralization. Zwick *et al.* [2003] (**antibody interactions**)
- IgG1b12: IgG1b12 neutralized many South African (5/8) and Malawian (4/8) clade C primary HIV-1 isolates, being more effective than 2F5 which neutralized only two Malawian and no South African isolates. 2G12 did not neutralize any of the 16 isolates. Bures *et al.* [2002] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- IgG1b12: This study examined Ab interactions, binding and neutralization with a B clade R5 isolate (92US660) and R5X4 isolate (92HT593). Abs generally bound and neutralized the R5X4 isolate better than the R5 isolate. Anti-gp41 MAb F240 enhanced the binding of CD4BS MAbs IgG1b12 and F105 to both R5X4 and R5 isolates, but had no effect on neutralization. Anti-V3 MAb B4a1 increased CD4BS MAbs IgG1b12 and F105 to R5X4 virions, but only IgG1b12 binding was increased by B4a1 to the R5 isolate, and neutralization was not impacted. Cavacini *et al.* [2002] (**antibody interactions**)
- IgG1b12: A modified gp140 (gp140ΔCFI), with C-term mutations intended to mimic a fusion intermediate and stabilize trimer formation, retained antigenic conformational determinants as defined by binding to CD4 and to MAbs 2F5, 2G12, F105, and b12, and enhanced humoral immunity without diminishing the CTL response in mice injected with a DNA vaccine. Chakrabarti *et al.* [2002]
- IgG1b12: Truncation of the gp41 cytoplasmic domain of X4, R5, and X4R5 viruses forces a conformation that more closely resembles the CD4 bound state of the external Envelope, enhancing binding of CD4i MAbs 17b and 48d and of CD4BS MAbs F105, b12, and in most cases of glycosylation site dependent MAb 2G12 and the anti-gp41 MAb 246D – in contrast, binding of the anti-V2 MAb 697D and the anti-V3 MAb 694/98D were not affected – viruses bearing the truncation were more sensitive to neutralization by MAbs 48d, b12, and 2G12 – the anti-C5 MAb 1331A was used to track levels of cell surface expression of the mutated proteins. Edwards *et al.* [2002] (**antibody binding site definition and exposure**)
- IgG1b12: Review of NAbs that notes IgG1b12 is a recombinant IgG1 from a phage displayed Fab generated against gp120 from a B clade infected individual, that it binds the CD4BS, that alone or in combination with other MAbs it can protect some macaques against SHIV infection, and that it has strong ADCC activity. Ferrantelli & Ruprecht [2002] (**review**)
- IgG1b12: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – the preincubation 31.5 C step did not alter the inhibitory activity of neutralizing Abs anti-gp41 2F5, or anti-gp120 2G12, IG1b12, 48d, and 17b. Golding *et al.* [2002b]
- IgG1b12: HIV-1 gp160ΔCT (cytoplasmic tail-deleted) proteoliposomes (PLs) containing native, trimeric envelope glycoproteins from R5 strains YU2 and JRFL, and X4 strain HXBc2, were made in a physiologic membrane setting as candidate immunogens for HIV vaccines—2F5 bound to gp160ΔCT with a reconstituted membrane ten-fold better than the same protein on beads—anti-CD4BS MAbs IgG1b12 and F105, A32 (C1-C4), C11 (C1-C5), and 39F (V3) MAbs bound gp160ΔCT PLs indistinguishably from gp160ΔCT expressed on the cell surface—non-neutralizing MAbs C11 and A32 bound with lower affinity than NAb IgG1b12—the MAb 17b was sCD4 inducible on gp160ΔCT PL. Grundner *et al.* [2002]
- IgG1b12: A broad review of NAbs that mentions IgG1b12 as an example of a NAb that does not alter the conformation of gp120, but interferes with CD4 binding. Klasse & Sattentau [2002] (**review**)
- IgG1b12: Called b12. Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the

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HXBc2 core. Enthalpy and entropy changes were divergent, but compensated. CD4 and MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs (17b, 48d, 1.5e, b6, F105 and F91) had large entropy contributions to free energy of binding to the gp120 monomer (mean: 26.1 kcal/mol, range 18.6-31.5), but the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. The high values suggest surface burial or protein folding and ordering of amino acids upon binding. NAb 2G12 had an entropy value of -1.6. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding that is not faced by other anti-gp120 antibodies. Kwong *et al.* [2002] (**structure**)

- IgG1b12: Recombinant adeno-associated virus was used to deliver the IgG1b12 gene into mice by injection. IgG1b12 was expressed in these mice for over 6 months after the primary injection. This strategy allows for predetermined Ab specificity, and could ultimately be used with synergistic Ab combinations. Lewis *et al.* [2002]
- IgG1b12: A pseudotyping assay showed that an X4 V3 loop peptide could enhance infectivity of X4 virus, R5 and R5X4 V3 loops peptides could enhance infectivity of an R5 virus, and R5X4 peptides could enhance infectivity of an R5X4 virus. Neither R5 nor R5X4 peptides influenced binding of CD4BS MAbs F105 and Ig1Gb12, but did increase binding of CD4i MAb 17b. Ling *et al.* [2002]
- IgG1b12: Review of NAbs that discusses mechanisms of neutralization, passive transfer of NAbs and protection in animal studies, and vaccine strategies. Liu *et al.* [2002] (**review**)
- IgG1b12: Deglycosylation of gp120 does not significantly affect IG1b12 binding, in contrast to MAB 2G12. Sanders *et al.* [2002] (**antibody binding site definition and exposure**)
- IgG1b12: The crystal structure of IgG1b12 is resolved and is the first structure of an intact human Ab with an ordered, full length hinge – the structure is extremely asymmetric and flexible with an antigen-binding site that has an unusually long CDR H3 region with a ten residue insertion that projects above the rest of the antigen-binding site – this loop may be required for recognition of the recessed CD4 binding site of gp120. Saphire *et al.* [2002] (**antibody binding site definition and exposure**, **antibody sequence variable domain**, **structure**)
- IgG1b12: Alanine scanning mutagenesis used in conjunction with competition and replacement studies of N-linked carbohydrates and sugars suggest that the 2G12 epitope is formed from mannose residues contributed by the glycans attached to N295 and N332, with the other N-linked carbohydrates in positions N339, N386, and N392 playing a role in maintaining conformation relevant to 2G12 binding – N295A and N332A mutants showed essentially unchanged anti-CD4BS NAb b12 binding affinities, while N339A, N386A and N392A mutants displayed significantly lowered b12 affinity, presumably due to conformational changes. Scanlan *et al.* [2002] (**antibody binding site definition and exposure**)
- IgG1b12: Ab binding characteristics of SOS gp140 were tested using SPR and RIPA – SOS gp140 is gp120-gp41 bound by a disulfide bond – NAbs 2G12, 2F5, IgG1b12, CD4 inducible 17b, and 19b bound to SOS gp140 better than uncleaved gp140 (gp140unc) and gp120 – non-neutralizing MAbs 2.2B (binds to gp41 in gp140unc) and 23A (binds gp120) did not bind SOS gp140 – SOS gp140-2F5-IgG1b12 formed multiple ring structures composed of two SOS gp140 proteins bridged by two Ab molecules, while 2F5 and 2G12 formed extended chains rather than closed rings. Schulke *et al.* [2002] (**vaccine antigen design**)
- IgG1b12: Oligomeric gp140 (o-gp140) derived from R5 primary isolate US4 was characterized for use as a vaccine reagent – antigen capture ELISA was used to compare the antigenicity of gp120 and o-gp140 using a panel of well characterized MAbs – Abs directed against the CD4 binding site (IgGCD4 and IgG1b12) reacted slightly more strongly with the gp120 monomer than with the oligomer, as did sCD4. Srivastava *et al.* [2002] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- IgG1b12: Called ARP3065: Herpesvirus saimiri-immortalized CD4+ T lymphocytes (HVS T cells) were used to isolate virus and perform HIV-1 neutralization assays, and compared with a standard PBMC protocol – neutralization sensitivities to a panel of MAbs and to homologous or heterologous plasma/sera were similar for HVS T cells (CN-2 cells) and PBMCs. Vella *et al.* [2002] (**neutralization**)
- IgG1b12: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91 was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b] (**antibody binding site definition and exposure**, **neutralization**)
- IgG1b12: Passive immunization of neonate macaques with a combination of F105+2G12+2F5 conferred complete protection against oral challenge with SHIV-vpu+ or – the combination b12+2G12+2F5 conferred partial protection against SHIV89.6 – such combinations may be useful for prophylaxis at birth and against milk born transmission – the synergistic combination of IgG1b12, 2G12, 2F5, and 4E10 neutralized a collection of HIV clade C primary isolates. Xu *et al.* [2002]
- IgG1b12: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibritin—stabilized oligomer gp140Δ683(-FT) showed strong preferential recognition by NAbs IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAbs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002] (**vaccine antigen design**)

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- IgG1b12: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002] (**antibody binding site definition and exposure**)
- IgG1b12: Called IgG1 b12. IgG1b12 induces strong ADCC and CDC cytoxicity of HIV-1 infected cells. A panel of mutants in the Fc region of IgG1b12 was generated. K322A reduced ADCC binding of FcγR and abolished complement-dependent cytotoxicity (CDC) and C1q binding. L234A plus L235 in the lower hinge region of the IgG1 heavy chain abolished both FcγR and C1q binding and ADCC and CDC. These mutants did not impact IgG1b12's ability to neutralize virus. Hezareh *et al.* [2001]
- IgG1b12: A combination of MAbs IgG1b12, 2F5, and 2G12 was given postnatally to four neonates macaques that were then challenged with highly pathogenic SHIV89.6P – one of the four infants remained uninfected after oral challenge, two infants had no or a delayed CD4(+) T-cell decline – the most potent combination included IgG1b12, which alone does not alone neutralize SHIV89.6P. Hofmann-Lehmann *et al.* [2001] (**antibody interactions**, **immunoprophylaxis**)
- IgG1b12: Mutations in two glcosylation sites in the V2 region of HIV-1 ADA at positions 190 and 197 (187 DNTSYR-LINCNTS) cause the virus to become CD4-independent and able to enter cells through CCR5 alone – these same mutations tended to increase the neutralization sensitivity of the virus, except the mutation 197 S/R which resulted in a carbohydrate addition to 195 N that disrupts the IgG1b12 binding site. Kolchinsky *et al.* [2001] (**antibody binding site definition and exposure**)
- IgG1b12: Intravenous passive transfer of MAb b12 provides dose-dependent protection from infection to macaques vaginally challenged with the R5 virus SHIV(162P4) – the primary isolate HIV-1SF162 is neutralized 90% (IC90) by b12 at 2 µg/ml, and SHIV162P4, derived from HIV-1SF162, was neutralized by 90% at 2 µg/ml in PHA-activated PBMC from rhesus macaques – the 90% neutralization titers achieved in three groups of animals that were given 25-, 5-, and 1-mg/kg doses were approximately 1:400, 1:80, and 1:16, respectively – the half-life of IgG1 b12 in plasma was about 1 week, but while the peak b12 plasma concentration was immediately after the infusion, the peak vaginal fluid concentration was 7-14 days later. Parren *et al.* [2001] (**immunoprophylaxis**, **kinetics**)
- IgG1b12: Structural aspects of the interaction of neutralizing Abs with HIV-1 Env are reviewed – Env essentially has three faces, one is largely inaccessible on the native trimer, and two that exposed but have low immunogenicity on primary viruses – neutralization is suggested to occur by inhibition of the interaction between gp120 and the target cell membrane receptors as a result of steric hindrance and it is noted that the attachment of approximately 70 IgG molecules per virion is required for neutralization, which is equivalent to about one IgG molecule per spike – the 2G12, 17b and b12 epitopes are discussed in detail – the structure of CD4-bound gp120 reveals features that HIV has evolved to escape anti-CD4BS Abs like IgG1b12 despite profound functional constraints – CD4BS Abs must first access the CD4 binding site, deeply recessed within the gp120 core, and the Fab of an Ab molecule is "wider" than CD4, and in addition the binding site is flanked by variable and glycosylated regions. Poignard *et al.* [2001] (**review**, **structure**)
- IgG1b12: This paper describes the technical aspects of the crystallization of b12 at a resolution of 2.7 angstroms with all 12 Ig domains resolved. Saphire *et al.* [2001a] (**structure**)
- IgG1b12: This paper describes the biological implications of the crystal structure of b12 – a remarkable feature of this antibody is a long protruding finger-like CDR H3 that can dock in the recessed CD4-binding site – a contact residues in gp120 are modeled, with numbering based on the variable loop-deleted crystal structure of gp120. Saphire *et al.* [2001b] (**structure**)
- IgG1b12: SHIV-HXBc2 is a neutralization sensitive non-pathogenic virus, and several *in vivo* passages through monkey's yielded highly pathogenic SHIV KU-1 – HXBc2 and the KU-1 clone HXBc2P3.2 differ in 12 amino acids in gp160 – substitutions in both gp120 and gp41 reduced the ability of sCD4, IgG1b12, F105 and AG1121 to Env achieve saturation and full occupancy, and neutralize KU-1 – 17b and 2F5 also bound less efficiently to HXBc2P3.2, although 2G12 was able to bind both comparably. Si *et al.* [2001]
- IgG1b12: A luciferase-reporter gene-expressing T-cell line was developed to facilitate neutralization and drug-sensitivity assays – luciferase and p24 antigen neutralization titer end points were found comparable using NAb from sera from HIV+ donors, and MAbs 2F5, 2G12 and IgG1b12. Spenlehauer *et al.* [2001] (**assay development**)
- IgG1b12: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 M Abs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001] (**antibody interactions**, **co-receptor**)
- IgG1b12: Twenty HIV clade C isolates from five different countries were susceptible to neutralization by anti-clade B MAbs in a synergistic quadruple combination of mAbs IgG1b12, 2G12, 2F5, and 4E10. Xu *et al.* [2001] (**subtype comparisons**)
- IgG1b12: Primary isolates YU2 and ADA are more resistant to IgG1b12 neutralization than HXBc2: 90% Neutralization of HXBc2 is observed with 1.25 ug of IgG1b12, while ADA and YU2 require 2.5 and 5 ug respectively to achieve 50% neutralization, and 90% neutralization could not be achieved with 10 or 20 ug of IgG1b12, respectively. Yang *et al.* [2001] (**variant cross-recognition or cross-neutralization**)

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- IgG1b12: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAbs alters some step after binding. York *et al.* [2001] (**variant cross-recognition or cross-neutralization**)
- IgG1b12: Neutralizing synergy between MAbs 1b12, 2G12 and 2F5 was studied using surface plasmon resonance to determine the binding kinetics for these three MAbs with respect to monomeric and oligomeric env protein gp160 IIIB – the 2G12 epitope is highly accessible on both monomeric and oligomeric Envs, 1b12 is highly accessible on monomers but not oligomers, and 2F5 on neither form – binding of 2G12 exposes the 2F5 epitope on gp160 oligomers. Zeder-Lutz *et al.* [2001] (**antibody interactions**)
- IgG1b12: b12 recognizes a conformational epitope that overlaps with the CD4 binding site – a phage displayed peptide library was used to identify a peptide which bound b12, called B2.1, which competes with b12 in competition assays – B2.1 has significant homology to the D loop of gp120: upper case letters indicate residues B2.1 shares with gp120, heRsymFS-DlenrcI – one of the goals of defining peptide mimics to the b12 epitope is to develop an immunogen that can stimulate b12-like antibodies, but B2.1 cross-linked to phage and ovalbumin bound IgG1b12 did not elicit cross-reactive gp120 Abs in mice or rabbits. Zwick *et al.* [2001a] (**antibody binding site definition and exposure**, **mimotopes**)
- IgG1b12: This paper primarily concerns 4E10 and Z13, MAbs that both bind proximally to the 2F5 binding site to a conserved epitope, and that neutralize some primary isolates from clades B, C, and E – broadly neutralizing MAbs 2F5, IgG1b12, and 4E10 and Z13 fail to neutralize different subsets of viruses. Zwick *et al.* [2001b] (**subtype comparisons**)
- IgG1b12: Neutralization synergy between anti-HIV NAbs b12, 2G12, 2F5, and 4E10 was studied – a classic fixed-ratio method was used, as well as a method where one Ab was fixed at a low neutralization titer and the other was varied – using primary isolates, a two-four fold enhancement of neutralization was observed with MAb pairs, and a ten-fold enhancement with a quadruple Ab combination – no synergy was observed with any MAb pair in the neutralization of TCLA strain HXB2 – whole IgG1b12 and b12 Fab fragments behaved similarly in the neutralization assays – there was no evidence for cooperativity of binding between b12 and 2G12 to envelope spikes expressed on the cell surface of TCLA or primary isolates. Zwick *et al.* [2001c] (**antibody interactions**)
- IgG1b12: To determine the antigenicity of virus killed by thermal and chemical inactivation, retention of conformation-dependent neutralization epitopes was examined, and exposure of CD4BS epitopes was found to be enhanced (MAbs IgG1b12, 205-46-9, and 205-43-1) – binding to 2G12 and 447-52D epitopes was essentially unaltered – the 17b CD4i epitope was also exposed. Grovit-Ferbas *et al.* [2000] (**vaccine antigen design**)
- IgG1b12: SF162 is a neutralization-resistant HIV-1 isolate – N-linked glycosylation modifications in the V2 loop of the SF162 gp120 revealed that these sites prevent neutralization by CD4BS MAbs (IgG1b12 and IgGCD4), and protect against neutralization by V3 MAbs (447-D and 391-95D) – V2-region glycosylation site mutations did not enhance neutralization resistance to V2 MAbs (G3.4 and G3.136) or CD4i MAbs (17b and 48d) – V2 glycosylation site modification allows increased infection of macrophages, probably due to glycosylated forms requiring fewer CCR5 molecules for viral entry. Ly & Stamatatos [2000] (**escape**)
- IgG1b12: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 CD4BS MAbs – CD4BS MAbs bound consistently to most isolates of clade D, but poorly to isolates of other clades with the exception of broadly reactive MAb IgG1b12, binding to 22 of 26 isolates tested – 8 MAbs were tested for neutralization and MAb IgG1b12 was most potent, with 90% neutralization of 3/5 isolates tested. Nyambi *et al.* [2000] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- IgG1b12: Fab b12 was used – six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000]
- IgG1b12: rgp120 derived from a R5X4 subtype B virus was used to vaccinate healthy volunteers and the resulting sera were compared with sera from HIV-1 positive subjects and neutralizing MAbs – TCLA strains showed enhanced IgG1b12 neutralization sensitivity relative to PBMC-adapted lines – IgG1b12 was able to bind, with low affinity, to the rgp120 monomer HIV-1 W61D. Beddows *et al.* [1999] (**co-receptor**)
- IgG1b12: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999] (**vaccine antigen design**)
- IgG1b12: Neutralization assays with rsCD4, MAbs, and serum samples from SHIV-infected macaques and HIV-1 infected individuals were used to characterize the antigenic properties of the env glycoprotein of six primary isolate-like or TCLA SHIV variants. IgG1b12 neutralized SHIV strains HXBc2, KU2, 89.6, but not 89.6P and KB9. 89.6

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is a dual tropic primary isolate that is not pathogenic in macaques, 89.6P is a highly pathogenic form of 89.6 obtained after passage in macaques, and KB9 is a molecular clone of 89.6P. Neutralization resistance was cell line independent. Crawford *et al.* [1999] (**variant cross-recognition or cross-neutralization**)

- IgG1b12: The presence of leukocyte function-associated molecule 1 (LFA-1) promotes virus infectivity and hinders neutralization, and anti-LFA-1 MAbs can enhance the neutralizing effect of anti-HIV V3 MAb 447-52D and anti-HIV CD4BS MAb IgG1b12 – non-neutralizing anti-HIV CD4BS MAb 654-D did not become neutralizing in the presence of anti-LFA-1 MAbs. Hioe *et al.* [1999] (**antibody interactions**)
- IgG1b12: does not inhibit attachment of virus to cells and was used as a control of a study of neutralization by a MAb F58 based micro antibody. Jackson *et al.* [1999]
- IgG1b12: A meeting summary presented results regarding neutralization – D. Burton and J. Mascola presented results concerning passive immunization and protection of hu-PBL-SCID mice and macaques, respectively, and both found combinations of MAbs that were able to achieve 99% neutralization *in vitro* corresponded to efficacy *in vivo*. Montefiori & Evans [1999] (**review**)
- IgG1b12: Hu-PBL-SCID mice were infected with HIV-1s JRCSF and SF162 to study the effect of NAbs on an established infection – at day 6 post infection, mice were given 50 mg/kg of b12, an amount that would have been protective if given up to 8 hours post-infection, and 100-fold higher than the amount required for 90% neutralization *in vitro* – no significant differences in the initial rate of decrease in viral load or the plateau levels of viral RNA between the b12 treated and control mice were seen – in most of the Ab treated mice escape mutants were observed with varying patterns of mutations – a combination of b12, 2G12 and 2F5 protected 1/3 mice, and an isolate from one of the other two was resistant to neutralization by all three MAbs. Poignard *et al.* [1999] (**escape**, **immunotherapy**)
- IgG1b12: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer – CD4BS MAbs 15e, F91 and IgG1b12 bound better to the deleted protein than to wild type. Binley *et al.* [1998] (**antibody binding site definition and exposure**)
- IgG1b12: Immunoprecipitation of gp120 and gp160 expressed from a rec Semliki Forest virus by F105 and IgG1b12 indicated that the SFV expressed HIV-1 Env was folded appropriately – and SVF-HIV-1 Env vaccine gave the strongest anti-HIV-1 Env response in mice, when compared to an HIV-1 Env DNA vaccine and a rgp160 protein. Brand *et al.* [1998] (**vaccine antigen design**)
- IgG1b12: Ab from gp120 vaccinated individuals prior to infection, who subsequently became HIV infected, could not achieve 90% neutralization of the primary virus by which the individuals were ultimately infected – these viruses were not particularly refractive to neutralization, as determined by their susceptibility to neutralization by MAbs 2G12, IgG1b12, 2F5 and 447-52D. Connor *et al.* [1998] (**variant cross-recognition or cross-neutralization**)
- IgG1b12: Binds JRSF oligomer with high affinity, as do 205-46-9 and 2G6, but IgG1b12 is neutralizing, the other two are not – conclusions of this paper contrast with Parren98 – authors propose a model where 205-46-9 and 2G6 may inhibit CD4 binding, but cause a conformational shift which enhances CCR5 binding and thus counteracts the neutralizing effect – rank order of CD4BS antibodies oligomer binding is IgG1b12 = 2G6 = 205-46-9 > 205-43-1 = 205-42-15 > 15e = 21h = F91, and the only thing notably distinguishing about neutralizing IgG1b12 is that it depends on residues in V2. Fouts *et al.* [1998] (**antibody binding site definition and exposure**)
- IgG1b12: Infection of dendritic cells cultured from CD14+ blood cells or from cadaveric human skin was blocked by neutralizing MAbs IgG1b12, or 2F5 and 2G12 delivered together, but not by control non-neutralizing anti-gp120 MAb 4.8D, indicating that NAbs could interrupt early mucosal transmission events. Frankel *et al.* [1998] (**antibody interactions**, **mucosal immunity**)
- IgG1b12: anti-C1 region MAb 87-135/9 blocks gp120 interaction with CD4+ cells – blocking activity is additive when combined with antibodies which bind in the C4 region of gp120 (F105, 388/389, and b12). Kropelin *et al.* [1998] (**antibody interactions**)
- IgG1b12: Enhances binding of Hx10 to CD4 positive or negative HeLa cells, inhibits binding to CD4+ T-cell line A3.01 – neutralizes HeLa and A3.01 cell Hx10 infection. Mondor *et al.* [1998]
- IgG1b12: IgG1b12, Fab b12 and 3B3 derived from b12 were all included in this study – the rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope – binding affinity of divalent IgG1b12 is 17-fold greater than monovalent Fab b12. Parren *et al.* [1998a] (**binding affinity**)
- IgG1b12: MAbs 2G12, 2F5 and b12 are broadly neutralizing, as are some human polyconal sera, but this paper describes a set of primary isolates that are resistant to all three MAbs and 2 broadly neutralizing sera – results indicate that resistance levels of pediatric isolates might be higher than adult isolates – resistance in general did not seem to be conferred by a loss of binding affinity for gp120 or gp41, rather by a more global perturbation of oligomeric Envelope. Parren *et al.* [1998b] (**variant cross-recognition or cross-neutralization**, **responses in children**)
- IgG1b12: MAbs 654-D100 and IgG1b12 neutralized viruses HIV-BRU and a mutated virus that lacks the V3 loop glycan equally effectively – in contrast, sera from guinea pigs immunized with BRU gp120 neutralize viruses more effectively that lack the V3 glycan. Schonning *et al.* [1998] (**antibody binding site definition and exposure**)
- IgG1b12: Deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in

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PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V2, but not V1, diminished neutralization by CD4BS MAb IgG1b12, in contrast to 654.30D and IgGCD4. Stamatatos & Cheng-Mayer [1998] (**vaccine antigen design**)

- IgG1b12: Fab b12 – the HIV-1 virus YU2 entry can be enhanced by MAbs binding to the CD4BS, V3 loop, and CD4i epitopes – the activation for this enhanced entry state could be conferred on HxB2 by introducing the YU2 V3 loop, or the YU2 V3 and V1/V2 loops – a similar effect is observed by sub-neutralizing concentrations of sCD4 and the effect is dependent of CCR5 – Fab fragment b12 also enhances YU2 entry, ruling out Fc interactions or Env cross-linking as a mechanism, while neutralizing HXBc2. Sullivan *et al.* [1998a]
- IgG1b12: Induces Complement-mediated lysis in MN but not primary isolates – primary isolates are refractive to CML. Takefman *et al.* [1998] (**complement**)
- IgG1b12: MAb was slightly more efficient at neutralization than Fab – inhibits viral binding to cells and viral entry – doesn't affect CD4-independent binding to T-cells. Valenzuela *et al.* [1998]
- IgG1b12: Summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAb binding – probable mechanism of neutralization by CD4BS Ab is direct interference with CD4 binding – IgG1b12 is an unusual CD4BS antibody because it is particularly potent as a neutralizing antibody and it is susceptible to changes in the V1-V2 stem loop structure, and so it may disrupt an interaction between CD4 and conserved amino acids on the V1-V2 stem. Wyatt *et al.* [1998] (**structure**)
- IgG1b12: Abs that recognize discontinuous epitopes can identify mimotopes from a phage peptide display library – IgG1b12 blocks CD4 binding and is the most potent neutralizing Ab – many 15 and 21-mer phage inserts were recognized, but it was not possible to derive a consensus – common features were a W and at least one acidic residue, and one sequence was found multiple times: NWPRWWEEFVDKHSS, and this peptide could compete with gp120 – two short stretches found in the phage peptides might mimic gp120 components of the epitope: positions 382-384, FFY(I), and 423-426 I(FV)I(V)NM. Boots *et al.* [1997] (**mimotopes**)
- IgG1b12: This is a review that includes a description of IgG1b12, noting approximately equivalent affinities for sgp120 and unprocessed gp160, and somewhat enhanced affinity for the native oligomer on TCLA viruses – primary viruses have reduced affinity, but still in the useful range for neutralization – there can be complete protection in hu-PBL-SCID mice with Ab even when administered several hours after viral challenge – competes with sCD4, but unlike other CD4BS antibodies, it is sensitive to mutations in V2. Burton & Montefiori [1997] (**review**)
- IgG1b12: In a multilab evaluation of monoclonal antibodies, only IgG1b12, 2G12, and 2F5 could neutralize at least half of the 9 primary test isolates at a concentration of < 25 mug per ml for 90% viral inhibition – IgG1b12 failed to neutralize only 1/9 primary isolates, although there was some variation between test sites. D'Souza *et al.* [1997] (**variant cross-recognition or cross-neutralization**, **assay standardization/improvement**)
- IgG1b12: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – IgG1b12 bound monomer, oligomer, and neutralized JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
- IgG1b12: b12 was used in its IgG1 form – of 14 human MAbs, the most potent neutralizer of SHIV-vpu+, which expressed HIV-1 IIIB env – all Ab combinations tested showed synergistic neutralization – b12 has a synergistic response with MAbs 694/98-D (anti-V3), 2F5, and 2G12. Li *et al.* [1997] (**antibody interactions**)
- IgG1b12: JRCSF was cultured in the presence of IgG1b12 until a 100-fold resistance to neutralization was selected – resistance was due to three changes: V2 substitution D182N and C3 substitution P365L conferred resistance, and V2 D164N was also required for a viable virus – IgG1b12 resistant virus remained sensitive to MAbs 2G12 and 2F5. Mo *et al.* [1997] (**escape**)
- IgG1b12: Review: MAbs 2F5, 2G12 and IgG1b12 have potential for use in combination with CD4-IgG2 as an immunotherapeutic or immunoprophylactic – homologous MAbs to these are rare in humans and vaccine strategies should consider including constructs that may enhance exposure of these MAbs' epitopes. Moore & Trkola [1997] (**review**)
- IgG1b12: Complete protection against HIV-1 infection was achieved in hu-PBL-SCID mice by passive immunization with physiologically relevant doses – pharmacokinetics showed serum half-life of 30.2 +/- 1.3 hours for Fab b12 and 7.4 +/- 0.7 days for IgG1 b12 in mice, but IgG1 half-lives in human are generally between 21-23 days. Parren *et al.* [1995]; Parren & Burton [1997] (**immunoprophylaxis**)
- IgG1b12: In this review, the technique and potential application of Fab expression and selection in phage display libraries, and subsequent production of IgG molecules is discussed – b12 is exceptionally potent at neutralization and can successfully neutralize most B clade primary isolates, and many isolates from other subtypes as well – 3B3 was derived from b12 by selection for higher affinity using the CDR walking strategy – 3B3 has 8-fold enhancement of binding, a linear correlation was found between neutralization and affinity, and 3B3 can neutralize strains b12 cannot. Parren & Burton [1997] (**binding affinity**, **review**)
- IgG1b12: Fab b12 is unusual in that it binds to gp140 and monomeric gp120 with similar affinities, and with a higher affinity to the native oligomer—authors propose this antibody may be exceptional because it binds the virus rather than viral debris—IgG1b12 can protect against infection prior to or shortly after challenge of hu-PBL-SCID mice with TCLA strains and primary strains, but the serum concentrations required *in vivo* were higher than for *in vitro* neutralization. Parren *et al.* [1997b,a] (**antibody binding site definition and exposure**, **immunoprophylaxis**)
- IgG1b12: Inhibited some SI- and NSI-env chimeric viruses but enhanced one NSI-env chimeric virus 3 fold. Schutten

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et al. [1997] (**enhancing activity**, **variant cross-recognition or cross-neutralization**)
- IgG1b12: Viral binding inhibition by IgG1b12 strongly correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5). Ugolini *et al.* [1997]
- IgG1b12: Major deletions in C1 and C5 and deletions of the V1V2 and V3 loops do not diminish binding. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
- IgG1b12: Saturation mutagenesis of the complementarity-determining region and optimization strategies were used to create very high affinity versions of this Fab – increased affinity was dominated by a slowing of the off rate. Yang *et al.* [1997c] (**binding affinity**)
- IgG1b12: 35 primary isolates were tested and all were neutralized by IgG1b12 (including 4, UG270, RW92/026, ZB20, and 301727 which been had reported as not neutralized by IgG1b12 Trkola *et al.* [1995]) – IgG1b12 could neutralize even when added after the virus to the culture – selection for 400-fold increased affinity did not enhance neutralization by antibody – IgG1b12 was more potent with greater breadth than MAb 2F5 Kessler II *et al.* [1997]. Kessler II *et al.* [1997]; Trkola *et al.* [1995] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- IgG1b12: Potent neutralizing *ex vivo* of virus taken directly from plasma of HIV-1 infected individuals – little correlation between neutralization sensitivity of passaged virus and plasma derived virus – more effective than MAb 19b. Gauduin *et al.* [1996] (**antibody interactions**)
- IgG1b12: Review: Unique among anti-CD4BS MAbs in terms of being potent against both lab adapted virus and primary isolates – one of three MAbs (IgG1b12, 2G12, and 2F5) generally accepted as having significant potency against primary isolates. Poignard *et al.* [1996b] (**review**)
- IgG1b12: Anti-CD4BS MAbs 15e, 21h, and IgG1b12 did not cause gp120 dissociation from virus, or exposure of the gp41 epitope of MAb 50-69, in contrast to CD4i MAb 48d and anti-V3 neutralizing MAbs. Poignard *et al.* [1996a] (**antibody interactions**)
- IgG1b12: Review: Only four epitopes have been described which can stimulate a useful neutralizing response to a broad spectrum of primary isolates, represented by the binding sites of MAbs: 447-52-D, 2G12, Fab b12, and 2F5. Sattentau [1996] (**review**)
- IgG1b12: Neutralizes JR-FL – inhibits gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a] (**antibody binding site definition and exposure**)
- IgG1b12: Because Fab b12 shows reduction in binding when the V2 loop is deleted and when aa 183/184 PI/SG substitutions are made competition studies were done with Fab L78 and anti-V2 MAbs SC258 and 684-238 and they do not compete with IgG1b12. Ditzel *et al.* [1995] (**antibody interactions**)
- IgG1b12: Called BM12 – broad cross-clade neutralization of primary isolates – additive neutralization in combination with MAb 2F5. Kessler *et al.* [1995] (**antibody interactions**)
- IgG1b12: Anti-CD4 binding site MAb – very potent neutralization of a number of primary isolates. Moore *et al.* [1995a]
- IgG1b12: Review: unusual properties for anti-CD4 BS MAb: sensitive to V2 substitutions, preferential recognition of the oligomer on the cell surface. Moore & Ho [1995] (**review**)
- IgG1b12: Formalin inactivation of virus at 0.1% formalin for 10 hours at 4 degrees was optimal for inactivation of virus while maintaining epitope integrity. Sattentau *et al.* [1995]
- IgG1b12: Fab b12 showed potent neutralization of T-cell-line-adapted strains, but much reduced neutralization of 3 primary isolates – 2 of the 3 primary isolates also had reduced binding affinity, but the third was as efficiently immunoprecipitated as HXBc2. Sullivan *et al.* [1995] (**variant cross-recognition or cross-neutralization**)
- IgG1b12: Could potently neutralize primary isolates from within clade B, but showed a slight reduction in efficacy outside of clade B. Trkola *et al.* [1995] (**subtype comparisons**)
- IgG1b12: Very potent neutralization, of primary and lab strains, at concentrations that could be achieved by passive immunization – reduced binding with A,C, and D clade viruses relative to B clade, poor reactivity with E clade – isolates that were refractive to neutralization by sera from HIV-1 + donors could be neutralized by IgG1 b12. Burton *et al.* [1994] (**variant cross-recognition or cross-neutralization**)
- IgG1b12: Cross-reactive with some gp120s, (but not all), from clades A-D – not reactive with gp120 from clades E or F. Moore *et al.* [1994b] (**variant cross-recognition or cross-neutralization**)
- IgG1b12: Anti-CD4 binding site Fab, potent neutralizing activity, greater affinity for a subpopulation of gp120 molecules suggested to be in a mature confirmation – mutations in gp120 that abrogate binding: 368 D/R or D/T, 370 E/R, and 477 D/V, of clone HXBc2 of LAI – sensitive to V1 and V2 substitutions. Roben *et al.* [1994] (**antibody binding site definition and exposure**)
- IgG1b12: The original Fab fragment was derived from a combinatorial phage library from bone marrow of an HIV-1 positive individual who had been asymptomatic for six years. Burton *et al.* [1991] (**antibody generation**)

No.	1401
MAb ID	IgGCD4 (IgG-CD4)
HXB2 Location	Env
Author Location	gp120
Epitope	
Neutralizing	
Immunogen	
Species (Isotype)	human (IgG)
Ab Type	gp120 CD4BS
References	Srivastava *et al.* 2008; Ching *et al.* 2008; Kalia *et al.* 2005; Srivastava *et al.* 2002; Ly & Stamatatos 2000; Stamatatos & Cheng-Mayer 1998; Capon *et al.* 1989
Keywords	antibody binding site definition and exposure, binding affinity, neutralization, subtype comparisons

- IgGCD4: The study explores how the V1 loop of Env influences the neutralization susceptibilities of heterologous viruses to antibodies elicited by the SF162gp140 immunogen. All viruses expressing the WT Envs were susceptible to neutralization by IgGCD4. Replacement of the V1 loops by that of SF162 did not alter the neutralization susceptibilities of the viruses, with the exception of one virus, which became more susceptible. Ching *et al.* [2008] (**neutralization**)

- IgGCD4: Trimeric envelope glycoproteins with a partial deletion of the V2 loop derived from subtype B SF162 and subtype C TV1 were compared. IgGCD4 recognized both subtype B and C trimers. Subtype C trimer had many biophysical, biochemical, and immunological characteristics similar to subtype B trimer, except for a difference in the three binding sites for CD4, which showed cooperativity of CD4 binding in subtype C but not in subtype B. Srivastava *et al.* [2008] (**subtype comparisons**)
- CD4-Ig: Point mutations in the highly conserved structural motif LLP-2 within the intracytoplasmic tail of gp41 resulted in conformational alternations of both gp41 and gp120. The alternations did not affect virus CD4 binding, coreceptor binding site exposure, or infectivity of the virus, but did result in decreased binding and neutralization by certain MAbs and human sera. CD4-Ig exhibited similar levels of binding to both the LLP-2 mutant and wildtype viruses, indicating that its epitope was not altered by the mutation. Kalia *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)
- IgGCD4: Oligomeric gp140 (o-gp140) derived from R5 primary isolate US4 was characterized for use as a vaccine reagent – antigen capture ELISA was used to compare the antigenicity of gp120 and o-gp140 using a panel of well characterized MAbs – Abs directed against the CD4 binding site (IgGCD4 and IgG1b12) reacted slightly more strongly with the gp120 monomer than with the oligomer, as did sCD4. Srivastava *et al.* [2002]
- IgGCD4: SF162 is a neutralization-resistant HIV-1 isolate – N-linked glycosylation modifications in the V2 loop of the SF162 gp120 revealed that these sites prevent neutralization by CD4BS MAbs (IgG1b12 and IgGCD4), and protect against neutralization by V3 MAbs (447-D and 391-95D) – V2-region glycosylation site mutations did not alter neutralization resistance to V2 MAbs (G3.4 and G3.136) or CD4i MAbs (17b and 48d) – V2 glycosylation site modification allows infection of macrophages, probably due to glycosylated forms requiring fewer CCR5 molecules for viral entry. Ly & Stamatatos [2000]
- IgGCD4: Deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V2 but not V1 slightly enhanced neutralization by CD4BS MAb IgGCD4. Stamatatos & Cheng-Mayer [1998]
- IgGCD4: An antibody-like immunoadhesins molecule was constructed incorporating the gp120-binding domain of CD4. Capon *et al.* [1989]

No. 1402
MAb ID L28
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 CD4BS
References Gorny & Zolla-Pazner 2004; Ditzel *et al.* 1995
Keywords antibody binding site definition and exposure, antibody sequence variable domain, review

- L28: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- L28: Substitutions at 257 T/R, 368 D/R, 370 E/R and 370 E/Q, 475 M/S 102 E/L and 463 N/D reduce binding – binding was enhanced by removal of the V3 loop and by substitutions 45 W/S, 298 R/G, 381 E/P, 382 F/L, 420 I/R, 435 Y/H or Y/R – binding is sensitive to deglycosylation – heavy and light chain variable region sequence is available. Ditzel *et al.* [1995] (**antibody binding site definition and exposure**, **antibody sequence variable domain**)

No. 1403
MAb ID L33
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 CD4BS
References Gorny & Zolla-Pazner 2004; Zwick *et al.* 2003; Ditzel *et al.* 1995
Keywords antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, review

- L33: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- L33: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- L33: binding is sensitive to deglycosylation – heavy and light chain variable region sequence is available. Ditzel *et al.* [1995] (**antibody binding site definition and exposure**, **antibody sequence variable domain**)

No. 1404
MAb ID L41
HXB2 Location Env
Author Location gp120
Epitope

B Cell

Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 CD4BS
References Gorny & Zolla-Pazner 2004; Ditzel *et al.* 1995
Keywords antibody binding site definition and exposure, antibody sequence variable domain, review

- L41: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- L41: Substitutions at 133 D/R, 256 S/Y, 257 T/R, 368 D/R or D/T, 370 E/Q or E/R, 384 Y/E, and 421 K/L reduce binding – paradoxically, this Fab was retrieved from the library after masking with known anti-CD4BS MAbs – binding is sensitive to deglycosylation – heavy and light chain variable region sequence is available. Ditzel *et al.* [1995] (**antibody binding site definition and exposure**, **antibody sequence variable domain**)

No. 1405
MAb ID L42
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 CD4BS
References Gorny & Zolla-Pazner 2004; Ditzel *et al.* 1995
Keywords antibody binding site definition and exposure, review

- L42: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- L42: Substitutions at 257 T/R, 368 D/R, 370 E/R, 266 A/E and 477 D/V reduce binding – binding was significantly enhanced by 381 E/P and 382 F/L – binding is sensitive to deglycosylation – heavy and light chain variable region sequence is available. Ditzel *et al.* [1995] (**antibody binding site definition and exposure**)

No. 1406
MAb ID L52
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 CD4BS
References Gorny & Zolla-Pazner 2004; Ditzel *et al.* 1995
Keywords antibody binding site definition and exposure, antibody sequence variable domain, review

- L52: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- L52: Binding is sensitive to deglycosylation – heavy and light chain variable region sequence is available. Ditzel *et al.* [1995] (**antibody binding site definition and exposure**, **antibody sequence variable domain**)

No. 1407
MAb ID L72
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype) mouse
Ab Type gp120 CD4BS
Research Contact Dr. Hariharam, IDEC Pharmaceuticals Corp La Jolla, CA
References Ditzel *et al.* 1997

- L72: Used to bind gp120 to solid phase to select MAbs from a phage selection library. Ditzel *et al.* [1997]

No. 1408
MAb ID M12
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4BS
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1994

- M12 database comment: There is a p15 and a gp120 mouse MAb both called M12 and a human gp41 Fab M12.
- M12: A comparison of 25 gp120 specific, conformation dependent MAbs was done – M12 is part of a group of MAbs labeled A1 – all A1 MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, blocked CD4 binding, were sensitive to mutations in gp120 positions 368 and 370 that directly contact CD4 – 50% neutralization of NL4-3 was achieved with 21 ug/ml of M12. Sugiura *et al.* [1999]
- M12: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1409
MAb ID M13
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing L
Immunogen vaccine

B Cell

Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4BS
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1994

- M13: A comparison of 25 gp120 specific, conformation dependent MAbs was done – M13 is part of a group of MAbs labeled A1 – all A1 MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, blocked CD4 binding, were sensitive to mutations in gp120 positions 368 and 370 that directly contact CD4 – 50% neutralization of NL4-3 was achieved with 35 ug/ml of M13. Sugiura *et al.* [1999]
- M13: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1410
MAb ID M6
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4BS
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Zhou *et al.* 2007; Zhang & Dimitrov 2007; Huang *et al.* 2005a; Sugiura *et al.* 1999; Earl *et al.* 1994
Keywords kinetics, review, structure

- m6: Novel approaches based on sequential (SAP) and competitive (CAP) antigen panning methodiologies, and use of antigens with increased exposure of conserved epitopes, for enhanced identification of broadly cross-reactive neutralizing Abs are reviewed. Abs identified by these methods are described. Zhang & Dimitrov [2007] (**review**)
- m6: The increase in the on-rate of this Ab was used to assess the degree to which stabilization 'preformed' the variant gp120 cores in the CD4-bound state. Zhou *et al.* [2007] (**kinetics**)
- m6: The structure of the V3 region in the context of gp120 core complexed to the CD4 receptor and to the m6 Ab was attempted to be determined by X-ray resolution, but only the structure for V3 complexed with CD4 and X5 Ab was solved. Huang *et al.* [2005a] (**structure**)
- M6: A comparison of 25 gp120 specific, conformation dependent MAbs was done – M6 is part of a group of MAbs labeled A1 – all A1 MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, blocked CD4 binding, were sensitive to mutations in gp120 positions 368 and 370 that directly contact CD4. Sugiura *et al.* [1999]
- M6: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1411
MAb ID MAG 116
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 CD4BS
Research Contact C. Y. Kang, IDEC Inc
References Kang *et al.* 1994

- MAG 116: Amino acid substitutions that reduce binding 10 fold: 256 S/Y, 257 T/R, 368 D/R or T, 370 E/R or Q, 384 Y/E, 421 K/L – neutralizes MN, IIIB and RF. Kang *et al.* [1994]

No. 1412
MAb ID MAG 12B
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 CD4BS
Research Contact C. Y. Kang, IDEC Inc
References Kang *et al.* 1994

- MAG 12B: Amino acid substitutions that reduce binding 10 fold: 257 T/R, 368 D/R or T, 370 E/R or Q, 384 Y/E, 477 D/V – weak neutralization of IIIB. Kang *et al.* [1994]

No. 1413
MAb ID MAG 29B
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 CD4BS
Research Contact C. Y. Kang, IDEC Inc
References Kang *et al.* 1994

- MAG 29B: Amino acid substitutions that reduce binding 10 fold: 257 T/R, 368 D/R or T, 370 E/R or Q, 384 Y/E, 386 N/Q, 421 K/L – weak neutralization of IIIB. Kang *et al.* [1994]

No. 1414
MAb ID MAG 3B
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120

B Cell

Species (Isotype) mouse
Ab Type gp120 CD4BS
Research Contact C. Y. Kang, IDEC Inc
References Kang *et al.* 1994

- MAG 3B: Amino acid substitutions that reduce binding 10 fold: 256 S/Y, 257 T/R or A or G, 262 N/T, 368 D/R or T, 370 E/R or Q, 381 E/P, 384 Y/E, 421 K/L, 475 M/S, 477 D/V. Kang *et al.* [1994]

No. 1415
MAb ID MAG 55 (#55)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 CD4BS
Research Contact C. Y. Kang, IDEC Inc
References Koefoed *et al.* 2005; Moore & Sodroski 1996; Kang *et al.* 1994
Keywords antibody binding site definition and exposure

- MAG 55: IgG antibody phage display libraries were created from HIV-1 + individuals after pre-selection of PBMC with gp120, as an alternative to using bone marrow for generating libraries. MAG 55 was among a set of Abs used for competition studies to define the binding sites of the newly isolated MAbs, representing a MAb with a CD4BS epitope. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**)
- MAG 55: Called #55 – binding reciprocally inhibited by other anti-CD4 binding site MAbs, and by some C1-C5 MAbs – binding enhanced by anti-V3 MAb 110.5 and anti-V2 MAbs G3-136 and G3-4 – enhances binding of many anti-V3 and -V2 MAbs. Moore & Sodroski [1996]
- MAG 55: Amino acid substitutions that reduce binding 10 fold: 256 S/Y, 257 T/R, 368 D/R or T, 370 E/R or Q, 384 Y/E, 421 K/L, 470 P/L, 475 M/S, 477 D/V – neutralizes MN, IIIB and RF. Kang *et al.* [1994]

No. 1416
MAb ID MAG 72 (L72)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 CD4BS
Research Contact C. Y. Kang or Dr. Hariharam, IDEC Pharmaceuticals Corp, La Jolla, CA
References Ditzel *et al.* 1997; Kang *et al.* 1994

- MAG 72: Called L72 – used to bind gp120 to solid phase to select MAbs from a phage selection library. Ditzel *et al.* [1997]
- MAG 72: Amino acid substitutions that reduce binding 10 fold: 257 T/R or A or G, 262 N/T, 368 D/R or T, 370 E/R or Q, 384 Y/E, 421 K/L, 477 D/V – neutralizes MN, IIIB and RF. Kang *et al.* [1994]

No. 1417
MAb ID MAG 86
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 CD4BS
Research Contact C. Y. Kang, IDEC Inc
References Kang *et al.* 1994

- MAG 86: Amino acid substitutions that reduce binding 10 fold: 256 S/Y, 257 T/R, 368 D/R or T, 370 E/R or Q, 384 Y/E, 421 K/L, 470 P/L, 477 D/V – neutralizes MN, IIIB and RF. Kang *et al.* [1994]

No. 1418
MAb ID MAG 96
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 CD4BS
Research Contact C. Y. Kang, IDEC Inc
References Koefoed *et al.* 2005; Kang *et al.* 1994
Keywords antibody binding site definition and exposure

- MAG 96: IgG antibody phage display libraries were created from HIV-1 + individuals after pre-selection of PBMC with gp120, as an alternative to using bone marrow for generating libraries. MAG 96 was among a set of Abs used for competition studies to define the binding sites of the newly isolated MAbs, representing a MAb with a CD4BS epitope. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**)
- MAG 96: Amino acid substitutions that reduce binding 10 fold: 256 S/Y, 257 T/R, 368 D/R or T, 370 E/R – weak neutralization of IIIB. Kang *et al.* [1994]

No. 1419
MAb ID MTW61D
HXB2 Location Env
Author Location gp120 (W61D)
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4BS
References Gorny & Zolla-Pazner 2004; Fouts *et al.* 1998; Sullivan *et al.* 1998a
Keywords enhancing activity, review

- MTW61D: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- MTW61D – the HIV-1 virus YU2 entry can be enhanced by MAbs binding to the CD4BS, V3 loop, and CD4i epitopes – the activation for this enhanced entry state could be conferred on HxB2 by introducing the YU2 V3 loop, or the YU2 V3 and V1/V2 loops – a similar effect is observed by sub-neutralizing concentrations of sCD4 and the effect is dependent of CCR5 – Fab fragment MTW61D also enhances YU2 entry, ruling out Fc interactions or Env cross-linking as a mechanism, while neutralizing HXBc2 – MTW61D was obtained by panning libraries derived from bone marrow from a long term asymptomatic donor against gp120 from primary isolate W61D. Sullivan *et al.* [1998a] (**enhancing activity**)

No. 1420
MAb ID S1-1
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 CD4BS
References Gorny & Zolla-Pazner 2004; Wisnewski *et al.* 1996; Moran *et al.* 1993; Lake *et al.* 1992
Keywords antibody binding site definition and exposure, antibody sequence variable domain, complement, enhancing activity, review

- S1-1: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- S1-1: S1-1 is V H1 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996] (**antibody sequence variable domain**)
- S1-1: Heavy (V HI) and light (V lambdaIII) chain sequenced – no enhancing activity – similar germline sequence to MAb 86, but very different activity. Moran *et al.* [1993] (**enhancing activity**, **antibody sequence variable domain**)
- S1-1: Neutralizes IIIB and MN without complement, and neutralizes RF and a clinical isolate with complement – binds to native but not denatured gp120 – inhibits sCD4-gp120 binding. Lake *et al.* [1992] (**antibody binding site definition and exposure**, **complement**)

No. 1421
MAb ID T13
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4BS
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1994

- T13: A comparison of 25 gp120 specific, conformation dependent MAbs was done – T13 is one of three MAbs labeled group Cb, that was type-specific for BH8 – T13 fully blocked CD4 binding, and the deletion of the V3 loop enhanced binding 10-fold. Sugiura *et al.* [1999]
- T13: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1422
MAb ID T49
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4BS
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1994

- T49: A comparison of 25 gp120 specific, conformation dependent MAbs was done – T49 is one of three MAbs labeled group Cb, that was type-specific for BH8 – T49 fully blocked CD4 binding, and the deletion of the V3 loop enhanced binding 10-fold. Sugiura *et al.* [1999]
- T49: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1423
MAb ID T56
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 CD4BS
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1994

- T56: A comparison of 25 gp120 specific, conformation dependent MAbs was done – T56 is one of three MAbs labeled group Cb, that was type-specific for BH8 – T56 fully blocked CD4 binding, and the deletion of the V3 loop enhanced binding 10-fold. Sugiura *et al.* [1999]
- T56: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1424

MAb ID TH9
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen
Species (Isotype) human (IgG1κ)
Ab Type gp120 CD4BS
Research Contact Michael Fung, Tanox Biosystem, USA
References Gorny & Zolla-Pazner 2004; Yang *et al.* 1998; D'Souza *et al.* 1995
Keywords assay development, review, subtype comparisons, variant cross-recognition or cross-neutralization

- TH9: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- TH9: A neutralization assay was developed based on hemi-nested PCR amplification of the LTR (HNPCR) – LTR-HNPCR consistently revealed HIV DNA and was shown to be a rapid, specific and reliable neutralization assay based on tests with 6 MAbs and 5 isolates. Yang *et al.* [1998] (**assay development**)
- TH9: Found to neutralize MN, but not JRCSF, two B subtype primary isolates, or a D subtype primary isolate, by most labs in a multi-laboratory study involving 11 labs. D'Souza *et al.* [1995] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1425
MAb ID anti-CD4BS summary
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 CD4BS
References Moore & Sodroski 1996; Thali *et al.* 1993

- Anti-CD4 binding site antibodies (CD4BS) competitively inhibit CD4 binding to monomeric gp120, and they differ in precise dependence on gp120 residues, but generally require Asp-368 and Glu-370. Moore & Sodroski [1996]
- Shared components of MAb epitopes and the discontinuous CD4 binding regions included Thr 257, Asp 368, Glu 370, Lys 421 through Trp 427 and Asp 457. Thali *et al.* [1993]

No. 1426
MAb ID b11
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 CD4BS
References Zhou *et al.* 2007; Gorny & Zolla-Pazner 2004; Parren *et al.* 1998a
Keywords binding affinity, review

- b11: This Ab was used to determine the degree to which fixation of gp120 in its CD4-bound conformation restricts antigenic recognition. b11 was not able to bind well to the stabilized gp120. Zhou *et al.* [2007]
- b11: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- b11: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**binding affinity**)

No. 1427
MAb ID b13
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 CD4BS
References Zhou *et al.* 2007; Gorny & Zolla-Pazner 2004; Parren & Burton 1997; Parren *et al.* 1998a; Parren *et al.* 1995
Keywords binding affinity, immunoprophylaxis, review

- b13: This Ab was used to determine the degree to which fixation of gp120 in its CD4-bound conformation restricts antigenic recognition. b13 was not able to bind well to the stabilized gp120. Zhou *et al.* [2007]
- b13: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- b13: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**binding affinity**)
- b13: Fab b13 was used as a control in a hu-PBL SCID mouse study – animals were protected from HIV-1 SF2 infection by IgG1b12, somewhat by Fab b12, but not by b13. Parren *et al.* [1995]; Parren & Burton [1997] (**immunoprophylaxis**)

No. 1428
MAb ID b14
HXB2 Location Env
Author Location gp120
Epitope

B Cell

Neutralizing Immunogen
Species (Isotype) human
Ab Type gp120 CD4BS
References Gorny & Zolla-Pazner 2004; Parren *et al.* 1998a
Keywords binding affinity, review

- b14: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- b14: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**binding affinity**)

No. 1429
MAb ID b3
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 CD4BS
References Zhou *et al.* 2007; Lin & Nara 2007; Srivastava *et al.* 2005; Selvarajah *et al.* 2005; Pantophlet *et al.* 2004; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Pantophlet *et al.* 2003a; Parren *et al.* 1998a; Parren *et al.* 1997b
Keywords antibody binding site definition and exposure, antibody interactions, binding affinity, neutralization, review, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- b3: Molecules designed to eliminate binding by b3 while preserving epitopes of other neutralizing Abs are discussed. Lin & Nara [2007] (**review**)
- b3: This Ab was used to determine the degree to which fixation of gp120 in its CD4-bound conformation restricts antigenic recognition. b3 was not able to bind well to the stabilized gp120. Zhou *et al.* [2007] (**binding affinity**)
- b3: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. CD4BS MAbs except Fab b12 (b6, b3, F105) did not bind to either GDMR or mCHO. Selvarajah *et al.* [2005] (**vaccine antigen design**, **vaccine-specific epitope characteristics**)
- b3: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **review**)
- b3: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- b3: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including b3. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- b3: Alanine scanning mutagenesis was used to compare substitutions that affected anti-CD4BS NAb b12 binding to those that affect binding of sCD4 and two non-neutralizing anti-CD4BS Abs b3 and b6 – while the epitope maps overlapped, there were some differences observed – binding of CD4 was never enhanced, indicating it had evolved to be optimal – rec gp120s were engineered to contain combinations of Alanine substitutions that enhanced b12 binding, and while binding of b12 to these gp120 monomers was generally maintained or increased, binding by five non-neutralizing anti-CD4bs MAbs (b3, b6, F105, 15e, and F91) was reduced or completely abolished – 2G12 binding was largely unperturbed, indicating these proteins were not grossly misfolded. Pantophlet *et al.* [2003a] (**antibody binding site definition and exposure**)
- b3: A gp120 molecule was design to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- b3: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)

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- b3: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**binding affinity**)
- b3: Neutralizes TCLA strains, but not primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)

No. 1430
MAb ID b6 (IgG1b6)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing N
Immunogen
Species (Isotype) human
Ab Type gp120 CD4BS
Research Contact Dennis Burton, Scripps, San Diego, CA, USA
References Vaine *et al.* 2008; Gopi *et al.* 2008; Crooks *et al.* 2008; Dey *et al.* 2008; Frey *et al.* 2008; Zhou *et al.* 2007; Lin & Nara 2007; Law *et al.* 2007; Dey *et al.* 2007b; Dey *et al.* 2007a; Moore *et al.* 2006; Derby *et al.* 2006; Srivastava *et al.* 2005; Selvarajah *et al.* 2005; Pancera & Wyatt 2005; Pantophlet *et al.* 2004; Binley *et al.* 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Pantophlet *et al.* 2003a; Poignard *et al.* 2003; Kwong *et al.* 2002; Parren *et al.* 1998a; Parren *et al.* 1997b
Keywords antibody binding site definition and exposure, antibody generation, antibody interactions, binding affinity, enhancing activity, neutralization, review, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- b6: The study compared Ab neutralization against the JR-FL primary isolate and trimer binding affinities judged by native PAGE. There was direct quantitative relationship between monovalent Fab-trimer binding and neutralization, implying that neutralization begins as each trimer is occupied by one Ab. In BN-PAGE, neutralizing Fabs and sCD4 were able to shift JR-FL trimers, In contrast, most non-neutralizing Fabs, b6 in particular, bound to monomer, but their epitopes were conformationally occluded on trimers, confirming the exclusive relationship of trimer binding and neutralization. Crooks *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- b6: Five amino acids in the gp41 N-terminal region that promote gp140 trimerization (I535, Q543, S553, K567 and R588) were considered. Their influence on the function and antigenic properties of JR-FL Env expressed on the surfaces of pseudoviruses and Env-transfected cells was studied. Various non-neutralizing antibodies bind less strongly to the Env mutant, but neutralizing antibody binding is unaffected. b6 captured significantly fewer mutant pseudovirions than wild type, and b6 failed to inhibit infection by either pseudovirus. Dey *et al.* [2008] (**antibody binding site definition and exposure**, **binding affinity**)
- b6: Molecular mechanism of neutralization by MPER antibodies, 2F5 and 4E10, was studied using preparations of trimeric HIV-1 Env protein in the prefusion, the prehairpin intermediate and postfusion conformations. MAb b6 was used to analyze antigenic properties of construct 92UG-gp140-Fd, derived from isolate 92UG037.8 and stabilized by a C-terminal foldon tag. 92UG-gp140-Fd failed to bind b6, despite high affinity of b6 for 92UG-gp120 core. Frey *et al.* [2008] (**binding affinity**)
- b6: A series of peptide conjugates were constructed via click reaction of both aryl and alkyl acetylenes with an internally incorporated azidoproline 6 derived from parent peptide RINNIPWSEAMM. Many of these conjugates exhibited increase in both affinity for gp120 and inhibition potencies at both the CD4 and coreceptor binding sites. All high affinity peptides inhibited the interactions of YU2 gp120 with b6 Ab. The aromatic, hydrophobic, and steric features in the residue 6 side-chain were found important for the increased affinity and inhibition of the high-affinity peptides. Gopi *et al.* [2008]
- b6: Sera from gp120 DNA prime-protein boost immunized rabbits competed for binding to b6 while sera from rabbits immunized with protein-only regimen did not, indicating elicitation of b6-like Abs in animals immunized with DNA prime-protein boost regimen. Vaine *et al.* [2008] (**vaccine antigen design**)
- b6: SOSIP Env proteins are modified by the introduction of a disulfide bond between gp120 and gp41 (SOS), and an I559P (IP) substitution in gp41, and form trimers. The KNH1144 subtype A virus formed more stable trimers than did the prototype subtype B SOSIP Env, JRFL. The stability of gp140 trimers was increased for JR-FL and Ba-L SOSIP proteins by substituting the five amino acid residues in the N-terminal region of gp41 with corresponding residues from KNH1144 virus. b12, 2G12, 2F5, 4E10 and CD4-IgG2 all bound similarly to the WT and to the stabilized JRFL SOSIP timers, suggesting that the trimer-stabilizing substitutions do not impair the overall antigenic structure of gp140 trimers. 17b binding was induced similarly by CD4 for the WT and stabilized forms. Non-neutralizing MAbs PA-1 (V3) and b6 (CD4BS) bound less efficiently to the stabilized trimer. Dey *et al.* [2007a] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- b6: gp120 proteins with double mutation T257S+S375W, which alters the cavity at the epicenter of the CD4 binding region, had no effect on binding to b6 Ab. Dey *et al.* [2007b] (**binding affinity**)
- b6: G1 and G2 recombinant gp120 proteins, consisting of 2F5 and 4E10, and 4E10 epitopes, respectively, engrafted into the V1/V2 region of gp120, were tested as an immunogen to see if they could elicit MPER antibody responses. Deletion of V1/V2 from gp120 or its replacement with G1 and G2 grafts reduced the affinity for b6, however shortening of the N and

C termini of the V3 loop did not greatly affect binding. Law *et al.* [2007] (**vaccine antigen design**)

- b6: Molecules designed to eliminate binding by b6 while preserving epitopes of other neutralizing Abs are discussed. Lin & Nara [2007] (**review**)
- b6: This Ab was used to determine the degree to which fixation of gp120 in its CD4-bound conformation restricts antigenic recognition. b6 was not able to bind well to the stabilized gp120. Zhou *et al.* [2007] (**binding affinity**)
- b6: Macaques were immunized with SF162gp140, ΔV2gp140, ΔV2ΔV3gp140 and ΔV3gp140 constructs and their antibody responses were compared to the broadly reactive NAb responses in a macaque infected with SHIV SF162P4, and with pooled sera from humans infected with heterologous HIV-1 isolates (HIVIG). b6-like Abs were generated in the SHIV-infected macaque, and may have been present at very low titers in macaques immunized with ΔV2gp140 and ΔV2ΔV3gp140. No b6 Abs were detected in the sera from F162gp140 immunized animals. Derby *et al.* [2006] (**antibody binding site definition and exposure**, **antibody generation**)
- b6: In addition to gp120-gp41 trimers, HIV-1 particles were shown to bear nonfunctional gp120-gp41 monomers and gp120-depleted gp41 stumps on their surface. b6 did not neutralize wildtype virus but it was shown to bind to gp12-gp41 monomers. Monomer binding did not correlate with neutralization, but it did correlate with virus capture. b6 blocked b12 binding to monomeric Env but not to trimeric Env. It is hypothesized that the nonfunctional monomers on the HIV-1 surface serve to divert the Ab response helping it to avoid neutralization. Moore *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**)
- IgG1b6: JR-FL and YU2 HIV-1 strains were not neutralized by IgG1b6. IgG1b6 and other non-neutralizing Abs only recognized JR-FL cleavage-defective glycoproteins, while the neutralizing Abs (2G12 and IgG1b12) recognized both cleavage competent and cleavage-defective glycoproteins. It is suggested that an inefficient env glycoprotein precursor cleavage exposes non-neutralizing determinants, while only neutralizing regions remain accessible on efficiently cleaved spikes. For YU2, both cleavage-competent and -defective glycoproteins were recognized by both neutralizing and non-neutralizing Abs. IgG1b6, along with other Abs able to neutralize lab-adapted isolates, displayed enhanced viral entry at higher Ab concentrations, whereas the Abs that cannot neutralize any virus did not display such enhancement. Pancera & Wyatt [2005] (**antibody binding site definition and exposure**, **enhancing activity**, **neutralization**, **binding affinity**)
- b6: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. CD4BS MAbs except Fab b12 (b6, b3, F105) did not bind to either GDMR or mCHO. Selvarajah *et al.* [2005] (**vaccine antigen design**, **vaccine-specific epitope characteristics**)
- b6: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **review**)
- b6: 93 viruses from different clades were tested for their neutralization cross-reactivity using a panel of HIV antibodies. b6 was included as an example of a CD4BS antibody that is not strongly neutralizing, and it only was able to neutralize a few highly sensitive primary viruses and T-cell adapted viral strains that were B clade. Steric restrictions probably block its binding site in most isolates. Binley *et al.* [2004] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- b6: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including b6. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- b6: Alanine scanning mutagenesis was used to compare substitutions that affected anti-CD4BS NAb b12 binding to those that affect binding of sCD4 and two non-neutralizing anti-CD4BS Abs b3 and b6 – while the epitope maps overlapped, there were some differences observed – binding of CD4 was never enhanced, indicating it had evolved to be optimal – rec gp120s were engineered to contain combinations of Alanine substitutions that enhanced b12 binding, and while binding of b12 to these gp120 monomers was generally maintained or increased, binding by five non-neutralizing anti-CD4bs MAbs (b3, b6, F105, 15e, and F91) was reduced or completely abolished – 2G12 binding was largely unperturbed, indicating these proteins were not grossly misfolded. Pantophlet *et al.* [2003a]
- b6: A gp120 molecule was design to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- b6: Virion capture assays are not a good predictor of neutralization, and the presentation of epitopes using this assay seems to be different from that of functional Envelope spikes on primary isolates – F105 and b6 could efficiently block the b12-mediated capture of infectious virions in a virus capture, but did not inhibit b12 neutralization – while b12 was potent at neutralizing the three primary virions JR-CSF, ADA, and 89.6, the Abs F105, 19b, and Fab b6 were overall very poor neutralizers. Poignard *et al.* [2003]

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- b6: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- b6: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar. Enthalpy and entropy changes were divergent, but compensated. Not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs (17b, 48d, 1.5e, b6, F105 and F91) had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, but the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. The high values suggest surface burial or protein folding an ordering of amino acids. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- b6: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- b6: Neutralizes TCLA strains, but not primary isolates. Parren *et al.* [1997b]

No. 1431
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein, virus-like particle (VLP) *Strain:* B clade LAI *HIV component:* CD4BS, Gag, V3
Species (Isotype) mouse
Ab Type gp120 CD4BS
References Truong *et al.* 1996

- Antibodies raised against recombinant anti-p55 virus-like particles with the p24 region 196-226 deleted, bearing inserts of either the V3 or the CD4BS regions of gp120 were studied – no neutralizing responses, weak Env and strong Gag responses were elicited – the major homology region (MHR) and proximal sequences was found to be required for capsid assembly. Truong *et al.* [1996]

No. 1432
MAb ID
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing yes
Immunogen
Species (Isotype) human
Ab Type gp120 CD4BS, gp120 CD4i, gp120 V2, gp120 V3
References Moore *et al.* 2001

- Moore and colleagues review structural aspects of gp120 and how they relate to antigenic domains, and review the data concerning the lack of a clear relationship between genetic subtype and serotype – they suggest the primary goal in vaccine efforts should be to design an immunogen that can be shown to elicit neutralizing antibodies against a significant proportion of primary isolates – assay artifacts that can result in confused interpretations are also discussed, such as Ab binding to defective spikes, which does not affect HIV-1 infectivity, but can dominant an assay signal. Moore *et al.* [2001]

No. 1433
MAb ID 17b (1.7b, sCD4-17b)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L P (wea
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4i, gp120 CCR5BS
Research Contact James Robinson, Tulane University, New Orleans, LA, USA
References Wu *et al.* 2008; Willey & Aasa-Chapman 2008; van Montfort *et al.* 2008; Taylor *et al.* 2008; Stricher *et al.* 2008; Srivastava *et al.* 2008; Pugach *et al.* 2008; Peters *et al.* 2008b; Martin *et al.* 2008; Liu *et al.* 2008; Keele *et al.* 2008; Gopi *et al.* 2008; Forsman *et al.* 2008; Dey *et al.* 2008; Frey *et al.* 2008; Forsell *et al.* 2008; Yuan *et al.* 2006; Pantophlet & Burton 2006; Yoshimura *et al.* 2006; Rits-Volloch *et al.* 2006; Sharma *et al.* 2006; Lam *et al.* 2006; Zhou *et al.* 2007; van Montfort *et al.* 2007; Shibata *et al.* 2007; Wang *et al.* 2007a; Phogat *et al.* 2007; McKnight & Aasa-Chapman 2007; McFadden *et al.* 2007; Lin & Nara 2007; Laakso *et al.* 2007; Huang *et al.* 2007b; Kramer *et al.* 2007; Kothe *et al.* 2007; Hu *et al.* 2007; Gao *et al.* 2007; Dunfee *et al.* 2007; DeVico *et al.* 2007; Dey *et al.* 2007b; Dey *et al.*

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2007a; Choudhry *et al.* 2007; Billington *et al.* 2007; Vu *et al.* 2006; Liao *et al.* 2006; Holl *et al.* 2006a; Dorfman *et al.* 2006; Derby *et al.* 2006; Cham *et al.* 2006; Choudhry *et al.* 2006; Binley *et al.* 2006; Yuan *et al.* 2005; Yang *et al.* 2005c; Varadarajan *et al.* 2005; Tuen *et al.* 2005; Teeraputon *et al.* 2005; Stanfield & Wilson 2005; Srivastava *et al.* 2005; Selvarajah *et al.* 2005; Robinson *et al.* 2005; Reeves *et al.* 2005; Pancera *et al.* 2005; Pancera & Wyatt 2005; Mc Cann *et al.* 2005; Martín-García *et al.* 2005; Lusso *et al.* 2005; Koefoed *et al.* 2005; Kang *et al.* 2005; Kalia *et al.* 2005; Huang *et al.* 2005a; Haynes *et al.* 2005a; Gao *et al.* 2005a; Burton *et al.* 2005; Pinter *et al.* 2004; Pantophlet *et al.* 2004; Nabatov *et al.* 2004; McCaffrey *et al.* 2004; Ling *et al.* 2004; Liao *et al.* 2004; Biorn *et al.* 2004; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Zhu *et al.* 2003; Ohagen *et al.* 2003; Xiang *et al.* 2003; Labrijn *et al.* 2003; Enshell-Seijffers *et al.* 2003; Dey *et al.* 2003; Choe *et al.* 2003; Cavacini *et al.* 2003; Binley *et al.* 2003; He *et al.* 2003; Ling *et al.* 2002; Finnegan *et al.* 2002; Cavacini *et al.* 2002; Arthos *et al.* 2002; Zhang *et al.* 2002; Basmaciogullari *et al.* 2002; Grundner *et al.* 2002; Edwards *et al.* 2002; Xiang *et al.* 2002a; Xiang *et al.* 2002b; Dowd *et al.* 2002; Yang *et al.* 2002; Schulke *et al.* 2002; Golding *et al.* 2002b; Srivastava *et al.* 2002; Kwong *et al.* 2002; Finnegan *et al.* 2001; Poignard *et al.* 2001; Zhang *et al.* 2001a; York *et al.* 2001; Kolchinsky *et al.* 2001; Si *et al.* 2001; Rizzuto & Sodroski 2000; Yang *et al.* 2000; Stamatatos *et al.* 2000; Salzwedel *et al.* 2000; Park *et al.* 2000; Ly & Stamatatos 2000; Grovit-Ferbas *et al.* 2000; Binley *et al.* 1999; Hoffman *et al.* 1999; Oscherwitz *et al.* 1999a; Stamatatos & Cheng-Mayer 1998; Binley *et al.* 1998; Sullivan *et al.* 1998a; Sullivan *et al.* 1998b; Rizzuto *et al.* 1998; Moore & Binley 1998; Wyatt *et al.* 1998; Kwong *et al.* 1998; Parren *et al.* 1997b; Wyatt *et al.* 1997; Cao *et al.* 1997b; Ditzel *et al.* 1997; Weinberg *et al.* 1997; Li *et al.* 1997; Fouts *et al.* 1997; Binley *et al.* 1997a; Trkola *et al.* 1996a; Wu *et al.* 1996; Poignard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; Wyatt *et al.* 1995; Beretta & Dalgleish 1994; Thali *et al.* 1994; Moore *et al.* 1993c; Thali *et al.* 1993

Keywords acute/early infection, antibody binding site definition and exposure, antibody generation, antibody interactions, assay development, assay standardization/improvement, binding affinity, brain/CSF, co-receptor, computational epitope prediction, dendritic cells, drug resistance, enhancing activity, escape, HAART, ART, immunoprophylaxis, immunotherapy, kinetics, mimotopes, neutralization, review, structure, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- 17b database comment: 48d and 17b have similar epitopes, and the pair are unique among human and rodent MAbs. (**antibody binding site definition and exposure**)
- 17b: NIH AIDS Research and Reference Reagent Program: 4091.
- 17b: Five amino acids in the gp41 N-terminal region that promote gp140 trimerization (I535, Q543, S553, K567 and R588) were considered. Their influence on the function and antigenic properties of JR-FL Env expressed on the surfaces of pseudoviruses and Env-transfected cells was studied. Various non-neutralizing antibodies bind less strongly to the Env mutant, but neutralizing antibody binding is unaffected. 17b captured both pseuduvirion preparations weakly in the absence of sCD4, but its binding was increased when sCD4 was also present. 17b failed to inhibit infection by either pseudovirus. Dey *et al.* [2008] (**binding affinity**)
- 17b: Requirements for elicitation of CD4i Abs were examined by immunizing non-primate monkeys, rabbits, and human-CD4 transgenic (huCD4) rabbits with trimeric gp140. The trimers were well recognized by 17b in the absence of CD4 but the relative binding affinity increased 2-5-fold in the presence of sCD4. The avidity of the trimers for 17b in the absence of CD4 was determined to be in the low nanomolar range. Sera from immunized monkeys were able to inhibit 17b binding at a 10-fold higher dilution than sera from immunized rabbits. 17b could bind to the gp140 trimers bound to cell-surface CD4 as well, confirming that the co-receptor site is accessible after trimer binding to membrane-bound CD4. Forsell *et al.* [2008] (**antibody binding site definition and exposure**, **binding affinity**)
- 17b: Variable domains of three heavy chain Abs, the VHH, were characterized. The Abs were isolated from llamas, who produce immunoglobulins devoid of light chains, immunized with HIV-1 CRF07_BC, to gp120. It was hypothesized that the small size of the VHH, in combination with their protruding CDR3 loops, and their preference for cleft recognition and binding into active sites, may allow for recognition of conserved motifs on gp120 that are occluded from conventional Abs.17b provided some inhibition of binding of the three neutralizing VHH Abs to gp120, suggesting that 17b imposes steric hinderance to binding of the VHH Abs to gp120. Forsman *et al.* [2008] (**antibody interactions**)
- 17b: Molecular mechanism of neutralization by MPER antibodies, 2F5 and 4E10, was studied using preparations of trimeric HIV-1 Env protein in the prefusion, the prehairpin intermediate and postfusion conformations. MAb 17b was used to analyze antigenic properties of construct 92UG-gp140-Fd, derived from isolate 92UG037.8 and stabilized by a C-terminal foldon tag. Uncleaved 92UG-gp140-Fd binds 17b, but only in the presence of CD4. Frey *et al.* [2008] (**binding affinity**)

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- 17b: A series of peptide conjugates were constructed via click reaction of both aryl and alkyl acetylenes with an internally incorporated azidoproline 6 derived from parent peptide RINNIPWSEAMM. Many of these conjugates exhibited increase in both affinity for gp120 and inhibition potencies at both the CD4 and coreceptor binding sites. All high affinity peptides inhibited the interactions of YU2 gp120 with 17b Ab. Inhibition was found to be concentration-dependent. The aromatic, hydrophobic, and steric features in the residue 6 side-chain were found important for the increased affinity and inhibition of the high-affinity peptides. No inhibition of gp120 binding to 17b was observed for position 7 homoalanine-derived conjugates. Gopi *et al.* [2008]
- 17b: A mathematical model was developed and used to derive transmitted or founder Env sequences from individuals with acute HIV-1 subtype B infection. All of the transmitted or early founder Envs were resistant to neutralization by 17b, while Envs from three chronically infected patients were unusually sensitive to neutralization by 17b. This indicated that the coreceptor binding surfaces on transmitted/founder Envs are conformationally masked. Keele *et al.* [2008] (**neutralization**, **acute/early infection**)
- 17b: Three-dimensional structures of trimeric Env displayed on native HIV-1 in complex with CD4 and the Fab fragment of 17b were compared to the unligated state, using cryo-electron tomography combined with three-dimensional image classification and averaging. Binding of 17b and CD4 resulted in dramatic conformational changes, including lever-like opening of the trimer. Binding of CD4 made way for exposure of gp41 stalk, and the V3 region was released from the lateral edge of the spike to point towards the target cell. V1/V2 and CD4 binding site moved away from the centre of the spike. Liu *et al.* [2008] (**antibody binding site definition and exposure**, **structure**)
- 17b: A new purification method was developed using a high affinity peptide mimicking CD4 as a ligand in affinity chromatography. This allowed the separation in one step of HIV envelope monomer from cell supernatant and capture of pre-purified trimer. Binding of 17b to gp120SF162 purified by the miniCD4 affinity chromatography and a multistep method was comparable, suggesting that the miniCD4 allows the separation of HIV-1 envelope with intact 17b epitope. gp140DF162ΔV2 was purified by the miniCD4 method to asses its ability to capture gp140 trimers. Binding of 17b to gp140DF162ΔV2 purified by the miniCD4 affinity chromatography and a multi-step method was comparable, suggesting that the SF162 trimer antigenicity was preserved. Martin *et al.* [2008] (**assay development**, **binding affinity**)
- 1.7b: Transmission of HIV-1 by immature and mature DCs to CD4+ T lymphocytes was significantly higher for CXCR4- than for CCR5-tropic strains. Preneutralization of R5 virus with 1.7b prior to capture efficiently blocked transmission to 44%, while preineutralization of X4 virus with 1.7b had no effect, indicating that 1.7b treatment results in more efficient transfer of X4 than of R5 HIV-1. van Montfort *et al.* [2008] (**co-receptor**, **neutralization**, **dendritic cells**)
- 17b: The sensitivity of R5 envelopes derived from several patients and sevaral tissue sites, including brain tissue, lymph nodes, blood, and semen, was tested to a range of inhibitors and Abs targeting CD4, CCR5, and various sites on the HIV envelope. All but one envelopes from brain tissue were macrophage-tropic while none of the envelopes from the lymph nodes were macrophage-tropic. Macrophage-tropic envelopes were also less frequent in blood and semen. None of the patient evnelopes were inhibited by 17b, indicating that 17b epitope is not more exposed on macrophage-tropic envelopes than on non-macrophage tropic ones. Peters *et al.* [2008b] (**neutralization**)
- 17b: In order to assess whether small molecule CCR5 inhibitor resistant viruses were more sensitive to neutralization by NAbs, two escape mutant viruses, CC101.19 and D1/85.16, were tested for their sensitivity to neutralization by 17b, compared to the sensitivity of CC1/85 parental isolate and the CCcon.19 control isolate. The CC101.19 escape mutant has 4 sequence changes in V3 while the D1/85.16 has no sequence changes in V3 and relies on other sequence changes for its resistance. None of the control or resistant viruses were sensitive to neutralization by 17b. Pugach *et al.* [2008] (**co-receptor**, **neutralization**)
- 17b: Trimeric envelope glycoproteins with a partial deletion of the V2 loop derived from subtype B SF162 and subtype C TV1 were compared. The magnitude of 17b binding to subtype C trimer was lower than to subtype B trimer, either in the presence or absence of CD4. However, the fold increase in binding of 17b in presence of CD4 was similar for both subtypes, indicating similar structural rearrangements. Subtype C trimer had many biophysical, biochemical, and immunological characteristics similar to subtype B trimer, except for a difference in the three binding sites for CD4, which showed cooperativity of CD4 binding in subtype C but not in subtype B. Srivastava *et al.* [2008] (**binding affinity**, **subtype comparisons**)
- 17b: Crystal structures of CD4M47 (a derivative of a synthetic miniprotein with HIV-1 gp120 binding surface of the CD4 receptor incorporated) and a phenylalanine variant ((Phe23)M47) were determined in ternary complexes with HIV-1 gp120 and 17b Ab. The structures revealed correlation between mimetic affinity of the miniprotein for gp120 and overall mimetic-gp120 interactive surface. Stricher *et al.* [2008] (**structure**)
- 17b: An R5 HIV variant, in contrast to its parental virus, was shown to infect T-cell lines expressing low levels of cell surface CCR5 and to infect cells in the absence of CD4. The variant was seven-fold more sensitive to neutralization by 17b than the parental virus, indicating that the CCR5 binding site of gp120 is partially exposed on the mutant virus without prior binding to CD4. These properties of the mutant virus were determined by alternations in gp41. Taylor *et al.* [2008] (**co-receptor**, **neutralization**)
- 17b: The various effects that neutralizing and non-neutralizing anti-envelope Abs have on HIV infection are reviewed, such as Ab-mediated complement activation and Fc-receptor mediated activities, that both can, through various mechanisms, increase and decrease the infectivity of the virus. The importance of these mechanisms in vaccine design is discussed. The unusual features of the 17b MAb are described. Willey & Aasa-Chapman [2008] (**review**)

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- 17b: Neutralization of JRFL, ADA, and YU2 isolates by 17b increased only modestly with increased dose of sCD4, and was never above 50%, indicating that the dose of sCD4, although enough to expose the V3 region, was insufficient to induce full conformational exposure of the co-receptor binding site. Wu *et al.* [2008] (**neutralization**)
- 17b: This Ab was found to be able to bind to a highly stable trimeric rgp140 derived from a HIV-1 subtype D isolate containing intermonomer V3-derived disulfide bonds and lacking gp120/gp41 cleavage. Protein disulfide isomerase treatment of rgp120 and rgp140 was found to severely inhibit binding of 17b, suggesting a structural need for V3-derived disulfide bonds in coreceptor binding. gp140 binding to 17b was 2-fold enhanced with by sCD4, indicating the proteolytically immature protein was able to undergo CD4i conformational changes. Billington *et al.* [2007] (**antibody binding site definition and exposure**, **co-receptor**, **vaccine antigen design**)
- 17b: Macaques were immunized with either CD4, gp120, cross-linked gp120-human CD4 complex (gp120-CD4 XL), and with single chain complex containing gp120 rhesus macaque CD4 domains 1 and 2 (rhFLSC). Sera from the rhFLSC immunized animals showed highest competition titers, being able to block gp120-CD4 complex interactions with 17b more efficiently than sera from animals immunized with the three other proteins. DeVico *et al.* [2007] (**neutralization**)
- 17b: SOSIP Env proteins are modified by the introduction of a disulfide bond between gp120 and gp41 (SOS), and an I559P (IP) substitution in gp41, and form trimers. The KNH1144 subtype A virus formed more stable trimers than did the prototype subtype B SOSIP Env, JRFL. The stability of gp140 trimers was increased for JR-FL and Ba-L SOSIP proteins by substituting the five amino acid residues in the N-terminal region of gp41 with corresponding residues from KNH1144 virus. b12, 2G12, 2F5, 4E10 and CD4-IgG2 all bound similarly to the WT and to the stabilized JRFL SOSIP timers, suggesting that the trimer-stabilizing substitutions do not impair the overall antigenic structure of gp140 trimers. 17b binding was induced similarly by sCD4 in the WT and stabilized forms. Non-neutralizing MAbs PA-1 and b6 bound less efficiently to the stabilized trimer. Dey *et al.* [2007a] (**vaccine antigen design**)
- 17b: gp120 proteins with double mutation T257S+S375W, which alters the cavity at the epicenter of the CD4 binding region, showed a weak interaction with 17b in the absence of CD4 and efficient interaction with maximal 17b binding in the presence of 17b. Similar results were observed with unmodified gp120, indicating that although properly folded, the mutant proteins were not completely stabilized in the CD4-bound conformation by the two mutations.The gp120 proteins with double mutation T257S+S375W were used to immunize rabbits. The ability of rabbit sera to affect binding of CD4 to unmodified gp120 proteins was tested. CD4 binding to gp120 was enhanced by 17b. Dey *et al.* [2007b] (**binding affinity**)
- 17b: A D386N change in the V4 region, which results in restoration of N-glycosylation at this site, did not have any impact on the neutralization of a mutant virus by 17b compared to wildtype. Also, there was no association between increased sensitivity to 17b neutralization and enhanced macrophage tropism. Dunfee *et al.* [2007] (**neutralization**)
- 17b: This review summarizes data on the development of HIV-1 centralized genes (consensus and ancestral) for induction of neutralizing antibody responses. Functionality and conformation of native epitopes in proteins based on the centralized genes was tested and confirmed by binding to 17b and other MAbs. Binding of 17b following CD4 also indicated presence of functionally relevant conformational changes of the proteins. Gao *et al.* [2007] (**review**)
- 17b: HIV-1 env clones resistant to cyanovirin (CV-N), a carbohydrate binding agent, showed amino acid changes that resulted in deglycosylation of high-mannose type residues in the C2-C4 region of gp120. Compared to their parental virus HIV-1 IIIB, these resistant viruses maintained similar sensitivity to 17b, as the glycan at position 301 in the V3 loop was intact. Hu *et al.* [2007] (**neutralization**, **escape**)
- 17b: The small molecule HIV-1 entry inhibitor IC9564 significantly enhanced binding of 17b Ab to gp120 on cell surface and on viral particles. The binding was independent of the presence of soluble CD4 suggesting that IC9564 induces conformational change in gp120 that exposes the concealed 17b epitope. Significant increase in neutralizing activity of 17b in the presence of IC9564 was observed for NLDH120 and NL4-3 virus strains. In contrast to CD4, IC9564 does not induce a conformational change in gp41, and inhibits CD4-induced gp41 conformational changes. Huang *et al.* [2007b] (**antibody binding site definition and exposure**)
- 17b: Four consensus B Env constructs: full length gp160, uncleaved gp160, truncated gp145, and N-linked glycosylation-site deleted (gp160-201N/S) were compared. All were packaged into virions, and all but the fusion defective uncleaved version mediated infection using the CCR5 co-receptor. CD4 inducible MAbs 17b and E51 were tested for the ability to neutralize the various forms of Con B; as anticipated gp160 and gp145 were not neutralized by these two MAbs, but the gp160-201N/S mutant was neutralized with IC50 values of 10 ug/ml, suggesting increased formation and/or exposure of the co-receptor binding site. The poorly infectious clone WITO4160.27 was also somewhat susceptible to neutralization by these clones. Kothe *et al.* [2007] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**)
- 17b: This review summarizes 17b Ab epitope, properties and neutralization activity. The effect of differential CCR5 cell surface expression on 17b neutralization activity is discussed. Kramer *et al.* [2007] (**co-receptor**, **neutralization**, **review**)
- 17b: V3 loop deletions were introduced into three different primary HIV-1 strains: R3A, DH12, and TYBE. The deletions included: ΔV3(12,12) containing the first and the last 12 residues of the V3 loop, ΔV3(9,9) containing first and last 9 residues, and ΔV3(6,6) ontaining first and last 6 residues. Only HIV-1 R3A ΔV3(9,9) was able to support cell fusion. Passaging of this virus resulted in a virus strain (TA1) that replicated with wildtype kinetics, and that acquired several adaptive changes in gp120 and gp41 while retaining the V3 loop truncation. 17b neutralized a ΔV1/V2 virus but failed to neutralize R3A or LAI. TA1 was 100-fold more sensitive to neutralization by 17b than the ΔV1/V2 virus. Laakso *et al.* [2007] (**neutralization**)

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- 17b: 17b structure, binding, neutralization, and strategies that can be used for vaccine antigen design to elicit 17b-like Abs, are reviewed in detail. Lin & Nara [2007] (**review**, **structure**)
- 17b: A chimeric protein entry inhibitor, L5, was designed consisting of an allosteric peptide inhibitor 12p1 and a carbohydrate-binding protein cyanovirin (CNV) connected via a flexible linker. The L5 chimera inhibited 17b-gp120 interaction, but the CNV alone had a limited effect, indicating that the chimera has the high affinity binding property of the CNV molecule and the inhibitory property of the 12p1 peptide. McFadden *et al.* [2007]
- 17b: This review summarizes data on possible vaccine targets for elicitation of neutralizing Abs and discusses whether it is more practical to design a clade-specific than a clade-generic HIV-1 vaccine. Development of a neutralizing Ab response in HIV-1 infected individuals is reviewed, including data that show no apparent division of different HIV-1 subtypes into clade-related neutralization groups. The neutralizing activity of CD4i Abs, such as 17b, is discussed. McKnight & Aasa-Chapman [2007] (**review**)
- 1.7b: 1.7b-neutralized HIV-1 captured on Raji-DC-SIGN cells or immature monocyte-derived DCs (iMDDCs) was successfully transfered to CD4+ T lymphocytes, indicating that the 1.7b-HIV-1 complex was disassembled upon capture by DC-SIGN-cells. van Montfort *et al.* [2007] (**neutralization**, **dendritic cells**)
- 17b: This review provides information on the HIV-1 glycoprotein properties that make it challenging to target with neutralizing Abs. 17b neutralization properties and binding to HIV-1 envelope, and current strategies to develop versions of the Env spike with functional trimer properties for elicitation of broadly neutralizing Abs, are discussed. In addition, approaches to target cellular molecules, such as CD4, CCR5, CXCR4, and MHC molecules, with therapeutic Abs are reviewed. Phogat *et al.* [2007] (**review**)
- 17b: Viruses with V2 mutations R166K, D167N and P175L were resistant to 17b and a reduction of binding 17b to these viral variants was observed. Shibata *et al.* [2007] (**escape**, **binding affinity**)
- 17b: Chimeric VLPs, containing chimeric Con-S ΔCFI Env proteins with heterologous signal peptide (SP), transmembrane (TM), and cytoplasmic tail (CT) sequences, were all induced to bind to 17b after binding to CD4, indicating that chimeric Envs in VLPs undergo conformational changes induced by CD4. Wang *et al.* [2007a] (**antibody binding site definition and exposure**, **vaccine antigen design**, **binding affinity**)
- 17b: This Ab bound to the Fc-gp120 construct, but only weakly to the chimeras lacking the V3 loop. sCD4 restored high affinity binding to all constructs. Binley *et al.* [2006] (**binding affinity**)
- 17b: Cloned Envs (clades A, B, C, D, F1, CRF01_AE, CRF02_AG, CRF06_cpx and CRF11_cpx) derived from donors either with or without broadly cross-reactive neutralizing antibodies were shown to be of comparable susceptibility to neutralization by 17b. Cham *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 17b: Neutralization of HIV-1 primary isolates from clade B by different formats of 17b was determined in cells expressing high or low surface concentrations of CD4 and CCR5 receptors. CD4 cell surface concentration had no effect on the inhibitory activity of this Ab while the CCR5 surface concentration had a significant effect decreasing the 50% inhibitory concentration of 17b in cell lines with low CCR5. Choudhry *et al.* [2006] (**co-receptor**, **neutralization**, **variant cross-recognition or cross-neutralization**)
- 17b: Macaques were immunized with SF162gp140, ΔV2gp140, ΔV2ΔV3gp140 and ΔV3gp140 constructs and their antibody responses were compared to the broadly reactive NAb responses in a macaque infected with SHIV SF162P4, and with pooled sera from humans infected with heterologous HIV-1 isolates (HIVIG). 17b bound to SF162gp140 and ΔV3gp140 more efficiently than to ΔV2gp140 and ΔV2ΔV3gp140. The neutralization of SF162 by 17b was enhanced in a concentration-dependent manner by pre-incubation with sCD4. Derby *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**)
- 17b: The CDR3 regions of CD4i Abs (E51, 412d, 17b, C12 and 47e) were cloned onto human IgG1 and tested for their ability to inhibit CCR5 binding. Only E51 successfully immunoprecipitated gp120. Dorfman *et al.* [2006] (**co-receptor**)
- 1.7b: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 17b: This Ab was used in a microcantilever deflection assay to detect gp120 from solution. Deflection twice that of the baseline that was detected upon specific binding of gp120 to cantilevers decorated on one side with A32 was further increased by subsequent incubation with 17b. Lam *et al.* [2006] (**assay development**, **assay standardization/improvement**)
- 17b: The gp140δCFI protein of CON-S M group consensus protein and gp140CFI and gp140CF proteins of CON6 and WT viruses from HIV-1 subtypes A, B and C were expressed in recombinant vaccinia viruses and tested as immunogens in guinea pigs. Both CD4 induced and A32 induced 17b was shown to bind specifically to all recombinant proteins except for the gp140δFI derived from subtype C virus. This Ab also bound specifically to one of the two tested subtype B gp120 proteins. The specific binding of his Ab to CON-S indicated that its conformational epitope was intact. Liao *et al.* [2006] (**antibody binding site definition and exposure**, **vaccine antigen design**, **subtype comparisons**)
- 17b: The neutralizing activity of coreceptor-binding site Abs, such as 17b, is reviewed. Pantophlet & Burton [2006] (**antibody binding site definition and exposure**, **neutralization**)
- 17b: Binding of 17b in the presence or absence of CD4 to wt gp120 and two constructs with 5 and 9 residues deleted in the middle of the beta3-beta5 loop in the C2 region of gp120 was examined. In concordance with previous studies, 17b did not bind wt gp120 in absence of CD4 but did bind it in the presence of CD4. In contrast, the two deletion constructs did not bind 17b regardless of presence or absence of CD4 indicating that the loop-deleted gp120 is unable to close up the bridging sheet and display the coreceptor site and the 17b epitope.

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Rits-Volloch *et al.* [2006] (**antibody binding site definition and exposure**, **binding affinity**)

- 17b: gp120 (monomer), gp120deltaV2 (trimer), gp140 (monomer) and gp140deltaV2 (trimer) from subtype B SF162 were expressed in cells and their affinity for 17b was assessed. All four Envs bound to 17b in the absence of CD4 but the monomers showed 3-fold higher affinity for this Ab than trimers. In the presence of CD4, the 17b epitope was upregulated in all Envs. Sharma *et al.* [2006] (**antibody binding site definition and exposure**, **binding affinity**)
- 17b: A fusion protein (FLSC R/T-IgG1) that targets CCR5 was expressed from a synthetic gene linking a single chain gp120-CD4 complex containing an R5 gp120 sequence with the hinge-Ch2-Ch3 portion of human IgG1. Binding of this protein to the CCR5 co-receptor was inhibited by MAb 17b in a dose-dependent manner. The fusion protein did not activate the co-receptor by binding, and it potently neutralized primary R5 HIV-1. Vu *et al.* [2006] (**co-receptor**)
- 17b: The G314E escape variant highly resistant to KD-247 was shown to be more sensitive to 17b Ab than the wildtype virus. 17b was shown to be able to bind and neutralize the escape virus even in the abscence of rsCD4 while rsCD4 was necessary for binding of 17b to the wildtype virus, indicating that the G314E mutation induces the expression of epitopes for Abs against CD4i epitope and V3 loop. Yoshimura *et al.* [2006] (**neutralization**, **escape**, **binding affinity**)
- 17b: Interactions of this Ab with gp120 monomer and two cleavage-defective gp140 trimers were studied. It was shown that 17b interactions with the soluble monomers and trimers were dramatically decreased by GA cross-linking of the proteins, indicating that the 17b epitope was affected by cross-linking. This Ab was associated with a large entropy change upon gp120 binding. 17b was shown to have a kinetic disadvantage as it bound to gp120 much slower than the highly neutralizing Abs 2G12 and IgG1b12. Yuan *et al.* [2006] (**antibody binding site definition and exposure**, **antibody interactions**, **kinetics**, **binding affinity**)
- 17b: The structure of the 17b MAb, particularly its CDRH3 region tyrosine sulfation, is reviewed. Also, the mechanism of its binding to the coreceptor binding site of gp120, and comparisons of the neutralizing potencies of 17b Ab fragments vs the whole IgG molecule are discussed. Engineering of Abs based on revealed structures of broadly neutralizing MAbs is discussed. Burton *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **review**, **structure**)
- 17b: Monomeric gp120 and trimeric gp140CF proteins synthesized from an artificial group M consensus Env gene (CON6) did not bind to 17b directly, but bound to it following binding to sCD4 and A32, indicating correct conformational change and subsequent exposure of the 17b epitope. Gao *et al.* [2005a] (**antibody binding site definition and exposure**, **binding affinity**)
- 17b: Called 1.7B. Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 1.7B has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)
- 17b: The structure of the V3 region in the context of gp120 core complexed to the CD4 receptor and to the 17b Ab was attempted to be determined by X-ray resolution, but only the structure for V3 complexed with CD4 and X5 Ab was solved. Accessibility of the co-receptor binding site to this MAb is shown in a 3D figure. Huang *et al.* [2005a] (**antibody binding site definition and exposure**, **structure**)
- 17b: Point mutations in the highly conserved structural motif LLP-2 within the intracytoplasmic tail of gp41 resulted in conformational alternations of both gp41 and gp120. The alternations did not affect virus CD4 binding, coreceptor binding site exposure, or infectivity of the virus, but did result in decreased binding and neutralization by certain MAbs and human sera. 17b exhibited similar levels of binding to both the LLP-2 mutant and wildtype viruses, indicating that sCD4 binding to the LLP-2 mutant successfully triggered conformational change of gp120 and exposure of the co-receptor binding site. Kalia *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)
- 17b: A series of genetically modified Env proteins were generated and expressed in both insect and animal cells to be monitored for their antigenic characteristics. For 17b, three of the modified proteins expressed in insect cells, including dV1V2 mutant (V1V2 deletions) followed by 3G-dV2-1G mutant (3G being mutations in three glycosylation sites and 1G being a mutation near the TM domain) and 3G-dV2 mutant, showed higher binding to the Ab than the wildtype did. This indicated that the dV1V2 mutant may expose 17b epitope better than the other Env proteins. When expressed in animal cells, only mutants 3G and dV2 showed enhanced binding to 17b but only at high concentrations of the MAb. Kang *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)
- 17b: IgG antibody phage display libraries were created from HIV-1 + individuals after pre-selection of PBMC with gp120, as an alternative to using bone marrow for generating libraries. 17b was among a set of Abs used for competition studies to define the binding sites of the newly isolated MAbs, representing a MAb with a CD4i epitope. Koefoed *et al.* [2005]
- 17b: The epitope for the MAb D19 is conserved and embedded in V3. D19 is unique in that for R5 viruses, it was cryptic and did not bind without exposure to sCD4, and for X4 and R5X4 isolates it was constitutively exposed. D19b is unqiue among CD4i antibodies in that it binds to the V3 loop. CD4i MAbs 17b and 48d were used as controls for CD4i characterization; in contrast to D19, other CD4i MAbs bind to the conserved bridging sheet and do not differentiate between R5 and X4 using strains. 17b, like D19, was able to neutralize the BaL isolate only in combination with sCD4. Lusso *et al.* [2005]
- 17b: The HIV-1 Bori-15 variant was adapted from the Bori isolate for replication microglial cells. Bori-15 had increased replication in microglial cells and a robust syncytium-forming phenotype, ability to use low levels of CD4 for infection, and increased sensitivity to neutralization by sCD4 and 17b. Four amino acid changes in gp120 V1-V2 were responsible for this change. Protein functionality and integrity of soluble, monomeric gp120-molecules derived from parental HIV-1

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Bori and microglia-adapted HIV-1 Bori-15 was assessed in ELISA binding assays using F105, IgG1b12, 17b and 48d, 2G12 and 447-52D. Association rates of sCD4 and 17b were not changed, but dissociation rates were 3-fold slower for sCD4 and 14-fold slower for 17b. Martín-García *et al.* [2005]

- 17b: R-FL and YU2 HIV-1 strains were not neutralized by 17b.17b and other non-neutralizing Abs only recognized JR-FL cleavage-defective glycoproteins, while the neutralizing Abs (2G12 and IgG1b12) recognized both cleavage competent and cleavage-defective glycoproteins. It is suggested that an inefficient env glycoprotein precursor cleavage exposes non-neutralizing determinants, while only neutralizing regions remain accessible on efficiently cleaved spikes. For YU2, both cleavage-competent and -defective glycoproteins were recognized by both neutralizing and non-neutralizing Abs.17b, along with other Abs able to neutralize lab-adapted isolates, displayed enhanced viral entry at higher Ab concentrations, whereas the Abs that cannot neutralize any virus did not display such enhancement. Pancera & Wyatt [2005] (**antibody binding site definition and exposure**, **enhancing activity**, **neutralization**, **binding affinity**)
- 17b: A stable trimerization motif, GCN4, was appended to the C terminus of YU2gp120 to obtain stable gp120 trimers (gp120-GCN4). Each trimer subunit was capable of binding IgG1b12, indicating that they were at least 85% active. D457V mutation in the CD4 binding site resulted in a decreased affinity of the gp120-GCN4 trimers for CD4 and for 17b. Both the CNG-gp120 trimers and the D457V mutants showed a restricted stochiometry to 17b of one Ab molecule binding per trimer. Removal of the V1-V2 loops resulted in binding of three 17b molecules per trimer. Pancera *et al.* [2005] (**binding affinity**, **structure**)
- 17b: Escape mutations in HR1 of gp41 that confer resistance to Enfuvirtide reduced infection and fusion efficiency and also delayed fusion kinetics of HIV-1. The mutations also conferred increased neutralization sensitivity of virus to 17b. Enhanced neutralization correlated with reduced fusion kinetics, indicating that the mutations result in Env proteins remaining in the CD4-triggered state for a longer period of time. Reeves *et al.* [2005] (**antibody binding site definition and exposure**, **drug resistance**, **neutralization**, **escape**, **HAART, ART**)
- 17b: A reverse capture assay was developed to asses what kind of human MAbs were produced in EBV B-cell transformation assays performed on PBMC sampled at different timepoints from three HIV-1 infected patients on HAART. The reverse capture assay was validated by the solid phase MAbs that could not capture biotin-MAbs of the same or overlapping specificity when reacted with patient virus envelope glycoproteins preincubated with or without sCD4. Reverse capture assay showed that the produced Abs from the patients were able to block binding of biotin-labeled 17b, indicating presence of CD4i Abs. These were the most frequently produced Abs from all three patients, suggesting that CD4i epitopes are much more immunogenic than previously appreciated. Robinson *et al.* [2005] (**antibody generation**, **assay development**, **HAART, ART**)
- 17b: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. CD4i MAbs (48d, 17b) did not bind to either GDMR or mCHO even with sCD4. Selvarajah *et al.* [2005] (**vaccine antigen design**, **vaccine-specific epitope characteristics**)
- 17b: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **review**, **structure**)
- 17b: This review summarizes data on 447-52D and 2219 crystallographic structures when bound to V3 peptides and their corresponding neutralization capabilities. 17b, like 447-52D and like other HIV-1 neutralizing Abs, was shown to have long CDR H3 loop, which is suggested to help Abs access recessed binding sites on the virus. Stanfield & Wilson [2005] (**antibody binding site definition and exposure**, **review**, **structure**)
- 17b: A T-cell line adapted strain (TCLA) of CRF01_AE primary isolate DA5 (PI) was more neutralization sensitive to 17b than the primary isolate. Mutant virus derived from the CRF01_AE PI strain, that lacked N-linked glycosylation at position 197 in the C2 region of gp120, was significantly more sensitive to neutralization by 17b then the PI strain. Deglycosylated subtype B mutants at positions 197 and 234 were slightly more neutralizable by 17b. Teeraputon *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **subtype comparisons**)
- 17b: This Ab bound with an intermediate affinity to gp120IIIb, it did not prevent uptake of gp120 by APCs, and had no inhibitory effect on gp120 antigen presentation by MHC class II. 17b disassociated from gp120 at acidic pH. Lysosomal enzyme digestion of gp120 treated with 17b yielded fragmentation similar to that of gp120 alone, and digestion rate was intermediate, between the rapid digestion of gp120 alone and the slow digestion of gp120 in complex with high-affinity Ab5145A. It is thus concluded that CD4i Ab 17b does not have an inhibitory effect on gp120 processing and presentation. Tuen *et al.* [2005] (**antibody interactions**, **binding affinity**)
- 17b: Conformation of two gp120 constructs, gp120 bound to CD4D12 (the first two domains of human CD4), and gp120 bound to M9 (a 27-residue CD4 analog), was characterized by binding assays with Ab b17 in the presence or absence of soluble CD4D12. JRFL gp120 alone did not bind to b17 in the absence of CD4D12 but did bind in the presence of CD4D12. The gp120-CD4D12 construct bound to b17 in the absence of soluble CD4D12, and no enhancement in binding was observed when soluble CD4D12 was present, suggesting that all of the single chain was properly folded in the CD4i conforma-

tion. gp120-M9 construct also bound to 17b but with much lower affinity, and the binding was enhanced with presence of soluble CD4D12. This suggested that gp120-M9 single chain may contain both molecules where gp120 is bound to M9 in the CD4i conformation, and molecules resembling free gp120. Varadarajan *et al.* [2005] (**antibody binding site definition and exposure**, **kinetics**, **binding affinity**)

- 17b: Ab neutralization of viruses with mixtures of neutralization-sensitive and neutralization-resistant envelope glycoproteins was measured. It was concluded that binding of a single Ab molecule is sufficient to inactivate function of an HIV-1 glycoprotein trimer. The inhibitory effect of the Ab was similar for neutralization-resistant and -sensitive viruses indicating that the major determinant of neutralization potency of an Ab is the efficiency with which it binds to the trimer. It was also indicated that each functional trimer on the virus surface supports HIV-1 entry independently, meaning that every trimer on the viral surface must be bound by an Ab for neutralization of the virus to be achieved. Yang *et al.* [2005c] (**neutralization**)
- 17b: A substantial fraction of soluble envelope glycoprotein trimers contained inter-subunit disulfide bonds. Reduction of these disulfide bonds decreased binding of 17b to the glycoprotein, indicating that the inter-S-S bonds contribute to the exposure of the CD4-induced region. Yuan *et al.* [2005] (**antibody binding site definition and exposure**)
- 17b: The peptide 12p1 (RINNIPWSEAMM) inhibits direct binding of YU2 gp120 or Env trimer to CD4, CCR5 and MAb 17b in a concentration-dependent allosteric manner. 12p1 is thought to bind to unbound gp120 near the CD4 binding site, with a 1:1 stoichiometry. 12p1 also inhibited MAb F105 binding presumably because F105 favors an unactivated conformation, but not MAbs 2G12 or b12. The 1:1 stoichiometry, the fact that the peptide binding site is accessible on the trimer, the non-CD4 like aspect of the binding, and an ability to inhibit viral infection in cell cultures make it a promising lead for therapeutic design. Biorn *et al.* [2004]
- 17b: This review summarizes MAbs directed to HIV-1 Env. There are six CD4 inducible MAbs and Fabs in the database. The MAb forms neutralize TCLA strains only, but the smaller Fabs and scFv fragments can neutralize primary isolates. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure**, **review**)
- 17b: A32-rgp120 complexes opened up the CCR5 co-receptor binding site, but did not induce neutralizing antibodies with greater breadth among B subtype isolates than did uncomplexed rgp120 in vaccinated guinea pigs. 17b was used as a control to show A32-bound rgp120 had enhanced binding to this CD4-inducible MAb. Liao *et al.* [2004] (**vaccine antigen design**)
- 17b: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of 17b was decreased by trypsin, but increased by thrombin. Thrombin may increase HIV-induced cell fusion in blood by causing a conformational activating shift in gp120. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 17b: Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The loss of the glycan within the V3 loop (GM299 V3) and two sites adjacent to V3, C2 (GM292 C2) and (GM329 C3), increased neutralization susceptibility to CD4i FAb X5, but each of the glycan mutants and SF162 were refractive to neutralization with 48d and 17b. The loss of sites in C4 (GM438 C4), or V5 (GM454 V5) did not increase neutralization susceptibility to FAb X5. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- 17b: A set of HIV-1 chimeras that altered V3 net charge and glycosylation patterns in V1V2 and V3, involving inserting V1V2 loops from a late stage primary isolate taken after the R5 to X4 switch, were studied with regard to phenotype, co-receptor usage, and MAb neutralization. The loops were cloned into a HXB2 envelope with a LAI viral backbone. It was observed that the addition of the late-stage isolate V1V2 region and the loss of V3-linked glycosylation site in the context of high positive charge gave an X4 phenotype. R5X4, R5, and X4 viruses were generated, and sCD4, 2G12 and b12 neutralization resistance patterns were modified by addition of the late stage V1V2, glycosylation changes, and charge in concert, while neutralization by 2F5 was unaffected. 15e, 17b, and 48d could not neutralize any of the variants tested. Nabatov *et al.* [2004] (**antibody binding site definition and exposure**, **co-receptor**)
- 17b: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 17b. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- 17b: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neturalization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12 which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Three CD4i MAbs were tested; all preferentially neutralized SF162, and JRFL became neutralization sensitive to CD4i Abs if the SF162 V1V2 loop was exchanged. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)

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- 17b: The SOS mutant envelope protein introduces a covalent disulfide bond between gp120 surface and gp41 transmembrane proteins into the R5 isolate JR-FL by adding cysteines at residues 501 and 605. Pseudovirions bearing this protein bind to CD4 and co-receptor bearing cells, but do not fuse until treatment with a reducing agent, and are arrested prior to fusion after CD4 and co-receptor engagement. CD4i Abs 17b and X5 were weakly neutralizing in all formats, WT, SOS, and when added postbinding. Binley *et al.* [2003] (**vaccine antigen design**)
- 17b: Called 1.7b. The MAb B4e8 binds to the base of the V3 loop, neutralizes multiple primary isolates and was studied for interaction with other MAbs. B4e8 enhanced binding of CD4i MAbs 4.8d, 1.7b, and A1g8 to R5X4 virus 92HT593, but only of 48d to the R5 virus 92US660, and there was only a modest impact of the combination of B4e8 and CD4i MAbs on neutralization. Cavacini *et al.* [2003] (**antibody interactions**, **co-receptor**)
- 17b: 17b was used as a negative control to test CDR3 tyrosine sulfation of MAbs 47e, 412d, CM51, E51, C12 and Sb1, since its CDR3 tyrosines are buried. As expected, 17b did not incorporate sulfates while the other MAbs did. Thus, the experssion of 17b, or its binding to gp120 bound to CD4-Ig, was not affected by sulfation-inhibition. In addition, 17b was used as a positive control to test whether MAbs 47e, 412d, E51, Sc1 and C12 are CD4i Abs. Binding efficiency of all MAbs to ADA gp120 was doubled in the presence of CD4, showing that they are CD4-induced. scFv 17b was shown to efficiently bind to gp120 of three R5 isolates and to the HXBc2 X4 isolate. Neutralization assays showed that 17b was less efficient at neutralizing primary R5 and R5X4 isolates than MAbs 412d and E51, however, it was more efficient at neutralizing X4 isolates than these MAbs. Choe *et al.* [2003] (**antibody binding site definition and exposure**, **neutralization**)
- 17b: A sCD4-17b single chain chimera was made that can bind to the CD4 binding site, then bind and block co-receptor interaction. This chimeric protein is a very potent neutralizing agent, more potent than IgG1b12, 2G12 or 2F5 against Ba-L infection of CCR5-MAGI cells. It has potential for prophylaxis or therapy. It neutralized 5/6 R5 and X4 strains from the B clade, but was only moderately protective against a D clade isolate, and did not neutralize clade A, C, E, and F isolates. Dey *et al.* [2003] (**co-receptor**, **immunoprophylaxis**, **variant cross-recognition or cross-neutralization**, **immunotherapy**, **subtype comparisons**)
- 17b: 17b is known to be comprised of elements from four discontinuous beta strands. Using 17b MAb to select peptides from a combinatorial library, and analyzing the peptides using a novel discontinuous epitope reconstruction program, enabled epitope prediction. Segments of gp120 were reconstructed as an antigenic protein mimetic recognized by 17b. Comparisons then were made with a similar prediction of contact residues for CG10, a CD4i MAb that competes with 17b, but has a distinct binding site. Enshell-Seijffers *et al.* [2003] (**antibody binding site definition and exposure**, **mimotopes**, **computational epitope prediction**)
- 17b: Vaccination of a gp120-CD4 fusion complex in six transgenic XMG2 XenoMouse mice that produce human IgG2 with K light chain did not produce any neutralizing antibodies. 36/39 MAbs derived from one of these mice were in one of two competition groups that were conformational and specific for the complex, suggesting this chimeric vaccine may be of little value, as immunodominant responses recognized epitopes not present in native Env. MAbs from the two CD4-gp120 complex-specific competition groups did not compete with MAbs with known targets on HIV-1 gp120, but their binding was enhanced by binding of 17b. He *et al.* [2003]
- 17b: This study shows the fragments of CD4i MAbs are better able to neutralize virus than whole IgG. Neutralization of HIV-1 R5 isolates JRFL, JR-CSF and ADA by CD4i MAbs X5, 17b, and 48d decreased with increased molecule size, the neutralizing potency of single-chain Fv (scFv) > than Fab fragments > whole Ab molecules. (With the exception of IgG 48d neutralization of HIV-1 ADA.) HIV-1 X4 isolates 89.6 and HxB2 are both relatively sensitive even to the larger IgG version. R5X4 isolate neutralization was dependent on the isolate and co-receptor usage. The CD4i MAb fragments neutralize HIV-1 subsequent to CD4 binding. The CD4i MAbs bind near the co-receptor binding sites on gp120. Co-receptors bind to the conserved beta19 strand and part of the V3 loop, regions that are masked by the V1V2 loops in the CD4-unbound state. When CD4 is bound, the co-receptor site is exposed near the membrane surface where it would be optimally accessible to co-receptors, and the smaller versions of the molecules are better able to overcome the steric hindrence. Labrijn *et al.* [2003] (**antibody binding site definition and exposure**, **co-receptor**, **variant cross-recognition or cross-neutralization**)
- 17b: Env genes derived from uncultured brain biopsy samples from four HIV-1 infected patients with late-stage AIDS were compared to env genes from PBMC samples. Brain isolates did not differ in the total number or positions of N-glycosylation sites, patterns of coreceptor usage, or ability to be recognized by gp160 and gp41 MAbs. 17b recognized most variants,some from each of the four individuals, by gp120 immunoprecipitation. Ohagen *et al.* [2003] (**brain/CSF**, **variant cross-recognition or cross-neutralization**)
- 17b: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- 17b: This paper describes the generation of CD4i MAb E51, that like CD4i MAb 17b, blocks CCR5 binding to sCD4-bound gp120. E51 has more cross-neutralizing potency than other prototype CD4i MAbs (17b) for B and C clade isolates. E51 and 17b both neutralized HIV-1 clade B strains HXBc2 and ADA, while JR-FL and 89.6 were only neutralized by E51, not 17b. Clade C strains MCGP1.3 and SA32 were both inhibited by 17b and E51, but E51 was more potent against SA32. The substitutions E381R, F383S, R419D I420R, K421D, Q422L, I423S, and Y435S (HXB2 numbering) all severely reduce 17b and E51 binding. All but I423S also diminish CCR5 binding by more than 50%. The mutation F383S also inhibits sCD4 binding and F105 binding,

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and K421D inhibits F105 binding, but not sCD4. Xiang *et al.* [2003] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

- 17b: The HIV-1 primary isolate DH012 has preserved the epitopes for the MAbs IgG1b12, 2G12, 17b, however natural DH012 infection in chimpanzees and DH012 gp120 vaccination in guinea pigs does not give rise to Abs against these epitopes. Zhu *et al.* [2003] (**vaccine-specific epitope characteristics**)
- 17b: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a CD4i MAb that had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
- 17b: The two N-terminal domains of CD4, termed D1 and D2, when expressed in the absence of the remaining domains of CD4 retain the capacity to bind to gp120—coding sequences of D1D2 and Igαtp were fused to create a large, multivalent rec protein D1D2Igαtp, which, unlike CD4, does not enhance infection at sub-optimal concentrations—the MAb 17b can also enhance viral replication at sub-optimal concentrations, but D1D2-Igα inhibited the 17b enhancement of two primary isolates. Arthos *et al.* [2002] (**variant cross-recognition or cross-neutralization**)
- 17b: gp120 mutants were used to define the CXCR4 binding site using CXCR4 displayed on paramagnetic proteoliposomes (PMPLs) to reduce non-specific gp120 binding—basic residues in the V3 loop and the β19 strand (RIKQ, positions 419-422) were involved, and deletion of the V1-V2 loops allowed CD4-independent CXCR4 binding—MAbs 17b (CD4i) and F105 (CD4BS) were used to study conformational changes in the mutants—the affinity of ΔV1 and ΔV1-V2 for 17b was dramatically increased and no longer inducible in the presence of sCD4—V3 mutants R298A and R327A were not recognized by 17b except in the presence of sCD4—mutations in the β19 strand dramatically reduced 17b affinity in the presence or absence of sCD4, consistent with known 17b contact residues in this region. Basmaciogullari *et al.* [2002]
- 17b: This study examined antibody interactions, binding and neutralization with a B clade R5 isolate (92US660) and R5X4 isolate (92HT593). Abs generally bound and neutralized the R5X4 isolate better than the R5 isolate. Anti-V3 MAb B4a1 increased binding of CD4i MAbs 48d, 17b and A1g8, but only A1g8 binding was increased by B4a1 to the R5 isolate. Additive affects on neutralizaton of the R5X4 isolate with B4a1 and CD4i MAbs was observed, presumably due to increased exposure of the CD4i binding site, but not for the R5 isolate. Anti-gp41 MAb F240 had a synergistic effect on neutralization with CD4i MAbs 48d and 17b, but not with A1g8 for the R5X4 virus. Cavacini *et al.* [2002] (**antibody interactions**, **co-receptor**, **variant cross-recognition or cross-neutralization**)
- 17b: CD4 residue Phe43 significantly contributes to the affinity of CD4-gp120 interactions – despite decreased affinities for gp120, CD4 proteins and CD4-mimetic peptides lacking a Phe side-chain enhance binding of gp120 to 17b in a manner similar to Phe-bearing ligands indicating the Phe42 interaction is not critical for CD4-induced conformational changes in gp120. Dowd *et al.* [2002]
- 17b: Truncation of the gp41 cytoplasmic domain of X4, R5, and X4R5 viruses forces a conformation that more closely resembles the CD4 bound state of the external Envelope, enhancing binding of CD4i MAbs 17b and 48d and of CD4BS MAbs F105, b12, and in most cases of glycosylation site dependent MAb 2G12 and the anti-gp41 MAb 246D – in contrast, binding of the anti-V2 MAb 697D and the anti-V3 MAb 694/98D were not affected – viruses bearing the truncation were more sensitive to neutralization by MAbs 48d, b12, and 2G12 – the anti-C5 MAb 1331A was used to track levels of cell surface expression of the mutated proteins. Edwards *et al.* [2002] (**vaccine-specific epitope characteristics**)
- 17b: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I and Cluster II MAbs required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor, binding to a fusion intermediate. 17b was used to demonstrate that the Cluster I and II MAbs bound to gp120/gp41 complexes, not to gp41 after shedding of gp120. Finnegan *et al.* [2002]
- 17b: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – the preincubation 31.5 C step did not alter the inhibitory activity of neutralizing Abs anti-gp41 2F5, or anti-gp120 2G12, IG1b12, 48d, and 17b. Golding *et al.* [2002b]
- 17b: HIV-1 gp160ΔCT (cytoplasmic tail-deleted) proteoliposomes (PLs) containing native, trimeric envelope glycoproteins from R5 strains YU2 and JRFL, and X4 strain HXBc2, were made in a physiologic membrane setting as candidate immunogens for HIV vaccines—2F5 bound to gp160ΔCT with a reconstituted membrane ten-fold better than the same protein on beads—anti-CD4BS MAbs IgG1b12 and F105, A32 (C1-C4), C11 (C1-C5), and 39F (V3) MAbs bound gp160ΔCT PLs indistinguishably from gp160ΔCT expressed on the cell surface—non-neutralizing MAbs C11 and A32 bound with lower affinity than NAb IgG1b12—the MAb 17b was sCD4 inducible on gp160ΔCT PL. Grundner *et al.* [2002] (**vaccine antigen design**)
- 17b: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar. Enthalpy and entropy changes were divergent, but compensated. Not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs (17b, 48d, 1.5e, b6, F105 and F91) had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120

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monomer, but the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. The high values suggest surface burial or protein folding an ordering of amino acids. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)

- 17b: A pseudotyping assay showed that an X4 V3 loop peptide could enhance infectivity of X4 virus, R5 and R5X4 V3 loops peptides could enhance infectivity of an R5 virus, and R5X4 peptides could enhance infectivity of an R5X4 virus. Neither R5 nor R5X4 peptides influenced binding of CD4BS MAbs F105 and Ig1Gb12, but did increase binding of CD4i MAb 17b. Ling *et al.* [2002] (**antibody binding site definition and exposure**, **co-receptor**)
- 17b: Ab binding characteristics of SOS gp140 were tested using SPR and RIPA – SOS gp140 is gp120-gp41 bound by a disulfide bond – NAbs 2G12, 2F5, IgG1b12, CD4 inducible 17b, and 19b bound to SOS gp140 better than uncleaved gp140 (gp140unc) and gp120 – non-neutralizing MAbs 2.2B (binds to gp41 in gp140unc) and 23A (binds gp120) did not bind SOS gp140. Schulke *et al.* [2002] (**vaccine antigen design**)
- 17b: Oligomeric gp140 (o-gp140) derived from R5 primary isolate US4 was characterized for use as a vaccine reagent – antigen capture ELISA was used to compare the antigenicity of gp120 and o-gp140 using a panel of well characterized MAbs – 17b recognized both gp120 monomer and o-gp140. Srivastava *et al.* [2002]
- 17b: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91 was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b] (**variant cross-recognition or cross-neutralization**)
- 17b: Five CD4i MAbs were studied, 17b, 48d and three new MAbs derived by Epstein-Barr virus transformation of PBMC from an HIV+ long term non-progressor – 23e and 21c were converted to hybridomas to increase Ab production – all compete with the well-characterized 17b CD4i MAb in an ELISA antigen capture assay – critical binding residues are mapped and the CD4i MAb epitopes were distinct but share a common element near isoleucine 420, also important for CCR5 binding, and all five can block CCR5 binding to a sCD4-gp120 complex – the MAb 48d has the epitope most similar to the CCR5 binding site. Xiang *et al.* [2002a] (**antibody binding site definition and exposure**)
- 17b: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibritin—stabilized oligomer gp140Δ683(-FT) showed strong preferential recognition by NAbs IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAbs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002]
- 17b: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002]
- 17b: Using a cell-fusion system, it was found CD4i antibodies 17b, 48d, and CG10 reacted faintly with Env expressing HeLA cells even in the absence of sCD4 or CD4 expressing target cells. Reactivity increased after sCD4 addition, but not after CD4 expressing target cell addition, and binding was not increased at the cell-to-cell CD4-Env interface. This suggests the CD4i co-receptor binding domain is largely blocked at the cell-fusion interface, and so CD4i antibodies would not be able access this site and neutralize cell-mediated viral entry. Finnegan *et al.* [2001]
- 17b: Mutations in two glycosylation sites in the V2 region of HIV-1 ADA at positions 190 and 197 (187 DNTSYR-LINCNTS 199) cause the virus to become CD4-independent and able to enter cells through CCR5 alone—these same mutations tended to increase the neutralization sensitivity of the virus, including to 17b—only the CD4i antibodies 17b and 48d showed an increased affinity of the CD4 independent viruses relative to wild-type. Kolchinsky *et al.* [2001] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 17b: Structural aspects of the interaction of neutralizing Abs with HIV-1 Env are reviewed – Env essentially has three faces, one is largely inaccessible on the native trimer, and two that exposed but have low immunogenicity on primary viruses – neutralization is suggested to occur by inhibition of the interaction between gp120 and the target cell membrane receptors as a result of steric hindrance and it is noted that the attachment of approximately 70 IgG molecules per virion is required for neutralization, which is equivalent to about one IgG molecule per spike – the 2G12, 17b and b12 epitopes are discussed in detail – the 17b epitope is masked prior to CD4 binding by the V1-V2 loop and in contrast to sCD4, the binding of cell surface CD4 to virus does not appear to make the epitope accessible to binding by 17b to allow neutralization. Poignard *et al.* [2001] (**antibody binding site definition and exposure**, **review**)
- SHIV-HXBc2 is a neutralization sensitive non-pathogenic virus, and several <i>in vivo</i> passages through monkey's

yielded highly pathogenic SHIV KU-1 – HXBc2 and the KU-1 clone HXBc2P3.2 differ in 12 amino acids in gp160 – substitutions in both gp120 and gp41 reduced the ability of sCD4, IgG1b12, F105 and AG1121 to Env achieve saturation and full occupancy, and neutralize KU-1 – 17b and 2F5 also bound less efficiently to HXBc2P3.2, although 2G12 was able to bind both comparably. Si *et al.* [2001] (**variant cross-recognition or cross-neutralization**)

- 17b: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAbs alters some step after binding – 17b bound at somewhat greater levels to 168C than to 168P, but this is not a general feature of 17b binding to primary versus TCLA strains. York *et al.* [2001] (**variant cross-recognition or cross-neutralization**)
- 17b: 17b binds to a CD4 inducible epitope which partially overlaps the CCR5 binding site – JRFL, YU2, 89.6, and HXB2 and their C1-, V1/V2-, C5 -deletion mutants were used to study how 17b binding affects gp120-CD4 interactions – 17b reduced CD4-gp120 interactions by decreasing the on-rate and increasing the off-rate of sCD4, while enhanced binding of sCD4 binding was observed for the 17b-bound, V1/V2 deleted gp120s – 17b was considered to be a surrogate for CCR5, and the authors suggest that 17b binding may shift V1/V2 into a position that interferes with CD4 binding, forcing a release. Zhang *et al.* [2001a] (**antibody binding site definition and exposure**, **kinetics**)
- 17b: To determine the antigenicity of virus killed by thermal and chemical inactivation, retention of conformation-dependent neutralization epitopes was examined, and exposure of CD4BS epitopes was found to be enhanced (MAbs IgG1b12, 205-46-9, and 205-43-1) – binding to 2G12 and 447-52D epitopes was essentially unaltered – the 17b CD4i epitope was also exposed. Grovit-Ferbas *et al.* [2000] (**vaccine antigen design**)
- 17b: SF162 is a neutralization-resistant HIV-1 isolate – N-linked glycosylation modifications in the V2 loop of the SF162 gp120 revealed that these sites prevent neutralization by CD4BS MAbs (IgG1b12 and IgGCD4), and protect against neutralization by V3 MAbs (447-D and 391-95D) – V2-region glycosylation site mutations did not alter neutralization resistance to V2 MAbs (G3.4 and G3.136) or CD4i MAbs (17b and 48d) – V2 glycosylation site modification allows infection of macrophages, probably due to glycosylated forms requiring fewer CCR5 molecules for viral entry. Ly & Stamatatos [2000] (**variant cross-recognition or cross-neutralization**)
- 17b: Six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000] (**antibody binding site definition and exposure**)
- 17b: Mutagenesis defines Ile-420, Lys-421, Gln-422, Pro-438, and Gly-441 to be important residues for CCR5 binding – these positions are located on two strands that connect the gp120 bridging sheet and outer domain, suggesting a mechanism for conformational shifts induced by CD4 binding to facilitate CCR5 binding. Rizzuto & Sodroski [2000] (**antibody binding site definition and exposure**)
- 17b: sCD4 can activate fusion between effector cells expressing Env and target cells expressing coreceptor (CCR5 or CXCR4) alone without CD4 – CD4i MAbs 17b and 48d have little effect on a standard cell fusion assay but potently block sCD4 activated fusion – 17b was broadly cross-reactive inhibiting sCD4 activated fusion with Env from clades A, B, C, D, E, F, and F/B. Salzwedel *et al.* [2000] (**subtype comparisons**)
- 17b: Soluble gp140 derived from SF162, a neutralization-resistant primary isolate, and SF162AV2 a neutralization-susceptible isolate with 30 amino acids deleted from the V2 loop, were generated with or without the gp120-gp41 cleavage site intact – all forms are recognized by oligomer-specific MAb T4 and show enhanced binding of CD4i MAb 17b when sCD4 is bound – the fused forms are less efficiently recognized than the cleaved forms by polyclonal neutralizing sera from HIV-infected patients – the V3 loop is more exposed on the fused form. Stamatatos *et al.* [2000] (**vaccine antigen design**)
- 17b: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000] (**vaccine antigen design**)
- 17b: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999] (**vaccine antigen design**)
- 17b: A CD4-independent viral variant of IIIB, IIIBx, was generated on CXCR4-expressing cells – IIIBx exhibited greater

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exposure of the 17b and 48d epitopes and enhanced neutralization by CD4i MAbs and by polyclonal human sera – the 17b epitope has significant overlap with the CCR5 coreceptor binding site. Hoffman *et al.* [1999] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)

- 17b: A panel of MAbs was shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer – CD4i MAbs 17b and 48d bound better to the deleted protein than to wild type. Binley *et al.* [1998] (**antibody binding site definition and exposure**)
- 17b: 17b Fab was co-crystallized with a gp120 core and CD4, and it's binding site can be directly visualized—17b binds to the "bridging sheet" of gp120, an antiparallel beta sheet region, contacting residues from the C4 region and the V1/V2 stem—the contact area is small for an Ab-antigen interactive surface, and dominated in the Ab by the heavy chain—the center of the binding region has hydrophobic interactions, and the periphery charge interactions, acidic on 17b and basic on gp120. Kwong *et al.* [1998] (**structure**)
- 17b: Moore and Binley provide a commentary on the papers by <cite>Rizzuto1998</cite>, <cite>Wyatt1998</cite> and <cite>Kwong1998</cite> – they point out 17b shares binding elements in gp120 with chemokine receptor molecules, and that CD4 needs to bind to gp120 first to make the 17b epitope accessible and it may be sterically blocked in the CD4 bound virus, thus making it a poor NAb for primary isolates <cite>Moore1998</cite>. Kwong *et al.* [1998]; Moore & Binley [1998]; Rizzuto *et al.* [1998]; Wyatt *et al.* [1998] (**review**, **structure**)
- 17b: Site directed mutagenesis of a WU2 protein with the V1-V2 loops deleted revealed key residues for 17b-gp120 interaction and interaction of gp120 and CCR5 – mutations in residues that reduced 17b by 70% were R/D 419, I/R 420, Q/L 422, Y/S 435, I/S 423, K/D 121 and K/D 421– 17b can neutralize HIV-1 strains that use different chemokine receptors, supporting a common region in gp120 in chemokine-receptor interaction. Rizzuto *et al.* [1998] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 17b: Deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V2 but not V1 enabled neutralization by CD4i MAbs 17b and 48d. Stamatatos & Cheng-Mayer [1998] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- 17b: sCD4 induces 17b binding in primary isolates and TCLA strains – amino acids that reduce the efficiency of binding were determined and found also to compromise syncytia formation and viral entry – V1V2 deletion or sCD4 binding can expose the 17b epitope for both HXBc2 and macrophage tropic YU2 – neutralizing potency of 17b is probably weak due to poor exposure of the epitope – 17b epitope exposure upon sCD4 binding can occur over a wide range of temperatures, consistent with the energy of CD4 binding being sufficient to drive the V1/V2 loop into a new conformation. Sullivan *et al.* [1998b] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 17b: The HIV-1 virus YU2 entry can be enhanced by MAbs binding to the CD4BS, V3 loop, and CD4i epitopes – the activation for this enhanced entry state could be conferred on HxB2 by introducing the YU2 V3 loop, or the YU2 V3 and V1/V2 loops, and the presence of V1/V2 increased the enhancement – a similar effect is observed by sub-neutralizing concentrations of sCD4 and the effect is dependent of CCR5 – 17b enhances YU2 enhanced viral entry 10-fold, whereas HXBc2 was neutralized. Sullivan *et al.* [1998a]
- 17b: Summary of the implications of the crystal structure of a gp120 core bound to CD4 and 17b, combined with what is known about mutations that reduce NAb binding to gp120 – probable mechanism of neutralization is interference with chemokine receptor binding – mutations in 88N, 117K, 121K, 256S, 257T, N262, Delta V3, E370, E381, F 382, R 419, I 420, K 421, Q 422, I 423, W 427, Y 435, P 438, M 475 of HXBc2 (IIIB) reduce binding – the only variable residues in gp120 that contact 17b are 202T and 434M – the contact points for 17b with the crystallized incomplete gp120 are mostly in the heavy chain of the Ab, and there is a gap between 17b's light chain and the partial gp120 which may be occupied by the V3 loop in a complete gp120 molecule – the authors propose that the V2 and V3 loops may mask the CD4i Ab binding site, and that the V2 loop may be repositioned upon CD4 binding. Wyatt *et al.* [1998] (**structure**)
- 17b: Virus with the V1-V2 loop deleted was viable and more susceptible to neutralization by CD4i MAb 17b, and anti-V3 MAbs 1121, 9284, and 110.4, but not to a CD4BS MAb, F105, or sCD4. Cao *et al.* [1997b] (**vaccine antigen design**)
- 17b: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – 17b bound monomer, oligomer, and neutralized JRFL in the presence of sCD4, but if sCD4 was not present, 17b only bound monomer. Fouts *et al.* [1997]
- 17b: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env – 17b has synergistic response in combination with anti-V3 MAb 694/98-D. Li *et al.* [1997]
- 17b: Neutralizes TCLA strains, but not primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 17b: 48d binds to the IIIB protein and not IIIB V3 peptide, while binding to the Can0A V3 peptide, suggesting Can0A V3 is a conformer that mimics the 48d – it does not bind to 17b, distinguishing the epitopes. Weinberg *et al.* [1997]
- 17b: Binds to sgp120 efficiently, but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding – partial re-exposure if sCD4 was bound – could not bind to HXBc2 gp120 if the 19 C-term amino acids were deleted in conjunction with amino acids 31-93 in C1, but binding was restored in the presence of sCD4. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
- 17b: Many MAbs inhibit binding (anti-C1, -C5, -C4, -CD4BS) – anti-V3 MAb 5G11 enhances binding, as do C1-

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C4 discontinuous epitopes A32 and 2/11c – enhances binding of some anti-V2 MAbs. Moore & Sodroski [1996] (**antibody interactions**)

- 17b: Binding did not result in significant gp120 dissociation from virion, in contrast to 48d, although the gp41 epitope of MAb 50-69 was exposed. Poignard *et al.* [1996a] (**antibody interactions**)
- 17b: Neutralizes JR-FL – inhibits gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]
- 17b: MIP-1α binding to CCR-5 expressing cells can be inhibited by gp120-sCD4 — binding of 17b blocks this inhibition. Wu *et al.* [1996]
- 17b: Binds with higher affinity to monomer and oligomer, slow association rate, poor neutralization of lab strain – this is in contrast to 48d, which has very different kinetics. Sattentau & Moore [1995] (**kinetics**, **binding affinity**)
- 17b: Studies using a V1/V2 deletion mutant demonstrated that enhanced binding of 17b in the presence sCD4 involves the V1/V2 loops, with more significant involvement of V2 – similar effect observed for 48d and A32. Wyatt *et al.* [1995] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- 17b: A mutation in gp41, 582 A/T, confers resistance to neutralization (also confers resistance to MAbs F105, 48d, 21h and 15e). Thali *et al.* [1994] (**variant cross-recognition or cross-neutralization**)
- 17b: Binding of 48d is much more influenced by sequence variation among molecular clones of LAI than is binding of 17b. Moore *et al.* [1993c] (**variant cross-recognition or cross-neutralization**)
- 17b: Epitope is better exposed upon CD4 binding to gp120 – competes with 15e and 21h, anti-CD4 binding site MAbs – 113 D/R, 252 R/W, 257 T/A or G, 370 E/D, 382 F/L, 420 I/R, 433A/L, 438 P/R and 475 M/S confer decreased sensitivity to neutralization. Thali *et al.* [1993] (**antibody binding site definition and exposure**, **antibody interactions**)

No. 1434
MAb ID 21c (2.1C)
HXB2 Location Env
Author Location gp120 (IIIB, J62)
Epitope
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4i, gp120 CCR5BS
Research Contact James Robinson, Tulane University, New Orleans, LA, USA
References Srivastava *et al.* 2005; Haynes *et al.* 2005a; Gorny & Zolla-Pazner 2004; Xiang *et al.* 2002b; Xiang *et al.* 2002a
Keywords antibody binding site definition and exposure, antibody generation, review, vaccine antigen design

- 21c: Called 2.1C. Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 2.1C has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)
- 21c: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **vaccine antigen design**, **review**)
- 21c: This review summarizes MAbs directed to HIV-1 Env. There are six CD4 inducible MAbs and Fabs in the database. The MAb forms neutralize TCLA strains only, but the smaller Fabs and scFv fragments can neutralize primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 21c: Five CD4i MAbs were studied, 17b, 48d and three new MAbs derived by Epstein-Barr virus transformation of PBMC from an HIV+ long term non-progressor – 23e and 21c were converted to hybridomas to increase Ab production – all compete with the well-characterized 17b CD4i MAb in an ELISA antigen capture assay – critical binding residues are mapped and the CD4i MAb epitopes were distinct but share a common element near isoleucine 420, also important for CCR5 binding, and all five can block CCR5 binding to a sCD4-gp120 complex – the MAb 48d has the epitope most similar to the CCR5 binding site. Xiang *et al.* [2002a] (**antibody binding site definition and exposure**, **antibody generation**)
- 21c: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91 was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b] (**antibody binding site definition and exposure**, **vaccine antigen design**)

No. 1435
MAb ID 23e (2.3E)
HXB2 Location Env
Author Location gp120 (IIIB, J62)
Epitope
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4i
Research Contact James Robinson, Tulane University, New Orleans, LA, USA
References Srivastava *et al.* 2008; Srivastava *et al.* 2005; Gorny & Zolla-Pazner 2004; Xiang *et al.* 2002b; Xiang *et al.* 2002a

Keywords antibody binding site definition and exposure, antibody generation, binding affinity, neutralization, review, subtype comparisons, vaccine antigen design

- 2.3E: Trimeric envelope glycoproteins with a partial deletion of the V2 loop derived from subtype B SF162 and subtype C TV1 were compared. The magnitude of 2.3E binding to subtype C trimer was lower than to subtype B trimer, either in the presence or absence of CD4. However, the fold increase in binding of 2.3E in presence of CD4 was similar for both subtypes, indicating similar structural rearrangements. Subtype C trimer had many biophysical, biochemical, and immunological characteristics similar to subtype B trimer, except for a difference in the three binding sites for CD4, which showed cooperativity of CD4 binding in subtype C but not in subtype B. Srivastava *et al.* [2008] (**binding affinity**, **subtype comparisons**)
- 23e: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **review**)
- 23e: This review summarizes MAbs directed to HIV-1 Env. There are six CD4 inducible MAbs and Fabs in the database. The MAb forms neutralize TCLA strains only, but the smaller Fabs and scFv fragments can neutralize primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 23e: Five CD4i MAbs were studied, 17b, 48d and three new MAbs derived by Epstein-Barr virus transformation of PBMC from an HIV+ long term non-progressor – 23e and 21c were converted to hybridomas to increase Ab production – all compete with the well-characterized 17b CD4i MAb in an ELISA antigen capture assay – critical binding residues are mapped and the CD4i MAb epitopes were distinct but share a common element near isoleucine 420, also important for CCR5 binding, and all five can block CCR5 binding to a sCD4-gp120 complex – the MAb 48d has the epitope most similar to the CCR5 binding site. Xiang *et al.* [2002a] (**antibody binding site definition and exposure**, **antibody generation**)
- 23e: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91 was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b] (**antibody binding site definition and exposure**, **vaccine antigen design**)

No. 1436
MAb ID 48d (4.8d, 4.8D, 48D)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L P (wea
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 CD4i
Research Contact James Robinson, Tulane University, New Orleans, LA, USA
References van Montfort *et al.* 2008; Srivastava *et al.* 2008; Nora *et al.* 2008; Martin *et al.* 2008; van Montfort *et al.* 2007; Lin & Nara 2007; Cham *et al.* 2006; Yuan *et al.* 2005; Yang *et al.* 2005c; Holl *et al.* 2006a; Tuen *et al.* 2005; Srivastava *et al.* 2005; Selvarajah *et al.* 2005; Reeves *et al.* 2005; Martín-García *et al.* 2005; Lusso *et al.* 2005; Kalia *et al.* 2005; Huang *et al.* 2005a; Pinter *et al.* 2004; Pantophlet *et al.* 2004; Nabatov *et al.* 2004; McCaffrey *et al.* 2004; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Labrijn *et al.* 2003; Choe *et al.* 2003; Cavacini *et al.* 2003; Cavacini *et al.* 2002; Zhang *et al.* 2002; Edwards *et al.* 2002; Xiang *et al.* 2002a; Xiang *et al.* 2002b; Yang *et al.* 2002; Golding *et al.* 2002b; Kwong *et al.* 2002; Finnegan *et al.* 2001; Verrier *et al.* 2001; Kolchinsky *et al.* 2001; Salzwedel *et al.* 2000; Yang *et al.* 2000; Park *et al.* 2000; Ly & Stamatatos 2000; Fortin *et al.* 2000; Hoffman *et al.* 1999; Oscherwitz *et al.* 1999a; Stamatatos & Cheng-Mayer 1998; Binley *et al.* 1998; Yang *et al.* 1998; Sullivan *et al.* 1998b; Parren *et al.* 1998a; Mondor *et al.* 1998; Wyatt *et al.* 1998; Frankel *et al.* 1998; Parren *et al.* 1997b; Wyatt *et al.* 1997; Ugolini *et al.* 1997; Lee *et al.* 1997; Weinberg *et al.* 1997; Li *et al.* 1997; Binley *et al.* 1997a; Trkola *et al.* 1996a; Poignard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; Sattentau *et al.* 1995; Wyatt *et al.* 1995; Sattentau 1995; D'Souza *et al.* 1995; Moore *et al.* 1994b; Thali *et al.* 1994; Moore *et al.* 1993c; Moore & Ho 1993; Thali *et al.* 1993
Keywords antibody binding site definition and exposure, antibody interactions, assay development, binding affinity, co-receptor, dendritic cells, drug resistance, escape, HAART, ART, kinetics, neutralization, review, structure, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- 48d database comment: 48d and 17b have similar epitopes, and the pair are unique among human and rodent MAbs.
- 48d: NIH AIDS Research and Reference Reagent Program: 1756.

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- 48D: A new purification method was developed using a high affinity peptide mimicking CD4 as a ligand in affinity chromatography. This allowed the separation in one step of HIV envelope monomer from cell supernatant and capture of pre-purified trimer. Binding of 48D to gp120SF162 purified by the miniCD4 affinity chromatography and a multi-step method was comparable, suggesting that the miniCD4 allows the separation of HIV-1 envelope with intact 48D epitope. gp140DF162ΔV2 was purified by the miniCD4 method to asses its ability to capture gp140 trimers. Purified gp140DF162ΔV2 was recognized by 48D, and the k-off value for 48D was reduced compared to gp120SF162 monomer, consistent with the gp140DF162ΔV2 trimeric conformation. Binding of 48D to gp140DF162ΔV2 purified by the miniCD4 affinity chromatography and a multi-step method was comparable, suggesting that the SF162 trimer antigenicity was preserved. Martin *et al.* [2008] (**assay development**, **kinetics**, **binding affinity**)
- 4.8d: Transmission of HIV-1 by immature and mature DCs to CD4+ T lymphocytes was significantly higher for CXCR4- than for CCR5-tropic strains. However, preneutralization of X4 virus with 4.8d prior to capture efficiently blocked transmission to 75%, while transmission of R5 was blocked to 46%. van Montfort *et al.* [2008] (**co-receptor**, **neutralization**, **dendritic cells**)
- 48d: Contemporaneous biological clones of HIV-1 were isolated from plasma of chronically infected patients and tested for their functional properties. The clones showed striking functional diversity both within and among patients, including differences in infectivity and sensitivity to inhibition by 48d. There was no correlation between clonal virus infectivity and sensitivity to 48d inhibition, indicating that these properties are dissociable. The sensitivity to 48d inhibition was, however, a property shared by viruses from a given patient, suggesting that the genetic determinants that define this sensitivity may lie in regions that are not necessarily subject to extensive diversity. Nora *et al.* [2008] (**neutralization**)
- 4.8d: Trimeric envelope glycoproteins with a partial deletion of the V2 loop derived from subtype B SF162 and subtype C TV1 were compared. The magnitude of 4.8d binding to subtype C trimer was lower than to subtype B trimer, either in the presence or absence of CD4. However, the fold increase in binding of 4.8d in presence of CD4 was similar for both subtypes, indicating similar structural rearrangements. Subtype C trimer had many biophysical, biochemical, and immunological characteristics similar to subtype B trimer, except for a difference in the three binding sites for CD4, which showed cooperativity of CD4 binding in subtype C but not in subtype B. Srivastava *et al.* [2008] (**binding affinity**, **subtype comparisons**)
- 48d: 48d structure, binding and neutralization activity, are reviewed in detail. Lin & Nara [2007] (**review**)
- 4.8d: 4.8d-neutralized HIV-1 captured on Raji-DC-SIGN cells or immature monocyte-derived DCs (iMDDCs) was successfully transferred to CD4+ T lymphocytes, indicating that the 4.8d-HIV-1 complex was disassembled upon capture by DC-SIGN-cells. van Montfort *et al.* [2007] (**neutralization**, **dendritic cells**)
- 48d: This Ab was shown to infrequently neutralize cloned Envs (clades A, B, C, D, F1, CRF01_AE, CRF02_AG, CRF06_cpx and CRF11_cpx) derived from donors with and without broadly cross-reactive neutralizing antibodies. Cham *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 4.8d: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 48d: The structure of the V3 region in the context of gp120 core complexed to the CD4 receptor and to the 48d Ab was attempted to be determined by X-ray resolution, but only the structure for V3 complexed with CD4 and X5 Ab was solved. Huang *et al.* [2005a] (**structure**)
- 48d: Point mutations in the highly conserved structural motif LLP-2 within the intracytoplasmic tail of gp41 resulted in conformational alternations of both gp41 and gp120. The alternations did not affect virus CD4 binding, coreceptor binding site exposure, or infectivity of the virus, but did result in decreased binding and neutralization by certain MAbs and human sera. 48d exhibited similar levels of binding to both the LLP-2 mutant and wildtype viruses, indicating that sCD4 binding to the LLP-2 mutant successfully triggered conformational change of gp120 and exposure of the co-receptor binding site. Kalia *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)
- 48d: The epitope for the MAb D19 is conserved and embedded in V3. D19 is unique in that for R5 viruses, it was cryptic and did not bind without exposure to sCD4, and for X4 and R5X4 isolates it was constitutively exposed. D19b is unqiue among CD4i antibodies in that it binds to the V3 loop. CD4i MAbs 17b and 48d were used as controls for CD4i characterization; in contrast to D19, other CD4i MAbs bind to the conserved bridging sheet and do not differentiate between R5 and X4 using strains. Lusso *et al.* [2005]
- 48d: The HIV-1 Bori-15 variant was adapted from the Bori isolate for replication microglial cells. Bori-15 had increased replication in microglial cells and a robust syncytium-forming phenotype, ability to use low levels of CD4 for infection, and increased sensitivity to neutralization by sCD4 and 17b. Four amino acid changes in gp120 V1-V2 were responsible for this change. Protein functionality and integrity of soluble, monomeric gp120-molecules derived from parental HIV-1 Bori and microglia-adapted HIV-1 Bori-15 was assessed in ELISA binding assays using F105, IgG1b12, 17b and 48d, 2G12 and 447-52D. Association rates of sCD4 and 17b were not changed, but dissociation rates were 3-fold slower for sCD4 and 14-fold slower for 17b. Equilibrium binding studies showed 48d bound better to Bori-15 than Bori in the absence of sCD4, while 17b bound identically. Martín-García *et al.* [2005] (**antibody binding site definition and exposure**)
- 48D: Escape mutations in HR1 of gp41 that confer resistance to Enfuvirtide reduced infection and fusion efficiency and also delayed fusion kinetics of HIV-1. The mutations also conferred increased neutralization sensitivity of virus to 48D. Enhanced neutralization correlated with reduced fusion kinetics, indicating that the mutations result in Env proteins remaining in the CD4-triggered state for a longer period of time. Reeves

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et al. [2005] (**antibody binding site definition and exposure**, **drug resistance**, **neutralization**, **escape**, **HAART, ART**)

- 48d: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. CD4i MAbs (48d, 17b) did not bind to either GDMR or mCHO even with sCD4. Selvarajah *et al.* [2005] (**vaccine antigen design**, **vaccine-specific epitope characteristics**)
- 48D: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **review**, **structure**)
- 48d: This Ab bound weakly to gp120IIIb and had no inhibitory effect on gp120 antigen presentation by MHC class II. 48d disassociated from gp120 at acidic pH. Lysosomal enzyme digestion of gp120 treated with 48d yielded fragmentation rate and pattern similar to that of gp120 alone. It is thus concluded that CD4i Ab 48d does not have an inhibitory effect on gp120 processing and presentation. Tuen *et al.* [2005] (**antibody interactions**, **binding affinity**)
- 48d: Ab neutralization of viruses with mixtures of neutralization-sensitive and neutralization-resistant envelope glycoproteins was measured. It was concluded that binding of a single Ab molecule is sufficient to inactivate function of an HIV-1 glycoprotein trimer. The inhibitory effect of the Ab was similar for neutralization-resistant and -sensitive viruses indicating that the major determinant of neutralization potency of an Ab is the efficiency with which it binds to the trimer. It was also indicated that each functional trimer on the virus surface supports HIV-1 entry independently, meaning that every trimer on the viral surface must be bound by an Ab for neutralization of the virus to be achieved. Yang *et al.* [2005c] (**neutralization**)
- 48d: A substantial fraction of soluble envelope glycoprotein trimers contained inter-subunit disulfide bonds. Reduction of these disulfide bonds decreased binding of 48d to the glycoprotein, indicating that the inter-S-S bonds contribute to the exposure of the CD4-induced region. Yuan *et al.* [2005] (**antibody binding site definition and exposure**)
- 48d: This review summarizes MAbs directed to HIV-1 Env. There are six CD4 inducible MAbs and Fabs in the database. The MAb forms neutralize TCLA strains only, but the smaller Fabs and scFv fragments can neutralize primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 48d: Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The loss of the glycan within the V3 loop (GM299 V3) and two sites adjacent to V3, C2 (GM292 C2) and (GM329 C3), increased neutralization susceptibility to CD4i FAb X5, but each of the glycan mutants and SF162 were refractive to neutralization with 48d and 17b. The loss of sites in C4 (GM438 C4), or V5 (GM454 V5) did not increase neutralization susceptibility to FAb X5. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- 48d: A set of HIV-1 chimeras that altered V3 net charge and glycosylation patterns in V1V2 and V3, involving inserting V1V2 loops from a late stage primary isolate taken after the R5 to X4 switch, were studied with regard to phenotype, co-receptor usage, and MAb neutralization. The loops were cloned into a HXB2 envelope with a LAI viral backbone. It was observed that the addition of the late-stage isolate V1V2 region and the loss of V3-linked glycosylation site in the context of high positive charge gave an X4 phenotype. R5X4, R5, and X4 viruses were generated, and sCD4, 2G12 and b12 neutralization resistance patterns were modified by addition of the late stage V1V2, glycosylation changes, and charge in concert, while neutralization by 2F5 was unaffected. 15e, 17b, and 48d could not neutralize any of the variants tested. Nabatov *et al.* [2004] (**antibody binding site definition and exposure**, **co-receptor**)
- 48d: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 48d. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- 48d: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neturalization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Three CD4i MAbs were tested; all preferentially neutralized SF162, and JRFL became neutralization sensitive to CD4i Abs if the SF162 V1V2 loop was exchanged. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 48d: Called 4.8d. The MAb B4e8 binds to the base of the V3 loop, neutralizes multiple primary isolates and was studied for interaction with other MAbs. B4e8 enhanced binding of CD4i MAbs 4.8d, 1.7b, and A1g8 to R5X4 virus 92HT593, but only of 48d to the R5 virus 92US660, and there was only a modest impact of the combination of B4e8 and CD4i MAbs on

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neutralization. Cavacini *et al.* [2003] (**antibody interactions**, **co-receptor**)

- 48d: 48d was used as a negative control to test CDR3 tyrosine sulfation of MAbs 47e, 412d, CM51 and E51, since it lacks CDR3 tyrosines. As expected, 48d did not incorporate sulfates while the other MAbs did. Neutralization assays showed that 48d was less efficient at neutralizing primary R5 and R5X4 isolates than MAbs 412d and E51, however, it was more efficient at neutralizing X4 isolates than these MAbs. Choe *et al.* [2003] (**antibody binding site definition and exposure**, **neutralization**)
- 48d: This study shows the fragments of CD4i MAbs are better able to neutralize virus than whole IgG. Neutralization of HIV-1 R5 isolates JRFL, JR-CSF and ADA by CD4i MAbs X5, 17b, and 48d decreased with increased molecule size, the neutralizing potency of single-chain Fv (scFv) > than Fab fragments > whole Ab molecules. (With the exception of IgG 48d neutralization of HIV-1 ADA being better than the Fab – for 48d, only the IgG and Fab forms were available, not the scFv.) HIV-1 X4 isolates 89.6 and HxB2 are both relatively sensitive even to the larger IgG version. R5X4 isolate neutralization was dependent on the isolate and co-receptor usage. The CD4i MAb fragments neutralize HIV-1 subsequent to CD4 binding. The CD4i MAbs bind near the co-receptor binding sites on gp120. Co-receptors bind to the conserved beta19 strand and part of the V3 loop, regions that are masked by the V1V2 loops in the CD4-unbound state. When CD4 is bound, the co-receptor site is exposed near the membrane surface where it would be optimally accessible to co-receptors, and the smaller versions of the molecules are better able to overcome the steric hindrence. Labrijn *et al.* [2003] (**antibody binding site definition and exposure**, **co-receptor**, **variant cross-recognition or cross-neutralization**)
- 48d: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- 48d: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a CD4i MAb that had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
- 48d: This study examined antibody interactions, binding and neutralization with a B clade R5 isolate (92US660) and R5X4 isolate (92HT593). Abs generally bound and neutralized the R5X4 isolate better than the R5 isolate. Anti-V3 MAb B4a1 increased binding of CD4i MAbs 48d, 17b and A1g8, but only A1g8 binding was increased by B4a1 to the R5 isolate. Additive affects on neutralizaton of the R5X4 isolate with B4a1 and CD4i MAbs was observed, presumably due to increased exposure of the CD4i binding site, but not for the R5 isolate. Anti-gp41 MAb F240 had a synergistic effect on neutralization with CD4i MAbs 48d and 17b, but not with A1g8 for the R5X4 virus. Cavacini *et al.* [2002] (**variant cross-recognition or cross-neutralization**)
- 48d: Truncation of the gp41 cytoplasmic domain of X4, R5, and X4R5 viruses forces a conformation that more closely resembles the CD4 bound state of the external Envelope, enhancing binding of CD4i MAbs 17b and 48d and of CD4BS MAbs F105, b12, and in most cases of glycosylation site dependent MAb 2G12 and the anti-gp41 MAb 246D – in contrast, binding of the anti-V2 MAb 697D and the anti-V3 MAb 694/98D were not affected – viruses bearing the truncation were more sensitive to neutralization by MAbs 48d, b12, and 2G12 – the anti-C5 MAb 1331A was used to track levels of cell surface expression of the mutated proteins. Edwards *et al.* [2002] (**co-receptor**)
- 48d: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – the preincubation 31.5 C step did not alter the inhibitory activity of neutralizing Abs anti-gp41 2F5, or anti-gp120 2G12, IG1b12, 48d, and 17b. Golding *et al.* [2002b]
- 48d: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar. Enthalpy and entropy changes were divergent, but compensated. Not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs (17b, 48d, 1.5e, b6, F105 and F91) had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, but the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. The high values suggest surface burial or protein folding an ordering of amino acids. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- 48d: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91 was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS

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MAbs. Xiang *et al.* [2002b]

- 48d: Five CD4i MAbs were studied, 17b, 48d and three new MAbs derived by Epstein-Barr virus transformation of PBMC from an HIV+ long term non-progressor – 23e and 21c were converted to hybridomas to increase Ab production – all compete with the well-characterized 17b CD4i MAb in an ELISA antigen capture assay – critical binding residues are mapped and the CD4i MAb epitopes were distinct but share a common element near isoleucine 420, also important for CCR5 binding, and all five can block CCR5 binding to a sCD4-gp120 complex – the MAb 48d has the epitope most similar to the CCR5 binding site. Xiang *et al.* [2002a] (**antibody binding site definition and exposure**, **co-receptor**)
- 48d: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibritin – stabilized oligomer gp140 delta683(-FT) showed strong preferential recognition by NAbs IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAbs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002]
- 48d: Called 4.8D – A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002] (**variant cross-recognition or cross-neutralization**)
- 48d: Using a cell-fusion system, it was found CD4i antibodies 17b, 48d, and CG10 reacted faintly with Env expressing HeLA cells even in the absence of sCD4 or CD4 expressing target cells. Reactivity increased after sCD4 addition, but not after CD4 expressing target cell addition, and binding was not increased at the cell-to-cell CD4-Env interface. This suggests the CD4i co-receptor binding domain is largely blocked at the cell-fusion interface, and so CD4i antibodies would not be able access this site and neutralize cell-mediated viral entry. Finnegan *et al.* [2001] (**antibody binding site definition and exposure**)
- 48d: Mutations in two glcosylation sites in the V2 region of HIV-1 ADA at positions 190 and 197 (187 DNTSYRLINC-NTS 199) cause the virus to become CD4-independent and able to enter cells through CCR5 alone – these same mutations tended to increase the neutralization sensitivity of the virus, including to 48d – only the CD4i antibodies 17b and 48d showed an increased affinity of the CD4 independent viruses relative to wild-type. Kolchinsky *et al.* [2001]
- 48d: Called 4.8d – A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001]
- 48d: Called 4.8D – host encoded intercellular adhesion molecule (ICAM-1) is incorporated by the HIV-1 virion and enhances viral infectivity – ICAM-1 does not modify virus sensitivity to antibodies 0.5beta or 4.8D or sCD4, but neutralizing ability of F105 was diminished in ICAM bearing virions in the presence of lymphocyte function-association antigen-1 (LFA-1) Ab. Fortin *et al.* [2000]
- 48d: SF162 is a neutralization-resistant HIV-1 isolate – N-linked glycosylation modifications in the V2 loop of the SF162 gp120 revealed that these sites prevent neutralization by CD4BS MAbs (IgG1b12 and IgGCD4), and protect against neutralization by V3 MAbs (447-D and 391-95D) – V2-region glycosylation site mutations did not alter neutralization resistance to V2 MAbs (G3.4 and G3.136) or CD4i MAbs (17b and 48d) – V2 glycosylation site modification allows infection of macrophages, probably due to glycosylated forms requiring fewer CCR5 molecules for viral entry. Ly & Stamatatos [2000]
- 48d: Six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000]
- 48d: sCD4 can activate fusion between effector cells expressing Env and target cells expressing coreceptor (CCR5 or CXCR4) alone without CD4 – CD4i MAbs 17b and 48d have little effect on a standard cell fusion assay but potently block sCD4 activated fusion. Salzwedel *et al.* [2000] (**co-receptor**)
- 48d: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000]
- 48d: A CD4-independent viral variant of IIIB, IIIBx, was generated on CXCR4-expressing cells – IIIBx exhibited greater exposure of the 17b and 48d epitopes and enhanced neutralization by CD4i MAbs and by polyclonal human sera. Hoffman *et al.* [1999]
- 48d: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer – CD4i MAbs 17b and 48d bound better to the deleted protein than to wild type. Binley *et al.* [1998]

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- 48d: Infection of dendritic cells cultured from CD14+ blood cells or from cadaveric human skin was blocked by neutralizing MAbs IgG1b12, or 2F5 and 2G12 delivered together, but not by control non-neutralizing anti-gp120 MAb 4.8D, indicating that NAbs could interrupt early mucosal transmission events. Frankel *et al.* [1998]
- 48d: Inhibits binding of Hx10 to both CD4 positive and CD4 negative HeLa cells. Mondor *et al.* [1998]
- 48d: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- 48d: Deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V2 but not V1 enabled neutralization by CD4i MAbs 17b and 48d. Stamatatos & Cheng-Mayer [1998]
- 48d: CD4i MAbs 17b and 48d compete with MAb CG10, and the binding sites may overlap – MAb A32 enhances binding of 17b, 48d and CG10. Sullivan *et al.* [1998b]
- 48d: Summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAb binding – probable mechanism of neutralization of 48d is interference with chemokine receptor binding – CD4 binding increases exposure of epitope due to V2 loop movement – 88N, 117K, 121K, 256S, 257T, N262, delta V3, E370, E381, F 382, R 419, I 420, K 421, Q 422, I 423, W 427, Y 435, P 438, M 475 mutations in HXBc2 (IIIB) decrease binding. Wyatt *et al.* [1998] (**structure**)
- 48d: A neutralization assay was developed based on hemi-nested PCR amplification of the LTR (HNPCR) – LTR-HNPCR consistently revealed HIV DNA and was shown to be a rapid, specific and reliable neutralization assay based on tests with 6 MAbs and 5 isolates. Yang *et al.* [1998]
- 48d: Prefers CD4-gp120 complex to gp120 alone, but does not enhance fusion, in contrast to MAb CG10, in fact it inhibits syncytium formation. Lee *et al.* [1997] (**antibody binding site definition and exposure**)
- 48d: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env – all Ab combinations tested showed synergistic neutralization – 48d has synergistic response with MAbs 694/98-D (anti-V3) and F105. Li *et al.* [1997] (**antibody interactions**)
- 48d: Neutralizes TCLA strains, but not primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 48d: Viral binding inhibition by 48d was strongly correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5). Ugolini *et al.* [1997]
- 48d: 48d binds to the IIIB protein and not IIIB V3 peptide, while binding to the Can0A V3 peptide, suggesting Can0A V3 is a conformer that mimics the 48d, (but not 17b), epitope. Weinberg *et al.* [1997] (**antibody binding site definition and exposure**)
- 48d: Binds efficiently to sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
- 48d: Many MAbs inhibit binding (anti-C1, -C5, -C4, -CD4BS) – anti-C1-C4 discontinuous epitope MAbs A32 and 2/11c enhance binding – reciprocal enhanced binding with some anti-V2 MAbs. Moore & Sodroski [1996] (**antibody interactions**)
- 48d: Binding resulted in gp120 dissociation from virion, mimicking sCD4, and exposure of the gp41 epitope of MAb 50-69, in contrast to CD4BS MAbs. Poignard *et al.* [1996a] (**antibody interactions**)
- 48d: Neutralizes JR-FL – slightly inhibits gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a] (**antibody binding site definition and exposure**, **co-receptor**)
- 48d: Called 4.8D – Found to neutralize MN, but not JRCSF, two B subtype primary isolates, or a D subtype primary isolate, by most labs in a multi-laboratory study involving 11 labs. D'Souza *et al.* [1995] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 48d: Formalin inactivation of virus at 0.1% formalin for 10 hours at 4 degrees was optimal for inactivation of virus while maintaining epitope integrity. Sattentau *et al.* [1995] (**vaccine antigen design**)
- 48d: Binds with similar affinity to monomer and oligomer, moderate association rate, potent neutralization – this is in contrast to 17b, which has very different kinetics. Sattentau & Moore [1995] (**antibody binding site definition and exposure**, **kinetics**, **binding affinity**)
- 48d: Studies using a V1/V2 deletion mutant demonstrated that enhanced binding of 48d in the presence of sCD4 involves the V1/V2 loops, with more significant involvement of V2 – similar effect observed for 17b and A32. Wyatt *et al.* [1995] (**vaccine antigen design**)
- 48d: Poor cross-reactivity with gp120 from most clades. Moore *et al.* [1994b] (**subtype comparisons**)
- 48d: A mutation in gp41, 582 A/T, confers resistance to neutralization (also confers resistance to MAbs F105, 21h, 15e and 17b). Thali *et al.* [1994] (**variant cross-recognition or cross-neutralization**)
- 48d: Called 4.8d – Neutralizes IIIB – reactive with SF-2 gp120 – does not inhibit HIV-1 sera from binding to IIIB gp120. Moore & Ho [1993] (**variant cross-recognition or cross-neutralization**)
- 48d: Binding of 48d is much more influenced by sequence variation among molecular clones of LAI than is binding of 17b. Moore *et al.* [1993c] (**variant cross-recognition or cross-neutralization**)
- 48d: Epitope is better exposed upon CD4 binding to gp120 – competes with ICR 39.13, 15e and 21h, anti-CD4 binding site MAbs – inhibited by anti-CD4BS MAb ICR 39.13g and linear anti-C4 MAbs G3-42 and G3-508 – 113 D/R, 252 R/W, 257 T/A or G, 370 E/D, 382 F/L, 420 I/R, 421 K/L, 433A/L, 438 P/R and 475 M/S confer decreased sensitivity to neutralization. Thali *et al.* [1993] (**antibody binding site definition and exposure**, **antibody interactions**)

No. 1437
MAb ID 49e
HXB2 Location Env

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Author Location gp120 (IIIB, J62)
Epitope
Subtype B
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
Ab Type gp120 CD4i
Research Contact James Robinson, Tulane University, New Orleans, LA, USA
References Srivastava *et al.* 2005; Gorny & Zolla-Pazner 2004; Xiang *et al.* 2002b; Xiang *et al.* 2002a
Keywords antibody binding site definition and exposure, antibody generation, review, vaccine antigen design

- 49e: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **vaccine antigen design**, **review**)
- 49e: This review summarizes MAbs directed to HIV-1 Env. There are six CD4 inducible MAbs and Fabs in the database. The MAb forms neutralize TCLA strains only, but the smaller Fabs and scFv fragments can neutralize primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 49e: Five CD4i MAbs were studied, 17b, 48d and three new MAbs derived by Epstein-Barr virus transformation of PBMC from an HIV+ long term non-progressor – 23e and 21c were converted to hybridomas to increase Ab production – all compete with the well-characterized 17b CD4i MAb in an ELISA antigen capture assay – critical binding residues are mapped and the CD4i MAb epitopes were distinct but share a common element near isoleucine 420, also important for CCR5 binding, and all five can block CCR5 binding to a sCD4-gp120 complex – the MAb 48d has the epitope most similar to the CCR5 binding site. Xiang *et al.* [2002a] (**antibody binding site definition and exposure**, **antibody generation**)
- 49e: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91 was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b] (**antibody binding site definition and exposure**, **vaccine antigen design**)

No. 1438
MAb ID Fbb21
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4i
References Zwick *et al.* 2003
Keywords antibody interactions

- Fbb21: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This is a novel CD4i Fab first used in this study. Fbb21, like other CD4i MAbs, did not inhibit or enhance 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)

No. 1439
MAb ID Fbb21
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4i
References Zwick *et al.* 2003
Keywords antibody interactions

- Fbb21: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This is a novel CD4i Fab first used in this study. Fbb21, like other CD4i MAbs, did not inhibit or enhance 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)

No. 1440
MAb ID X5 (Fab X5)
HXB2 Location Env
Author Location gp120 (JRFL)
Epitope
Subtype B
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 CD4i

References Willey & Aasa-Chapman 2008; Vaine *et al.* 2008; Polonis *et al.* 2008; Pantophlet *et al.* 2008; Martin *et al.* 2008; Liu *et al.* 2008; Crooks *et al.* 2008; Zhang & Dimitrov 2007; Phogat *et al.* 2007; McKnight & Aasa-Chapman 2007; Lin & Nara 2007; Kramer *et al.* 2007; Joos *et al.* 2007; DeVico *et al.* 2007; Crooks *et al.* 2007; Bowley *et al.* 2007; Nelson *et al.* 2008; Moore *et al.* 2006; Derby *et al.* 2006; Cham *et al.* 2006; Choudhry *et al.* 2006; Binley *et al.* 2006; Stanfield & Wilson 2005; Srivastava *et al.* 2005; Miller *et al.* 2005; Mc Cann *et al.* 2005; Huang *et al.* 2005a; Crooks *et al.* 2005; Burton *et al.* 2005; Pinter *et al.* 2004; Pantophlet *et al.* 2004; McCaffrey *et al.* 2004; Darbha *et al.* 2004; Binley *et al.* 2004; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2004; Zwick *et al.* 2003; Zhang *et al.* 2003; Labrijn *et al.* 2003; Binley *et al.* 2003; Moulard *et al.* 2002

Keywords antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, assay development, assay standardization/improvement, binding affinity, coreceptor, kinetics, neutralization, review, structure, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- X5: The study compared Ab neutralization against the JR-FL primary isolate and trimer binding affinities judged by native PAGE. There was direct quantitative relationship between monovalent Fab-trimer binding and neutralization, implying that neutralization begins as each trimer is occupied by one Ab. In BN-PAGE, neutralizing Fabs and sCD4 were able to shift JR-FL trimers. In contrast, most non-neutralizing Fabs, bound to monomer, but their epitopes were conformationally occluded on trimers, confirming the exclusive relationship of trimer binding and neutralization. Fab X5 did not bind effectively to gp120/gp41 monomers and may therefore recognize other forms of Env. Crooks *et al.* [2008] (**neutralization**, **binding affinity**)
- X5: Coordinates of the three-dimensional structure of trimeric Env displayed on native HIV-1 in complex with X5 were fitted on a density map, to reveal the structure of the trimeric glycoprotein spike on native HIV-1. Liu *et al.* [2008] (**antibody binding site definition and exposure**, **structure**)
- X5: A new purification method was developed using a high affinity peptide mimicking CD4 as a ligand in affinity chromatography. This allowed the separation in one step of HIV envelope monomer from cell supernatant and capture of pre-purified trimer. Binding of X5 to gp120SF162 purified by the miniCD4 affinity chromatography and a multi-step method was comparable, suggesting that the miniCD4 allows the separation of HIV-1 envelope with intact X5 epitope. gp140DF162ΔV2 was purified by the miniCD4 method to asses its ability to capture gp140 trimers. Purified gp140DF162ΔV2 was recognized by X5, and the k-off value for X5 was reduced compared to gp120SF162 monomer, consistent with the gp140DF162ΔV2 trimeric conformation. Binding of X5 to gp140DF162ΔV2 purified by the miniCD4 affinity chromatography and a multi-step method was comparable, suggesting that the SF162 trimer antigenicity was preserved. Martin *et al.* [2008] (**assay development**, **kinetics**, **binding affinity**)
- X5: Immobilized X5 was able to capture infectious HIV-1 whole virions in a standard virus capture assay, unlike mAbs 8K8 and D5. Addition of soluble CD4 enhanced significantly virion capture by X5. Nelson *et al.* [2008]
- X5: The structure of a soluble CD4-FabX5-complexed gp120 core with the V3 loop attached was used to project the results of MAb mapping onto V3 in order to obtain better understanding of the spatial organization of residues identified as important for V3 MAb binding. Pantophlet *et al.* [2008] (**structure**)
- X5: This minireview summarizes data on differences in neutralizing activities of MAbs and pooled human sera using a traditional primary cell neutralization assay and the more standardized TZM-bl reporter cell line assay. Also, suggestions are made on how to improve and standardize neutralization assays for comparable use in different laboratories. It has previously been shown that X5 neutralizes considerably better in the PBMC assay, where the CD4/CCR5 ratio is approximately 10-fold larger than in the TZM-assay cells, underscoring the role of the cell substrate in neutralization assays. In total, however, the assay discordances were shown to be bi-directional and not attributable to assay sensitivity. Polonis *et al.* [2008] (**neutralization**, **review**, **assay standardization/improvement**)
- X5: Sera from both gp120 DNA prime-protein boost immunized rabbits and from protein-only immunized rabbits did not compete for binding to X5, indicating no elicitation of X5-like Abs by either of the immunization regimens. Vaine *et al.* [2008] (**vaccine antigen design**)
- X5: The various effects that neutralizing and non-neutralizing anti-envelope Abs have on HIV infection are reviewed, such as Ab-mediated complement activation and Fc-receptor mediated activities, that both can, through various mechanisms, increase and decrease the infectivity of the virus. The importance of these mechanisms in vaccine design is discussed. The unusual features of the X5 MAb are described. Willey & Aasa-Chapman [2008] (**review**)
- X5: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. X5 was identified using both methods. Bowley *et al.* [2007] (**antibody generation**, **binding affinity**, **antibody sequence variable domain**, **assay standardization/improvement**)
- X5: Guinea pigs were immunized with gp120 protein or with three types of VLPs containing disulfide-shackled functional trimers (SOS-VLP), uncleaved nonfunctional Env (UNC-VLP), naked VLP bearing no Env. Most of the Env-VLP sera and HIV-1 + plasma effectively blocked X5 capture. Crooks *et al.* [2007] (**neutralization**)

- X5: Macaques were immunized with either CD4, gp120, cross-linked gp120-human CD4 complex (gp120-CD4 XL), and with single chain complex containing gp120 rhesus macaque CD4 domains 1 and 2 (rhFLSC). Sera from the rhFLSC immunized animals showed highest competition titers, being able to block gp120-CD4 complex interactions with X5 more efficiently than sera from animals immunized with the three other proteins. DeVico *et al.* [2007] (**neutralization**)
- X5: HIV-1 env sequence evolution was studied in 20 HIV-1 infected individuals undergoing treatment interruptions. By using the 3D structure of gp120 in complex with CD4 and X5, the amino acid residues that were found to be under positive selection mapped exclusively to the externally accessible residues of the gp120. There was no correlation between the number of positively selected amino acid sites and neutralizing Ab titers. Joos *et al.* [2007]
- X5: This review summarizes X5 Ab epitope, properties and neutralization activity. The effect of differential CCR5 cell surface expression on X5 neutralization activity is discussed. Kramer *et al.* [2007] (**co-receptor**, **neutralization**, **review**)
- X5: X5 structure, sulfation, binding, and neutralization activity are reviewed in detail. Improvement of potency and breadth of X5 neutralization is discussed. Vaccine strategies for elicitation of CD4i Abs are summarized. Lin & Nara [2007] (**review**)
- X5: This review summarizes data on possible vaccine targets for elicitation of neutralizing Abs and discusses whether it is more practical to design a clade-specific than a clade-generic HIV-1 vaccine. Development of a neutralizing Ab response in HIV-1 infected individuals is reviewed, including data that show no apparent division of different HIV-1 subtypes into clade-related neutralization groups. Also, a summary of the neutralizing activity of mAb X5 in different HIV-1 clades is provided. McKnight & Aasa-Chapman [2007] (**variant cross-recognition or cross-neutralization**, **review**)
- X5: This review provides information on the HIV-1 glycoprotein properties that make it challenging to target with neutralizing Abs. X5 neutralization properties and binding to HIV-1 envelope, and current strategies to develop versions of the Env spike with functional trimer properties for elicitation of broadly neutralizing Abs, are discussed. In addition, approaches to target cellular molecules, such as CD4, CCR5, CXCR4, and MHC molecules, with therapeutic Abs are reviewed. Phogat *et al.* [2007] (**review**)
- X5: Novel approaches based on sequential (SAP) and competitive (CAP) antigen panning methodiologies, and use of antigens with increased exposure of conserved epitopes, for enhanced identification of broadly cross-reactive neutralizing Abs are reviewed. Abs identified by these methods are described. Zhang & Dimitrov [2007] (**review**)
- X5: Virus was not neutralized by X5 in a standard neutralization assay, while pre-incubation of virus with sCD4 resulted in neutralization by X5 as its epitope was exposed upon binding to CD4. Binley *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)
- X5: Cloned Envs (clades A, B, C, D, F1, CRF01_AE, CRF02_AG, CRF06_cpx and CRF11_cpx) derived from donors either with or without broadly cross-reactive neutralizing antibodies were shown to be of comparable susceptibility to neutralization by X5. Cham *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- X5: Neutralization of HIV-1 primary isolates from different clades (B, C, D and E) by X5 was determined in cells expressing high or low surface concentrations of CD4 and CCR5 receptors. CD4 cell surface concentration had no effect on the inhibitory activity of this Ab while the CCR5 surface concentration had a significant effect decreasing the 50% inhibitory concentration of X5 in cell lines with low CCR5. Choudhry *et al.* [2006] (**co-receptor**, **neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- X5: Macaques were immunized with SF162gp140, ΔV2gp140, ΔV2ΔV3gp140 and ΔV3gp140 constructs and their antibody responses were compared to the broadly reactive NAb responses in a macaque infected with SHIV SF162P4, and with pooled sera from humans infected with heterologous HIV-1 isolates (HIVIG). X5-like Abs were elicited at low titers by ΔV3gp140 but not by the other immunogens. They were also present in the SHIV-infected macaque. Derby *et al.* [2006] (**antibody binding site definition and exposure**, **antibody generation**)
- X5: In addition to gp120-gp41 trimers, HIV-1 particles were shown to bear nonfunctional gp120-gp41 monomers and gp120-depleted gp41 stumps on their surface. X5 did not neutralize wildype virus particles and it did not bind to functional gp12-gp41 trimers. It did, however, partially react with SOS, a mutant containing a disulfide bond between gp120 and gp41. X5 is able to recognize gp120-gp41 monomers and monomeric gp120. It is hypothesized that the nonfunctional monomers on the HIV-1 surface serve to divert the Ab response, helping the virus to avoid neutralization. Moore *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**)
- X5: The structure of the X5 MAb, particularly its CDRH3 region tyrosine sulfation, is reviewed. Also, the mechanism of its binding to the coreceptor binding site of gp120, and comparisons of the neutralizing potencies of X5 Ab fragments vs the whole IgG molecule are discussed. Engineering of Abs based on revealed structures of broadly neutralizing MAbs is discussed. Burton *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **review**, **structure**)
- X5: X5 was investigated in differnt neutralization formats, including the standard format that measures activity over the entire infection period and several formats that emphasize various stages of infection. Significant activity of X5 was induced in the post-CD4 format while it did not neutralize JR-FL in the standard format. X5 did not have any activity in the post-CD4/CCR5 format. This suggests that the post-CD4, pre-CCR5 phase of infection is a narrow window of opportunity for neutralization of JR-FL by X5 Ab. Truncation of the gp160 cytoplasmic tail or addition of a disulfide bridge linking gp120 and gp41 did not increase X5 activity. Visualization of Env-Ab binding was conducted by BN-PAGE band shifts. Crooks *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **assay standardization/improvement**)

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- X5: The structure of the V3 region in the context of gp120 core complexed to the CD4 receptor and to the X5 Ab was determined by X-ray resolution. Comparison of free and bound X5 structure showed a large structural difference for the third complementary loop of the X5 heavy chain, representing one of the largest induced fits observed for an antibody. Accessibility of co-receptor binding site to this MAb is shown in a 3D figure. Huang *et al.* [2005a] (**antibody binding site definition and exposure**, **structure**)
- X5: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **review**)
- X5: Used as a positive control in an HIVRP assay to confirm specificity of the inhibition of viral and cellular membrane fusion by the screened scFvs. Miller *et al.* [2005]
- X5: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **review**)
- X5: This review summarizes data on 447-52D and 2219 crystallographic structures when bound to V3 peptides and their corresponding neutralization capabilities. X5, like 447-52D and like other HIV-1 neutralizing Abs, was shown to have long CDR H3 loop, which is suggested to help Abs access recessed binding sites on the virus. Stanfield & Wilson [2005] (**antibody binding site definition and exposure**, **review**, **structure**)
- X5: 93 viruses from different clades were tested for their neutralization cross-reactivity using a panel of HIV antibodies. X5 is a CD4i antibody and neutralized only the most sensitive B-clade envelopes in the pseudovirus assay, but was able to neutralize 2/25 non-B isolates in the PBMC assay, possibly due to differential corecptor expression. Binley *et al.* [2004] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- X5: The structure of the Fab X5 was determined at 1.9 angstrom resolution. The binding site is a long, 22 amino acid CDR H3 with a hook shape. Long CDR H3s are also found in IgG1b12 (18 residues) and 17b (19 residues). FAb X5 has a W100, F100Y in the CDR H3 hook shown to be important for binding through site specific mutagenesis. Compared to JRCSF, Ala substitutions at eight residues reduced binding more than 3 fold: C119, K207, G367, M426, W427, V430, I423, and K432. Only I423A and K432A were thought to possibly directly interact with X5, the other mutations were thought likely to disrupt the overall structure or CD4 binding. Darbha *et al.* [2004] (**antibody binding site definition and exposure**, **structure**)
- X5: This review summarizes MAbs directed to HIV-1 Env. There are six CD4 inducible MAbs and Fabs in the database. The MAb forms neutralize TCLA strains only, but the smaller Fabs and scFv fragments can neutralize primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- X5: Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The loss of the glycan within the V3 loop (GM299 V3) and two sites adjacent to V3, C2 (GM292 C2) and (GM329 C3), increased neutralization susceptibility to CD4i FAb X5, but each of the glycan mutants and SF162 were refractive to neutralization with 48d and 17b. The loss of sites in C4 (GM438 C4), or V5 (GM454 V5) did not increase neutralization susceptibility to FAb X5. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure**, **vaccine antigen design**)
- X5: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including X5. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- X5: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neturalization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Three CD4i MAbs were tested; all preferentially neutralized SF162, and JRFL became neutralization sensitive to CD4i Abs if the SF162 V1V2 loop was exchanged. FAb X5 could neutralize both viruses, but had reduced potency against JRFL. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- X5: Called Fab X5. This paper is a study of the 2F5 NAb complexed to peptide ELDKWAS; the peptide was found to interact with amino acids near the base of the very long (22 residue) CDR 3H region of the Ab, although a Phe at the apex of the loop was also important. The authors suggest that particularly long CDR H3 regions may be a common feature of HIV-1 neuturalizing antibodies – there are 22 residues in 2F5's H3, 18 in b12's H3, and 22 residues in X5's H3. They ex-

press concern that because small animals like mice are unable to elicit Ab responses with such long H3s, they may be poor model systems for HIV vaccine studies. Zwick *et al.* [2004] (**antibody interactions**)

- X5: The SOS mutant envelope protein introduces a covalent disulfide bond between gp120 surface and gp41 transmembrane proteins into the R5 isolate JR-FL by adding cysteines at residues 501 and 605. Pseudovirions bearing this protein bind to CD4 and co-receptor bearing cells, but do not fuse until treatment with a reducing agent, and are arrested prior to fusion after CD4 and co-receptor engagement. CD4i Abs X5 and 17b were weakly neutralizing in all formats, WT, SOS, and when added postbinding. Binley *et al.* [2003] (**vaccine antigen design**)
- X5: This study shows the fragments of CD4i MAbs are better able to neutralize virus than whole IgG. Neutralization of HIV-1 R5 isolates JRFL, JR-CSF and ADA by CD4i MAbs X5, 17b, and 48d decreased with increased molecule size, the neutralizing potency of single-chain Fv (scFv) > than Fab fragments > whole Ab molecules. (With the exception of IgG 48d neutralization of HIV-1 ADA.) HIV-1 X4 isolates 89.6 and HxB2 are both relatively sensitive even to the larger IgG version. R5X4 isolate neutralization was dependent on the isolate and co-receptor usage. The CD4i MAb fragments neutralize HIV-1 subsequent to CD4 binding. The CD4i MAbs bind near the co-receptor binding sites on gp120. Co-receptors bind to the conserved beta19 strand and part of the V3 loop, regions that are masked by the V1V2 loops in the CD4-unbound state. When CD4 is bound, the co-receptor site is exposed near the membrane surface where it would be optimally accessible to co-receptors, and the smaller versions of the molecules are better able to overcome the steric hindrence. Labrijn *et al.* [2003] (**antibody binding site definition and exposure**, **co-receptor**, **variant cross-recognition or cross-neutralization**)
- X5: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- X5: The Fab m18 was selected from a human phage display library by a new method called sequential antigen panning (SAP), using a series of antigens to screen the library to pick broadly cross-reactive isolates. The ability to block cell mediated fusion by m18 was compared to Fabs X5 and b12 for a clade A, CRF01 EA, G, and 6 clade B isolates, and the inhibitory activity of m18 was slightly lower but comparable to neutralizing Fabs b12 and X5. It also showed broad cross-neutralization; 11/15 pseudotyped Envs from primary isolates from clades A-F were inhibited in an IC50 assay at concentration less than or equal to 100 ug/ml; X5 was also tested and somewhat more potent, generally requiring lower concentrations and inhibiting 13/15 primary isolates. Zhang *et al.* [2003] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- X5: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a CD4i MAb that had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
- X5: The human Fab X5 was selected from a phage display library derived from an HIV-1 positive donor with a highly neutralizing serum – it was selected for binding to purified gp120-CD4-coreceptor complexes – the Fab neutralizes PBMC infection by a selection of HIV-1 primary isolates from clades A, B, C, D, E, F, and G, and neutralizes R5, X4, and R5X4 isolates – it binds to a conserved epitope on gp120 induced by CD4 binding, its binding is slightly enhanced by CCR5 binding – while CD4i MAb 17b binds the CCR5 binding site, X5 also competes with Fab b12 which overlaps with the CD4 binding site, suggesting the epitope for is near both the CD4 and CCR5 binding sites. Moulard *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No.	1441
MAb ID	8F101
HXB2 Location	Env
Author Location	gp120
Epitope	
Neutralizing	
Immunogen	vaccine *Vector/Type:* sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype)	mouse (IgG)
Ab Type	gp120 CD4i, gp120-CD4 complex
Research Contact	Ranajiit Pal, Advanced BioScience Lab, Inc.
References	Finnegan *et al.* 2002; Finnegan *et al.* 2001; DeVico *et al.* 1995
Keywords	antibody binding site definition and exposure, antibody generation, kinetics

- 8F101: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I and Cluster II MAbs required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor, binding to a fusion intermediate. 8F101 selectively stains gp120-CD4 complexes after dissociation from gp41, and did not stain cells arrested earlier than 30 min of co-culture, but 8F101 and cluster I and II MAbs co-localized at fusing cell interfaces at 30 min coculture. After extended co-culture, only 8F101 bound. Finnegan *et al.* [2002] (**antibody binding site definition and exposure**, **kinetics**)
- 8F101: Using a cell-fusion system, it was found CD4i antibodies 17b, 48d, and CG10 reacted faintly with Env expressing HeLA cells even in the absence of sCD4 or CD4 expressing target cells. Reactivity increased after sCD4 addition, but not after CD4 expressing target cell addition, and binding was not increased at the cell-to-cell CD4-Env interface. This suggests the CD4i co-receptor binding domain is largely blocked

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at the cell-fusion interface, and so CD4i antibodies would not be able access this site and neutralize cell-mediated viral entry. However, CD4i MAbs 8F101 and A32, that bind outside the co-receptor domain, had a different pattern. They reacted after the formation of gp120-CD4-CXCR4 tri-complexes, so co-receptor interactions allowed exposure of their epitopes. Finnegan *et al.* [2001] (**antibody binding site definition and exposure**)
- 8F101: MAbs specifically reactive to crosslinked gp120 and CD4 were derived (8F101, 8F102) – conformation dependent – competition studies indicate the epitope is immunogenic in infected humans. DeVico *et al.* [1995] (**antibody generation**)

No. 1442
MAb ID T22
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type Env oligomer
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Otteken *et al.* 1996; Earl *et al.* 1994
- T22: A comparison of 25 gp120 specific, conformation dependent MAbs was done – T22 is part of a group of MAbs labeled AII – all AII MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, and could only partially blocked CD4 binding. Sugiura *et al.* [1999]
- T22: Pulse label experiments of 4 MAbs (D20, D27, T20, and T22) binding to noncleavable gp140 revealed that these anti-CD4BS MAbs bound with a delay, and that the epitope formed with a t 1/2 of about 10 minutes. Otteken *et al.* [1996]
- T22: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1443
MAb ID 2A2
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type N-term
References Weissenhorn *et al.* 1996
- Soluble gp41(21-166) forms a rod like structure that can be visualized with electron microscopy, and 2A2 binds to one end of the rod. Weissenhorn *et al.* [1996]

No. 1444
MAb ID AC4
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing yes
Immunogen vaccine
Vector/Type: protein *HIV component:* gp160
Species (Isotype) mouse
Ab Type N-term
References Dickey *et al.* 2000
- AC4: Three MABs, ID6, AC4, and AD3 that bind to a discontinuous N-term first 204 aa of gp120 and generate ADCC were elicited through vaccination of BALBc mice with rec gp160 – these MAbs do not depend on glycosylation and are cross-reactive with viruses from clades B and CRF01(AE). Dickey *et al.* [2000]

No. 1445
MAb ID AD3
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing yes
Immunogen vaccine
Vector/Type: protein *HIV component:* gp160
Species (Isotype) mouse
Ab Type N-term
References Cook *et al.* 1994; Dickey *et al.* 2000
- AD3: There may be two Abs with this name that bind to the N-term region of gp120. Cook *et al.* [1994]; Dickey *et al.* [2000]
- AD3: Three MABs, ID6, AC4, and AD3 that bind to a discontinuous N-term first 204 aa of gp120 and generate ADCC were elicited through vaccination of BALBc mice with rec gp160 – these MAbs do not depend on glycosylation and are cross-reactive with viruses from clades B and CRF01(AE). Dickey *et al.* [2000]

No. 1446
MAb ID AD3
HXB2 Location Env
Author Location gp120 (BH10)
Epitope
Neutralizing
Immunogen
Species (Isotype) mouse (IgG1)
Ab Type N-term
References Dickey *et al.* 2000; Cook *et al.* 1994; Ugen *et al.* 1993
- AD3: NIH AIDS Research and Reference Reagent Program: 2342.
- AD3: There may be two Abs with this name that bind to the N-term region of gp120. Cook *et al.* [1994]; Dickey *et al.* [2000]
- AD3: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – MAbs against the N-terminal half of gp120 do not inhibit gp120 binding to GalCer – binding of GalCer to gp120 does not inhibit MAb binding. Cook *et al.* [1994]

No. 1447
MAb ID ID6

HXB2 Location Env
Author Location gp120 (1–193 BH10)
Epitope
Neutralizing
Immunogen
Species (Isotype) mouse (IgG1)
Ab Type N-term
References Dickey *et al.* 2000; Cook *et al.* 1994; Ugen *et al.* 1993

- ID6: NIH AIDS Research and Reference Reagent Program: 2343.
- ID6: There may be two Abs with this name that bind to the N-term region of gp120. Cook *et al.* [1994]; Dickey *et al.* [2000]
- ID6: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – MAbs against the N-terminal half of gp120 do not inhibit gp120 binding to GalCer – binding of GalCer to gp120 does not inhibit MAb binding. Cook *et al.* [1994]

No. 1448
MAb ID ID6
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing yes
Immunogen vaccine
Vector/Type: protein *HIV component:* gp160
Species (Isotype) mouse (IgG2a)
Ab Type N-term
References Cook *et al.* 1994; Dickey *et al.* 2000

- ID6: There may be two Abs with this name that bind to the N-term region of gp120. Cook *et al.* [1994]; Dickey *et al.* [2000]
- ID6: Three MABs, ID6, AC4, and AD3 that bind to a discontinuous N-term first 204 aa of gp120 and generate ADCC were elicited through vaccination of BALBc mice with rec gp160 – these MAbs do not depend on glycosylation and are cross-reactive with viruses from clades B and CRF01(AE). Dickey *et al.* [2000]

No. 1449
MAb ID 11/68b
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L (HXB2)
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) rat (IgG1)
Ab Type gp120 V1-V2
Research Contact Shotton and Dean
References Holl *et al.* 2006a; Peet *et al.* 1998; Shotton *et al.* 1995; McKeating *et al.* 1993b
Keywords dendritic cells, neutralization

- 11/68b: 435 (Y/H) in C4 does not abrogate binding (John Moore, per comm, 1996).
- 11/68b: UK Medical Research Council AIDS reagent: ARP3041.
- 11/68b: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 11/68b: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind – 11/68b was not affected by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]
- 11/68b: Cross-competes with MAbs 62c, 66c, 66a, and CRA-4 – similar to MAb 62c – HXB2 neutralization escape mutant had a D/N substitution at residue 185 – non-reciprocal inhibition of binding of CRA-3 and CRA-6. Shotton *et al.* [1995]
- 11/68b: Changes at residues 183/184 (PI/SG) within V2, 435 (Y/H) in C4, abrogate binding. McKeating *et al.* [1993b]

No. 1450
MAb ID 62c
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) rat (IgG1)
Ab Type gp120 V1-V2
References Holl *et al.* 2006a; Shotton *et al.* 1995
Keywords dendritic cells, neutralization

- 62c: UK Medical Research Council AIDS reagent: ARP3075.
- 62c: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 62c: Cross-competes with MAbs 11/68b, 66c, 66a, and CRA-4 – same cross-competition group as MAb 11/68b – non-reciprocal inhibition of binding of CRA-3 and CRA-6 – substitutions 176-177 FY/AT, 179-180 LD/DL, 183-184 PI/SG, and 191-193 YSL/GSS abrogate binding – binds but does not neutralize Hx10. Shotton *et al.* [1995]

No. 1451
MAb ID CRA-6 (CRA6)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen
Species (Isotype) mouse
Ab Type gp120 V1-V2
References Shotton *et al.* 1995

- CRA-6: Called CRA6 – same competition group as CRA-3. Shotton *et al.* [1995]

No. 1452
MAb ID L15
HXB2 Location Env
Author Location gp120
Epitope

Neutralizing P (weak)
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
Ab Type gp120 V1-V2
References Gorny & Zolla-Pazner 2004; Parren *et al.* 1997b; Ditzel *et al.* 1997
Keywords review, variant cross-recognition or cross-neutralization

- L15: In a review of Envelope binding MAbs in this database, V2-specific MAbs are noted to have some ability to neutralize HIV-1, but generally weak with limited cross-reactivity. L15 and L17 are Fabs specific for V2. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- L15: gp120 immobilized on solid phase by capture with anti-CD4 BS MAb L72 was used for selection of Fabs – 2 anti-V2 Fabs were obtained with very similar epitopes, L15 and L17 – deletions in V1 and V2 abolished binding, and rodent anti-V2 MAbs SC258, CRA3, G3-G4,G3-136, BAT-085, and 52-684 all compete with L15. Ditzel *et al.* [1997]
- L15: Does not neutralize TCLA strains but neutralizes some primary isolates weakly. Parren *et al.* [1997b]

No. 1453
MAb ID T52
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 V1-V2
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1994

- T52: A comparison of 25 gp120 specific, conformation dependent MAbs was done – T52 is one of two MAbs labeled B-II, that had limited cross-reactivity with seven clade B isolates and did not fully blocked CD4 binding – deletion of V1/V2 loops abrogated binding. Sugiura *et al.* [1999]
- T52: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1454
MAb ID T54
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 V1-V2
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1994

- T54: A comparison of 25 gp120 specific, conformation dependent MAbs was done – T54 is one of two MAbs labeled B-II, that had limited cross-reactivity with seven clade B isolates and did not fully blocked CD4 binding – deletion of V1/V2 loops abrogated binding. Sugiura *et al.* [1999]
- T54: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1455
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Neutralizing yes
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V1-V2 and V3-V5
References Gordon & Delwart 2000

- Primary isolates have great differences in susceptibility to neutralization – the variation in V1V2 and V3-V5 was measured by HTA in a set of viruses with a range of neutralization susceptibilities, and greater variability was uncorrelated with resistance to neutralization. Gordon & Delwart [2000]

No. 1456
MAb ID 1088
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 V2
References Berman *et al.* 1997

- 1088: Binds weakly to 2/7 isolates from breakthrough cases from a MN gp120 vaccine trial. Berman *et al.* [1997]

No. 1457
MAb ID 110-B
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: HIV infected-cell lysate *Strain:* B clade BRU *HIV component:* HIV-1
Species (Isotype) mouse
Ab Type gp120 V2
Research Contact Hybridolabs, Institute Pasteur, Paris, France
References Moore *et al.* 1993a

- 110-B: specific for BH10, does not bind to MN, RF, or SF-2 gp120 – binding inhibited by deletion of the V2 loop, and the following amino acid substitutions: 168 K/L, 176/177 FY/AT, 179/180 LD/DL, 183/184 PI/SG, and 192-194 YSL/GSS. Moore *et al.* [1993a]

No. 1458
MAb ID 1357

HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype) human (IgG1κ)
Ab Type gp120 V2
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Gorny & Zolla-Pazner 2004; Ling *et al.* 2002; Nyambi *et al.* 2000; Gorny *et al.* 2000; Nyambi *et al.* 1998
Keywords antibody binding site definition and exposure, co-receptor, review

- 1357: This broad review of anti-Envelope MAbs notes that V2 MAbs are generally weakly neutralizing at best, and somewhat strain specific. Anti-V2 MAbs 1357, 1361, 1393 are non-neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
- 1357: A pseudotyping assay showed that an X4 V3 loop peptide could enhance infectivity of X4 virus, R5 and R5X4 V3 loops peptides could enhance infectivity of an R5 virus, and R5X4 peptides could enhance infectivity of an R5X4 virus. Neither R5 nor R5X4 peptides influenced binding of CD4BS MAbs F105 and Ig1Gb12, but did increase binding of CD4i MAb 17b. Of three V2 MAbs, only 830A, not 2158 or 1357 was enhanced by V3 peptide binding. Ling *et al.* [2002] (**antibody binding site definition and exposure**, **co-receptor**)
- 1357: Blocks binding of MAb 697-D to rgp120, and doesn't react with a protein from which V1V2 has been deleted – binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – V2 MAbs 697-D, 1357 and 1361 favored the monomer by approximately 2 fold. Gorny *et al.* [2000]
- 1357: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 anti-V2 MAbs, which showed weak and sporadic binding, with the most frequent binding to C and D clades. Nyambi *et al.* [2000]
- 1357: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 anti-V2 MAbs, which showed weak and sporadic binding, with the most frequent binding to C and D clades. Nyambi *et al.* [2000]
- 1357: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – V2 Abs 697-D, 1361, and 1357 tended to bind very weakly with a similar pattern of specificity to virions, but bound well to soluble gp120: weak binding only to subtype D MAL. Nyambi *et al.* [1998]

No. 1459
MAb ID 1361
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* gp120
Species (Isotype) human (IgG1κ)
Ab Type gp120 V2
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Nyambi *et al.* 2000; Gorny *et al.* 2000; Nyambi *et al.* 1998

- 1361: Blocks binding of MAb 697-D to rgp120, and doesn't react with a protein from which V1V2 has been deleted – binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – V2 MAbs 697-D, 1357 and 1361 favored the monomer by approximately 2 fold. Gorny *et al.* [2000]
- 1361: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 anti-V2 MAbs, which showed weak and sporadic binding, with the most frequent binding to C and D clades. Nyambi *et al.* [2000]
- 1361: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – V2 Abs 697-D, 1361, and 1357 tended to bind weakly with a similar pattern of specificity to virions, but bound well to soluble gp120: weak binding to 1/4 B clade viruses (CA5), and also weak binding to a subtype D virus, MAL. Nyambi *et al.* [1998]

No. 1460
MAb ID 1393A
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype)
Ab Type gp120 V2
References Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000
Keywords review, subtype comparisons

- 1393A: This broad review of anti-Envelope MAbs notes that V2 MAbs are generally weakly neutralizing at best, and somewhat strain specific. Anti-V2 MAbs 1357, 1361, 1393A are non-neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
- 1393A: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 anti-V2 MAbs, which showed weak and sporadic binding, with the most frequent binding to C and D clades. Nyambi *et al.* [2000] (**subtype comparisons**)

No. 1461
MAb ID 2158
HXB2 Location Env
Author Location gp120 (LAI)
Epitope
Subtype B
Neutralizing
Immunogen
Species (Isotype) human (IgG1κ)

Ab Type gp120 V2
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Pinter *et al.* 2004; Ling *et al.* 2004; Ling *et al.* 2002
Keywords antibody binding site definition and exposure, co-receptor, variant cross-recognition or cross-neutralization

- 2158: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of 17b and F105 was decreased by trypsin, but increased by thrombin. V2 MAbs 830A and 2158 were decreased by trypsin, uneffected by thrombin. Thrombin may increase HIV-induced cell fusion in blood by causing a conformational activating shift in gp120. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 2158: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neturalization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Three anti-V2 MAb were tested – both 2158 and 830A bound more strongly to JRFL, but neutralized SF162, and not neutralize JRFL. Thus V2 domains are better neutralization targets in SF162. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 2158: A pseudotyping assay showed that an X4 V3 loop peptide could enhance infectivity of X4 virus, R5 and R5X4 V3 loops peptides could enhance infectivity of an R5 virus, and R5X4 peptides could enhance infectivity of an R5X4 virus. Neither R5 nor R5X4 peptides influenced binding of CD4BS MAbs F105 and Ig1Gb12, but did increase binding of CD4i MAb 17b. Of three V2 MAbs, only 830A, not 2158 or 1357 was enhanced by V3 peptide binding. Ling *et al.* [2002] (**antibody binding site definition and exposure**, **co-receptor**)

No. 1462
MAb ID 66a
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L (HXB2)
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 V2
References Shotton *et al.* 1995

- 66a: UK Medical Research Council AIDS reagent: ARP3074.
- 66a: Substitutions 176-177 FY/AT, 179-180 LD/DL, 183-184 PI/SG, and 191-193 YSL/GSS abrogate binding – same competition group as CRA4. Shotton *et al.* [1995]

No. 1463
MAb ID 66c
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L (HXB2)
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 V2
References Shotton *et al.* 1995

- 66c: Substitutions 176-177 FY/AT, 179-180 LD/DL, 183-184 PI/SG, and 191-193 YSL/GSS abrogate binding – same competition group as CRA4. Shotton *et al.* [1995]

No. 1464
MAb ID 684-238 (52-684-238, 52-684)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 V2
Research Contact Gerry Robey, Abbott Laboratories
References Ditzel *et al.* 1997; Moore & Sodroski 1996; Ditzel *et al.* 1995; Gorny *et al.* 1994; Thali *et al.* 1993; Moore *et al.* 1993a

- 684-238: Limited reciprocal enhancement of binding with anti-V3 and C4 region antibodies – reciprocal inhibition with V2 region antibodies. Moore & Sodroski [1996]
- 684-238: Does not compete with IgG1b12, reciprocal inhibition with MAbs L39, L40, and L78. Ditzel *et al.* [1995]
- 684-238: Weakly neutralizing, IC 50 = 84 mug/ml. Gorny *et al.* [1994]
- 684-238: Specific for BH10 or HXB2, does not bind to MN, RF, or SF-2 gp120 – neutralizes BH10 – binding inhibited by deletion of the V2 loop, and the following amino acid substitutions: 176/177FY/AT, 179/180LD/DL, 183/184PI/SG, and 192-194YSL/GSS. Moore *et al.* [1993a]

No. 1465
MAb ID 830A
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype)
Ab Type gp120 V2
Research Contact Susan Zolla-Pazner

References Gorny *et al.* 2005; Pinter *et al.* 2004; Ling *et al.* 2004; Gorny & Zolla-Pazner 2004; Ling *et al.* 2002; Nyambi *et al.* 2000

Keywords antibody binding site definition and exposure, co-receptor, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 830A: 2909 is a human anti-Env NAb that was selected by neutralization assay and binds to the quaternary structure on the intact virion. ELISA-based competition assays and subsequent mutational analysis determined that the CD4BS and V2 and V3 loops contribute to the 2909 epitope: 2909 binding was inhibited by MAbs 447-52d (anti-V3), 830A (anti-V2), and IgG1b12 (anti-CD4BS) and sCD4. 2909 was not inhibited by MAbs 670, 1418, nor 2G12. Gorny *et al.* [2005]
- 830A: This broad review of anti-Envelope MAbs notes that V2 MAbs are generally weakly neutralizing at best, and somewhat strain specific. 830A neutralizes SF162. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- 830A: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of 17b and F105 was decreased by trypsin, but increased by thrombin. V2 MAbs 830A and 2158 were decreased by trypsin, uneffected by thrombin. Thrombin may increase HIV-induced cell fusion in blood by causing a conformational activating shift in gp120. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 830A: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neutralization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Three anti-V2 MAb were tested – both 2158 and 830A bound more strongly to JRFL, but neutralized SF162, and did not neutralize JRFL. Thus V2 domains are better neutralization targets in SF162. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 830A: A pseudotyping assay showed that an X4 V3 loop peptide could enhance infectivity of X4 virus, R5 and R5X4 V3 loops peptides could enhance infectivity of an R5 virus, and R5X4 peptides could enhance infectivity of an R5X4 virus. Neither R5 nor R5X4 peptides influenced binding of CD4BS MAbs F105 and Ig1Gb12, but did increase binding of CD4i MAb 17b. Of three V2 MAbs, only 830A, not 2158 or 1357 was enhanced by V3 peptide binding. Ling *et al.* [2002] (**antibody binding site definition and exposure**, **co-receptor**)
- 830A: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 anti-V2 MAbs, which showed weak and sporadic binding, with the most frequent binding to C and D clades. Nyambi *et al.* [2000] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1466
MAb ID CRA-3 (CRA3)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) mouse (IgG2a)
Ab Type gp120 V2
Research Contact Mark Page, NIBSC AIDS reagent project, Potters Bar, Herts, UK
References Holl *et al.* 2006a; Ditzel *et al.* 1997; Moore & Sodroski 1996; Shotton *et al.* 1995; Thali *et al.* 1993; Moore *et al.* 1993a; Moore & Ho 1993
Keywords dendritic cells, neutralization

- CRA-3: UK Medical Research Council AIDS reagent: ARP324.
- CRA3: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- CRA-3: Many MAbs enhance binding, including some anti-C5, C1, V4, and C4 MAbs – enhances binding of only a small number of anti-V3 loop MAbs. Moore & Sodroski [1996]
- CRA-3: Called CRA3 – Same competition group as CRA6. Shotton *et al.* [1995]
- CRA-3: Conformational, does not bind well to denatured gp120. Moore & Ho [1993]
- CRA-3: specific for BH10 or HXB2, does not bind to MN, RF, or SF-2 gp120 – binding inhibited by deletion of the V2 loop, and the following amino acid substitutions: 176/177 FY/AT, 179/180 LD/DL, 183/184 PI/SG, and 192-194 YSL/GSS – epitope probably involves stem of V1/V2 loop structure. Moore *et al.* [1993a]

No. 1467
MAb ID CRA-4 (CRA4)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L (HXB2)
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120 V2
Research Contact Mark Page, NIBS, MRC AIDS reagent repository, ARP 325
References Holl *et al.* 2006a; Moore & Sodroski 1996; Shotton *et al.* 1995; Thali *et al.* 1993; Moore *et al.* 1993a; Moore & Ho 1993; McKeating *et al.* 1993b
Keywords dendritic cells, neutralization

B Cell

- CRA-4: UK Medical Research Council AIDS reagent: ARP325.
- CRA-4: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- CRA-4: The only MAbs that enhanced binding were anti-V3 MAb 5G11 and anti-C1 MAb 135/9 binding – reciprocal inhibition of anti-V2 MAbs. Moore & Sodroski [1996]
- CRA-4: Cross-competes with MAbs 11/68b, 62c, 66c, 66a – similar to 66c and 66a – non-reciprocal inhibition by MAbs 12b, 60b and CRA-6. Shotton *et al.* [1995]
- CRA-4: Changes at residues 191/192/193 (YSL/GSS) within V2, 435 (Y/H) in C4, abrogate binding – type-specific neutralization. McKeating *et al.* [1993b]
- CRA-4: Conformational, does not bind well to denatured gp120. Moore & Ho [1993]
- CRA-4: Specific for BH10 and HXB2, does not bind to MN, RF, or SF-2 gp120 – binding inhibited by deletion of the V2 loop, and the following amino acid substitutions: 176/177 FY/AT, 179/180 LD/DL, 183/184 PI/SG, and 192-194 YSL/GSS. Moore *et al.* [1993a]

No. 1468
MAb ID L17
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 V2
References Gorny & Zolla-Pazner 2004; Kwong *et al.* 2002; Parren *et al.* 1998a; Ditzel *et al.* 1997
Keywords antibody binding site definition and exposure, binding affinity, review, variant cross-recognition or cross-neutralization

- L17: In a review of Envelope binding MAbs in this database, V2-specific MAbs are noted to have some ability to neutralize HIV-1, but generally weakly with limited cross-reactivity. L15 and L17 are Fabs specific for V2. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **review**)
- L17: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-2999) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- L17: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**binding affinity**)

No. 1469
MAb ID SC258 (52-581-SC258)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse
Ab Type gp120 V2
Research Contact Gerry Robey, Abbott Laboratories
References He *et al.* 2002; Ditzel *et al.* 1997; Trkola *et al.* 1996a; Moore & Sodroski 1996; Ditzel *et al.* 1995; Moore *et al.* 1994b; Yoshiyama *et al.* 1994; Gorny *et al.* 1994; Thali *et al.* 1993; Moore *et al.* 1993a

- SC258: Transgenic mice carrying human genes allowing production of fully human MAbs were used to rapidly create a panel of anti-HIV gp120 MAb producing hybridomas by immunization with HIV SF162 gp120 – the previously described human MAbs 5145A(CD4BS) , 4117C (plus others, V3) and 697D (and SC258, V2) were used as controls. He *et al.* [2002]
- SC258: Several MAbs binding to various gp120 epitopes enhance binding, but the only MAb that SC258 enhanced binding of was anti-CD4 binding site MAb F91 – reciprocal inhibition with V2 region antibodies. Moore & Sodroski [1996]
- SC258: Does not inhibit gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study – listed as not neutralizing. Trkola *et al.* [1996a]
- SC258: Does not compete with IgG1b12 – reciprocal inhibition with MAbs L39, L40, and L78. Ditzel *et al.* [1995]
- SC258: Very poor reactivity with gp120 molecules outside of clade B. Moore *et al.* [1994b]
- SC258: HIV-1 RF V2 substitutions 177 Y/H and 179 L/P in the V2 loop of RF reduce affinity – 177 Y/H inhibits SC258 neutralization. Yoshiyama *et al.* [1994]
- SC258: Called 52-581-SC258 – binds to BH10, MN, and RF gp120 – neutralizes BH10 – binding inhibited by deletion of the V2 loop, and the following amino acid substitutions: 176/177 FY/AT, 179/180 LD/DL, 183/184 PI/SG, and 192-194 YSL/GSS. Moore *et al.* [1993a]

B Cell

No. 1470
MAb ID L25
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L (weak)
Immunogen HIV-1 infection
Species (Isotype) human (IgG1)
Ab Type gp120 V2-CD4BS
References Gorny & Zolla-Pazner 2004; Parren *et al.* 1997b; Ditzel *et al.* 1997; Ditzel *et al.* 1995
Keywords antibody binding site definition and exposure, review, variant cross-recognition or cross-neutralization

- L25: In a review of Envelope binding MAbs in this database, V2-specific MAbs are noted to have some ability to neutralize HIV-1, but generally weakly with limited cross-reactivity. L25, L39, L40 and L78 are Fabs specific for a complex binding site involving V2 and elements of the sCD4 binding site regions; among these only L25 and L78 mediate weak neutralization of some TCLA strains. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **review**)
- L25: gp120 immobilized on solid phase by capture with anti-CD4 BS MAb L72 was used for selection of Fabs – a single anti-V2-CD4 BS Fab was obtained with with sensitivity to substitutions in the V2 and CD4 BS regions – rodent anti-V2 MAb SC258 competes with L25. Ditzel *et al.* [1997]
- L25: Neutralizes TCLA strains weakly, but not primary isolates. Parren *et al.* [1997b]

No. 1471
MAb ID L39
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 V2-CD4BS
References Gorny & Zolla-Pazner 2004; Ditzel *et al.* 1995
Keywords antibody binding site definition and exposure, review, variant cross-recognition or cross-neutralization

- L39: In a review of Envelope binding MAbs in this database, V2-specific MAbs in are noted have some ability to neutralize HIV-1, but generally weakly with limited cross-reactivity. L25, L39, L40 and L78 are Fabs specific for a complex binding site involving V2 and elements of the sCD4 binding site regions; among these only L25 and L78 mediate weak neutralization of some TCLA strains. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **review**)
- L39: This Fab does not inhibit sCD4 binding, but is inhibited by sCD4, probably due to conformational changes – it is competed by anti-V2 MAbs, and sensitive to amino acid substitutions in the V3 loop (similar patterns were observed for L39 and L78 gp120 amino acid substitutions enhancing or reducing binding) – does not compete with CD4BS MAbs, but is sensitive to amino acid changes at positions 368 and 370 – binding unaffected by deglycosylation – reciprocal inhibition with V2 MAbs SC258 and 684-238 – heavy and light chain variable region sequence is available. Ditzel *et al.* [1995]

No. 1472
MAb ID L40
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 V2-CD4BS
References Gorny & Zolla-Pazner 2004; Ditzel *et al.* 1995
Keywords antibody binding site definition and exposure, responses in children, variant cross-recognition or cross-neutralization

- L40: In a review of Envelope binding MAbs in this database, V2-specific MAbs are noted to have some ability to neutralize HIV-1, but generally weakly with limited cross-reactivity. L25, L39, L40 and L78 are Fabs specific for a complex binding site involving V2 and elements of the sCD4 binding site regions; among these only L25 and L78 mediate weak neutralization of some TCLA strains. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **responses in children**)
- L40: This Fab does not inhibit sCD4 binding, but is inhibited by sCD4, probably due to conformational changes – it is competed by anti-V2 MAbs, and sensitive to amino acid substitutions in the V3 loop (similar patterns were observed for L40 and L78 gp120 amino acid substitutions enhancing or reducing binding) – does not compete with CD4BS MAbs, but is sensitive to amino acid changes at positions 368 and 370 – binding only partially affected by deglycosylation – reciprocal inhibition with V2 MAbs SC258 and 684-238 – heavy and light chain variable region sequence is available. Ditzel *et al.* [1995]

No. 1473
MAb ID L78
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp120 V2-CD4BS
References Gorny & Zolla-Pazner 2004; Kwong *et al.* 2002; Ditzel *et al.* 1995
Keywords antibody binding site definition and exposure, antibody sequence variable domain, review, variant cross-recognition or cross-neutralization

- L78: In a review of Envelope binding MAbs in this database, V2-specific MAbs are noted to have some ability to neutralize HIV-1, but generally weakly with limited cross-reactivity. L25, L39, L40 and L78 are Fabs specific for V2 that are also associated with sCD4 binding site regions; among these only L25 and L78 mediate weak neutralization of some TCLA strains. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **review**)

- L78: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-2999) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- L78: Substitutions at V2: (152/153 GE/SM, 183/184 PI/SG, 191/193 YL/GS), 262 N/T, V3 (314 G/W), CD4BS (257 T/R, 368 D/R, 370 E/R) inhibit binding, and some C4 and C5 substitutions enhance binding – this Fab does not inhibit sCD4 binding, but is inhibited by sCD4, probably due to conformational changes – it is competed by anti-V2 MAbs, and sensitive to amino acid substitutions in the V3 loop – does not compete with CD4BS MAbs, but is sensitive to amino acid changes at positions 368 and 370 – Fab neutralizes MN and LAI – binding unaffected by deglycosylation – reciprocal inhibition with V2 MAbs SC258 and 684-238 – heavy and light chain variable region sequence is available. Ditzel *et al.* [1995] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **antibody sequence variable domain**)

No. 1474
MAb ID
HXB2 Location Env
Author Location gp120
Epitope
Subtype A, B, C
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V3
References Gilljam *et al.* 1999

- Sera from individuals with infections of HIV-1 subtype A-E were tested against purifed proteins from primary PBMC cultures. Sera reactivity tended not to be strongly related to subtype, rather probably reflected the sum of reactivities to conserved and variable regions in the proteins. V3 peptide comparisons showed some preference for within subtype binding. Gilljam *et al.* [1999]

No. 1475
MAb ID 10D8
HXB2 Location Env
Author Location gp160 (V3) (303–338)
Epitope
Subtype B
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 V3
References Callahan *et al.* 1991

- 10D8: Polyanionic polysaccharides were proposed to inhibit viral functions such as binding and syncytia formation through interations mediated through the local high positive charge density in the V3 loop. The binding of this anti-V3 antibody is inhibited by dextransulfate. Callahan *et al.* [1991]

No. 1476
MAb ID 10F6
HXB2 Location Env
Author Location gp160 (V3) (303–338)
Epitope
Subtype B
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 V3
References Callahan *et al.* 1991

- 10F6: Polyanionic polysaccharides were proposed to inhibit viral functions such as binding and syncytia formation through interations mediated through the local high positive charge density in the V3 loop. The binding of this anti-V3 antibody is inhibited by dextransulfate. Callahan *et al.* [1991]

No. 1477
MAb ID 110.J
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 V3
Research Contact F. Traincard, Pasteur Institute, France
References Moore & Sodroski 1996; Thali *et al.* 1993

- 110.J: Binds to carboxy-terminal side of the V3 loop – reciprocal binding inhibition with other anti-V3 and anti-C4 MAbs – and reciprocal enhanced binding of some anti-V2 MAbs and anti-CD4 binding site MAbs. Moore & Sodroski [1996]
- 110.J: Inhibits sCD4-inducible anti-CD4 binding site MAb 48d. Thali *et al.* [1993]

No. 1478
MAb ID 11G5
HXB2 Location Env
Author Location gp160 (V3) (303–338)
Epitope

B Cell

Subtype B
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 V3
References Callahan *et al.* 1991

- 11G5: Polyanionic polysaccharides were proposed to inhibit viral functions such as binding and syncytia formation through interations mediated through the local high positive charge density in the V3 loop. The binding of this anti-V3 antibody is inhibited by dextransulfate. Callahan *et al.* [1991]

No. 1479
MAb ID 2182
HXB2 Location Env
Author Location (JRCSF)
Epitope
Subtype B
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Kramer *et al.* 2007; Krachmarov *et al.* 2006; Gorny *et al.* 2006; Srivastava *et al.* 2005; Mc Cann *et al.* 2005; Li *et al.* 2005a; Pinter *et al.* 2004; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Gorny *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, assay standardization/improvement, binding affinity, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 2182: This review summarizes 2182 Ab epitope, properties and neutralization activity. Kramer *et al.* [2007] (**review**)
- 2182: This MAb was derived from plasma from a patient with env clade A virus with the GPGR V3 motif. When cross-reactivity was tested, this Ab bound only the V3subtypeB-fusion protein containing GPGR motif and not V3subtypeA-fusion protein containing GPGQ motif. This Ab was also shown to be able to neutralize clade B psSF162 (GPGR) but not clade C psMW965 (GPGQ) virus and to neutralize subtype B primary isolates but not non-B primary isolates. Gorny *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)
- 2182: This Ab was shown to neutralize SF162 and the neutralization sensitivity increased in the SF162 variant with a JR-FL V3 loop, SF162(JR-FL V3). In contrast, no neutralization was observed of the SF162(JR-FL V1/V2) variant and was somewhat restored in the SF162(JR-FL V1/V2/V3) variant, indicating that the masking of the V1/V2 loop plays a much greater role in restricting neutralization sensitivity than the variations in V3. This Ab did not neutralize viruses with V3 sequences from several different subtypes (B, F, A1, H, C, CRF02_AG and CRF01_AE) and also failed to neutralize SF162(JR-FL V1/V2) with V3 derived from different HIV-1 clades. The effect on the neutralization sensitivity of the residue at the crown of the V3 loop (position 18) was shown to be great for this Ab. Krachmarov *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2182: Full-length gp160 clones were derived from acute and early human HIV-1 infections and used as env-pseudotyped viruses in neutralization assays for their characterization as neutralization reference agents. 2 out of 19 pseudoviruses were sensitive to neutralization by 2182, as was the SF162.LS strain. Li *et al.* [2005a] (**neutralization**, **assay standardization/improvement**)
- 2182: This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. MAbs included in this review are: 2F5, Clone 3 (CL3), 4E10, Z13, IgG1b12, 2G12, m14, 447-52D, 17b, X5, m16, 47e, 412d, E51, CM51, F105, F425, 19b, 2182, DO142-10, 697-D, 448D, 15e and Cβ1. Mc Cann *et al.* [2005] (**antibody binding site definition and exposure**, **review**)
- 2182: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**neutralization**, **variant cross-recognition or cross-neutralization**, **review**, **subtype comparisons**)
- 2182: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. The set that can cross-neutralize primary isolates (2182, 2191, 2219, 2412, 2442, 2456) bind V3 but are conformationally senstitive, suggesting some structural conservation despite sequence variation. These MAbs have distinct epitopes relative to 447-52D, a MAb directed at the tip of the V3 loop that also can neutralize many primary isolates. Inter-clade cross-neutralization by these anti-V3 MAbs is reduced. Gorny & Zolla-Pazner [2004] (**review**, **subtype comparisons**)
- 2182: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using a JR-CSF fusion protein, and could neutralize 6/13 B clade viruses. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 2182: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neturalization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the

B Cell

SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. 5/6 anti-V3 MAbs had similar binding affinity to soluble SF162 and JR-FL rgp120s, although the V3 loop differs at three positions (HigpgrafyTtgE for JR-FL and TigpgrafyAtgD for SF162). Only the V3 MAb that had a different affinity was 2182, which bound to JRFL with higher affinity. Even 2182 preferentially neutralized SF162, however, the JRFL gp120 backbone with the SF162 V1V2 region was the more neutralization sensitive than pure SF162. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)

- 2182: Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated from cells of asymptomatic HIV-1-infected individuals by selection of heterhybridomas using a V3-fusion protein (V3-fp), the HIV-1 JRCSF V3 loop inserted into a truncated murine leukemia virus gp70 – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions of clades A(N=2), B(N=4), and F(N=2), limited binding to C(N=3) and D(N=3), and did not bind to CRF01(subtype E, N=2) – the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control), MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades) – 5/6 MAbs were derived from individuals infected in the US, presumably with clade B, and one, 2182, was derived from an individual who was infected abroad with clade A who is presently living in New York city – 2412 and 2456 were produced from cells obtained from the same individual, while the other MAbs were each generated from different subjects – 2182 bound to 8/16 of the diverse isolates, not to any clade C or CRF01. Gorny *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No.	1480
MAb ID	2191
HXB2 Location	Env
Author Location	(JRCSF)
Epitope	
Subtype	B
Neutralizing	P
Immunogen	HIV-1 infection
Species (Isotype)	human (IgG1λ)
Ab Type	gp120 V3
Research Contact	Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References	Krachmarov *et al.* 2006; Gorny *et al.* 2006; Pinter *et al.* 2005; Li *et al.* 2005a; Pinter *et al.* 2004; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Gorny *et al.* 2002
Keywords	antibody binding site definition and exposure, antibody generation, assay standardization/improvement, binding affinity, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 2191: This MAb was derived from plasma from a patient with env clade B virus with the GPGR V3 motif. When cross-reactivity was tested, this Ab bound to the V3subtypeB-fusion protein containing GPGR motif but not to V3subtypeA-fusion protein containing GPGQ motif. This Ab was also shown to be able to neutralize both clade B psSF162 (GPGR) and clade C psMW965 (GPGQ) virus and three of subtype B and three non-B primary isolates. Gorny *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)
- 2191: This Ab was shown to equally neutralize SF162 and the SF162 variant with a JR-FL V3 loop, SF162(JR-FL V3). In contrast, a reduction in sensitivity to neutralization was observed in the SF162(JR-FL V1/V2) variant and was somewhat restored in the SF162(JR-FL V1/V2/V3) variant, indicating that the masking of the V1/V2 loop plays a much greater role in restricting neutralization sensitivity than the variations in V3. This Ab was shown to neutralize viruses with V3 sequences from several different subtypes (B, F, A1, C and CRF02_AG) except subtypes H and CRF01_AE. This Ab failed to neutralize SF162(JR-FL V1/V2) with V3 derived from different HIV-1 clades indicating effective V1/V2-mediated masking of several HIV-1 clades. The effect on the neutralization sensitivity of the residue at the crown of the V3 loop (position 18) was shown to be low for this Ab. Krachmarov *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2191: Full-length gp160 clones were derived from acute and early human HIV-1 infections and used as env-pseudotyped viruses in neutralization assays for their characterization as neutralization reference agents. 3 out of 19 pseudoviruses were sensitive to neutralization by 2191, as was the SF162.LS strain. Two additional pseudoviruses were sensitive at higher Ab concentrations. Li *et al.* [2005a] (**neutralization**, **assay standardization/improvement**)
- 2191: This study is about the V2 MAb C108g, that is type-specific and neutralizes BaL and HXB2. JR-FL is a neutralization resistant strain; modification of JRFL at V2 positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potently neutralize the modified JR-FL. The modification in V2 also increased neutralization sensitivity to V3 MABs 4117c, 2219, 2191, and 447-52D, but only had minor effects on neutralization by CD4BS MAb 5145A, and broadly neutralizing MAbs IgG1b12, 2G12, and 2F5. Pinter *et al.* [2005] (**antibody binding site definition and exposure**)
- 2191: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. The set that can cross-neutralize primary isolates (2182, 2191, 2219, 2412, 2442, 2456) bind V3 but are conformationally senstitive, suggesting some structural conservation despite sequence variation. These MAbs have distinct epitopes relative to 447-52D, a MAb directed at the tip of the V3 loop that also can neutralize many primary isolates. Interclade cross-neutralization by these anti-V3 MAbs is reduced. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**, **subtype comparisons**)

B Cell

- 2191: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using a JR-CSF fusion protein, and could neutralize 8/13 B clade viruses. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 2191: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neturalization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. 5/6 anti-V3 MAbs, including 2191, had similar binding affinity to soluble SF162 and JR-FL rgp120s, although the V3 loop differs at three positions (HigpgrafyTtgE for JR-FL and TigpgrafyAtgD for SF162). Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 2191: Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated from cells of asymptomatic HIV-1-infected individuals by selection of heterhybridomas using a V3-fusion protein (V3-fp), the HIV-1 JRCSF V3 loop inserted into a truncated murine leukemia virus gp70 – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions of clades A(N=2), B(N=4), and F(N=2), limited binding to C(N=3) and D(N=3), and did not bind to CRF01(subtype E, N=2) – the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control), MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades) – 5/6 MAbs were derived from individuals infected in the US, presumably with clade B, and one, 2182, was derived from an individual who was infected abroad with clade A who is presently living in New York city – 2412 and 2456 were produced from cells obtained from the same individual, while the other MAbs were each generated from different subjects – 2191 bound to 10/16 of the diverse isolates, not to any clade D or CRF01. Gorny *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1481
MAb ID 2219
HXB2 Location Env
Author Location (JRCSF)
Epitope
Subtype B
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Wu *et al.* 2008; Pantophlet *et al.* 2008; Sirois *et al.* 2007; Lin & Nara 2007; Krachmarov *et al.* 2006; Stanfield *et al.* 2006; Gorny *et al.* 2006; Stanfield & Wilson 2005; Pinter *et al.* 2005; Li *et al.* 2005a; Pinter *et al.* 2004; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Gorny *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, assay standardization/improvement, neutralization, review, structure, subtype comparisons, variant cross-recognition or cross-neutralization

- 2219: Angle of interaction between 2219 and V3 was shown by superimposing the Fab fragment of the Ab with V3. Pantophlet *et al.* [2008] (**antibody binding site definition and exposure**, **structure**)
- 2219: To test whether the conformation change of Env induced by CD4 affects the breadth and potency of 2219 neutralization, 2219 was tested in the presence or absence of sCD4 in neutralization of a panel of 12 subtype B and 12 subtype C Env-pseudoviruses. Without sCD4, 2219 neutralized 2 subtype B and 0 subtype C viruses. With sCD4 present, 2219 neutralized 9 subtype B and 1 subtype C virus, indicating that neutralization resistance of some viruses to 2219 is due to a lack of exposure of the V3 loop. Neutralization of JRFL, ADA, and YU2 isolates by 2219 increased with increased dose of sCD4. Wu *et al.* [2008] (**neutralization**, **variant cross-recognition or cross-neutralization**)
- 2219: 2219 structure, binding, neutralization, and strategies that can be used for vaccine antigen design to elicit anti-V3 Abs, are reviewed in detail. Lin & Nara [2007] (**review**)
- 2219: Data is summarized on the X-ray crystal structures resolution and NMR studies of 2219. Sirois *et al.* [2007] (**review**, **structure**)
- 2219: This MAb was derived from plasma from a patient with env clade B virus with the GPGR V3 motif. When cross-reactivity was tested, this Ab bound to the V3subtypeB-fusion protein containing GPGR motif and to V3subtypeA-fusion protein containing GPGQ motif. This Ab was also shown to be able to neutralize both clade B psSF162 (GPGR) and clade C psMW965 (GPGQ) virus and three of subtype B but only one of non-B primary isolates. Gorny *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2219: This Ab was shown to neutralize SF162 and the neutralization sensitivity increased somewhat in the SF162 variant with a JR-FL V3 loop, SF162(JR-FL V3). In contrast, a great reduction in sensitivity to neutralization was observed in the SF162(JR-FL V1/V2) variant and was somewhat restored in the SF162(JR-FL V1/V2/V3) variant, indicating that the masking of the V1/V2 loop plays a much greater role in restricting neutralization sensitivity than the variations in V3. This Ab was shown to neutralize viruses with V3 sequences from several different subtypes (B, F, A1, C, CRF02_AG,

B Cell

CRF01_AE and H). This Ab failed to neutralize SF162(JR-FL V1/V2) with V3 derived from different HIV-1 clades indicating effective V1/V2-mediated masking of several HIV-1 clades. The effect on the neutralization sensitivity of the residue at the crown of the V3 loop (position 18) was shown to be low for this Ab. Krachmarov *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

- 2219: Structure of 2219 Ab in contact with three different V3 peptides was determined in order to gain insight in the structural basis for its cross-reactivity with different HIV-1 clades. It is shown that Fab 2219 binds to one face of the variable V3 beta-hairpin, primarily contacting conserved residues, leaving the V3 crown largely accessible. Twisting of the V3 loop is shown to alter the relative dispositions and pairing of amino acids. 2219 was shown to cross-react with V3 sequences from clades A, B and C and to neutralize viruses from clades A, B and F. Stanfield *et al.* [2006] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**, **structure**)
- 2219: Full-length gp160 clones were derived from acute and early human HIV-1 infections and used as env-pseudotyped viruses in neutralization assays for their characterization as neutralization reference agents. 4 out of 19 pseudoviruses were sensitive to neutralization by 2219, as was the SF162.LS strain. One additional pseudovirus was sensitive at higher Ab concentrations. Li *et al.* [2005a] (**neutralization**, **assay standardization/improvement**)
- 2219: This study is about the V2 MAb C108g, that is type-specific and neutralizes BaL and HXB2. JR-FL is a neutralization resistant strain; modification of JRFL at V2 positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potently neutralize the modified JR-FL. The modification in V2 also increased neutralization sensitivity to V3 MABs 4117c, 2219, 2191, and 447-52D, but only had minor effects on neutralization by CD4BS MAb 5145A, and broadly neutralizing MAbs IgG1b12, 2G12, and 2F5. Binding to CCR5 was completely inhibited by two V3 MAbs, 4117C and 2219, and was substantially inhibited by 2G12, but was not inhibited by C108g. Pinter *et al.* [2005] (**antibody binding site definition and exposure**)
- 2219: This review summarizes data on 2219-V3 and 2219-V3 peptide X-ray crystallographic structures and its neutralization capabilities. The binding mechanism of this Ab to V3 explains its ability to neutralize a wide array of HIV-1 primary isolates from different clades. Stanfield & Wilson [2005] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**, **review**, **structure**)
- 2219: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. The set that can cross-neutralize primary isolates (2182, 2191, 2219, 2412, 2442, 2456) bind V3 but are conformationally senstitive, suggesting some structural conservation despite sequence variation. These MAbs have distinct epitopes relative to 447-52D, a MAb directed at the tip of the V3 loop that also can neutralize many primary isolates. Interclade cross-neutralization by these anti-V3 MAbs is reduced. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**, **subtype comparisons**)
- 2219: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using a JR-CSF fusion protein, and could neutralize 6/13 B clade viruses. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 2219: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neturalization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. 5/6 anti-V3 MAbs, including 2219, had similar binding affinity to soluble SF162 and JR-FL rgp120s, although the V3 loop differs at three positions (HigpgrafyTtgE for JR-FL and TigpgrafyAtgD for SF162). Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 2219: Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated from cells of asymptomatic HIV-1-infected individuals by selection of heterhybridomas using a V3-fusion protein (V3-fp), the HIV-1 JRCSF V3 loop inserted into a truncated murine leukemia virus gp70 – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions of clades A(N=2), B(N=4), and F(N=2), limited binding to C(N=3) and D(N=3), and did not bind to CRF01(subtype E, N=2) – the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control), MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades) – 5/6 MAbs were derived from individuals infected in the US, presumably with clade B, and one, 2182, was derived from an individual who was infected abroad with clade A who is presently living in New York city – 2412 and 2456 were produced from cells obtained from the same individual, while the other MAbs were each generated from different subjects – 2219 bound to 13/16 of the diverse isolates. Gorny *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1482
MAb ID 2412
HXB2 Location Env
Author Location gp120 (V3) (JRCSF)
Epitope
Subtype B

B Cell

Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Krachmarov *et al.* 2006; Gorny *et al.* 2006; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Gorny *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, binding affinity, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 2412: This MAb was derived from plasma from a patient with env clade B virus with the GPGR V3 motif. When cross-reactivity was tested, this Ab bound to the V3subtypeB-fusion protein containing GPGR motif but not to V3subtypeA-fusion protein containing GPGQ motif. This Ab was also shown to be able to neutralize clade B psSF162 (GPGR) but not clade C psMW965 (GPGQ) virus, and three of subtype B but only two of non-B primary isolates. Gorny *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)
- 2412: This Ab was shown to neutralize SF162 and the neutralization sensitivity increased in the SF162 variant with a JR-FL V3 loop, SF162(JR-FL V3). In contrast, no neutralization was observed of the SF162(JR-FL V1/V2) variant and was somewhat restored in the SF162(JR-FL V1/V2/V3) variant, indicating that the masking of the V1/V2 loop plays a much greater role in restricting neutralization sensitivity than the variations in V3. This Ab was shown to neutralize viruses with V3 sequences from several different subtypes (B, F, and A1) except subtypes C, CRF02_AG, H and CRF01_AE. This Ab failed to neutralize SF162(JR-FL V1/V2) with V3 derived from different HIV-1 clades indicating effective V1/V2-mediated masking of several HIV-1 clades. The effect on the neutralization sensitivity of the residue at the crown of the V3 loop (position 18) was shown to be great for this Ab. Krachmarov *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2412: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. The set that can cross-neutralize primary isolates (2182, 2191, 2219, 2412, 2442, 2456) bind V3 but are conformationally senstitive, suggesting some structural conservation despite sequence variation. These MAbs have distinct epitopes relative to 447-52D, a MAb directed at the tip of the V3 loop that also can neutralize many primary isolates. Interclade cross-neutralization by these anti-V3 MAbs is reduced. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure**, **review**)
- 2412: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using a JR-CSF fusion protein, and could neutralize 4/13 B clade viruses. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 2412: Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated from cells of asymptomatic HIV-1-infected individuals by selection of heterhybridomas using a V3-fusion protein (V3-fp), the HIV-1 JRCSF V3 loop inserted into a truncated murine leukemia virus gp70 – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions of clades A(N=2), B(N=4), and F(N=2), limited binding to C(N=3) and D(N=3), and did not bind to CRF01(subtype E, N=2) – the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control), MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades) – 5/6 MAbs were derived from individuals infected in the US, presumably with clade B, and one, 2182, was derived from an individual who was infected abroad with clade A who is presently living in New York city – 2412 and 2456 were produced from cells obtained from the same individual, while the other MAbs were each generated from different subjects – 2412 bound to 7/16 of the diverse isolates, and did not bind to any of the clade C, D or CRF01 viruses. Gorny *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1483
MAb ID 2442
HXB2 Location Env
Author Location (JRCSF)
Epitope
Subtype B
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Krachmarov *et al.* 2006; Gorny *et al.* 2006; Louder *et al.* 2005; Li *et al.* 2005a; Grundner *et al.* 2005; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Gorny *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, assay standardization/improvement, binding affinity, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 2442: This MAb was derived from plasma from a patient with env clade B virus with the GPGR V3 motif. When

B Cell

cross-reactivity was tested, this Ab bound to the V3subtypeB-fusion protein containing GPGR motif but not to V3subtypeA-fusion protein containing GPGQ motif. This Ab was also shown to be able to neutralize clade B psSF162 (GPGR) but not clade C psMW965 (GPGQ) virus, and three of subtype B but only one of non-B primary isolates. Gorny *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)

- 2442: This Ab was shown to neutralize SF162 and the neutralization sensitivity increased in the SF162 variant with a JR-FL V3 loop, SF162(JR-FL V3). In contrast, a great reduction in sensitivity to neutralization was observed in the SF162(JR-FL V1/V2) variant and was somewhat restored in the SF162(JR-FL V1/V2/V3) variant, indicating that the masking of the V1/V2 loop plays a much greater role in restricting neutralization sensitivity than the variations in V3. This Ab was shown to neutralize viruses with V3 sequences from several different subtypes (B, F, A1 and H) except subtypes C, CRF02_AG and CRF01_AE. This Ab failed to neutralize SF162(JR-FL V1/V2) with V3 derived from different HIV-1 clades except A1, indicating effective V1/V2-mediated masking of several HIV-1 clades. The effect on the neutralization sensitivity of the residue at the crown of the V3 loop (position 18) was shown to be low for this Ab. Krachmarov *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2442: This Ab was used as a control in a peptide adsorption assay. 2442 neutralized the SF162 primary isolate to 99%. When 2442 was pre-incubated with BaL or YU2 V3 loop peptides, nearly all neutralizing activity was inhibited. Grundner *et al.* [2005] (**neutralization**)
- 2442: Full-length gp160 clones were derived from acute and early human HIV-1 infections and used as env-pseudotyped viruses in neutralization assays for their characterization as neutralization reference agents. 3 out of 19 pseudoviruses were sensitive to neutralization by 2442, as was the SF162.LS strain. Li *et al.* [2005a] (**neutralization**, **assay standardization/improvement**)
- 2442: Pseudoviruses expressing HIV-1 envelope glycoproteins from BL01, BR07 and 89.6 strains were compared in neutralization assays to replication competent clone derived from transfection of 293T cells (IMC-293T) and to the IMC-293T derived from a single passage through PBMC (IMC-PBMC). The neutralization responses of pseudoviruses and corresponding IMC-293T to 2442 were similar, while a significant decrease in viral neutralization sensitivity to 2442 was observed the 89.6 IMC-PBMC virus. The decrease was associated with an increase in average virion envelope glycoprotein content on the PBMC-derived virus. Louder *et al.* [2005] (**neutralization**, **assay standardization/improvement**)
- 2442: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. The set that can cross-neutralize primary isolates (2182, 2191, 2219, 2412, 2442, 2456) bind V3 but are conformationally senstitive, suggesting some structural conservation despite sequence variation. These MAbs have distinct epitopes relative to 447-52D, a MAb directed at the tip of the V3 loop that also can neutralize many primary isolates. Interclade cross-neutralization by these anti-V3 MAbs is reduced. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- 2442: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using a JR-CSF fusion protein, and could neutralize 9/13 B clade viruses. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 2442: Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated from cells of asymptomatic HIV-1-infected individuals by selection of heterhybridomas using a V3-fusion protein (V3-fp), the HIV-1 JRCSF V3 loop inserted into a truncated murine leukemia virus gp70 – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions of clades A(N=2), B(N=4), and F(N=2), limited binding to C(N=3) and D(N=3), and did not bind to CRF01(subtype E, N=2) – the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control), MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades) – 5/6 MAbs were derived from individuals infected in the US, presumably with clade B, and one, 2182, was derived from an individual who was infected abroad with clade A who is presently living in New York city – 2412 and 2456 were produced from cells obtained from the same individual, while the other MAbs were each generated from different subjects – 2442 bound to 13/16 of the diverse isolates. Gorny *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**, **variant cross-recognition or cross-neutralization**, **review**)

No.	1484
MAb ID	2456
HXB2 Location	Env
Author Location	(JRCSF)
Epitope	
Subtype	B
Neutralizing	P
Immunogen	HIV-1 infection
Species (Isotype)	human (IgG1λ)
Ab Type	gp120 V3
Research Contact	Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References	Krachmarov *et al.* 2006; Gorny *et al.* 2006; Li *et al.* 2005a; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Gorny *et al.* 2002
Keywords	antibody binding site definition and exposure, assay standardization/improvement,

B Cell

neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 2456: This Ab was shown to neutralize SF162 and the neutralization sensitivity increased in the SF162 variant with a JR-FL V3 loop, SF162(JR-FL V3). In contrast, a great reduction in sensitivity to neutralization was observed in the SF162(JR-FL V1/V2) variant and was somewhat restored in the SF162(JR-FL V1/V2/V3) variant, indicating that the masking of the V1/V2 loop plays a much greater role in restricting neutralization sensitivity than the variations in V3. This Ab was shown to neutralize viruses with V3 sequences from several different subtypes (B, F, A1, H, C, CRF02_AG and CRF01_AE). This Ab failed to neutralize SF162(JR-FL V1/V2) with V3 derived from different HIV-1 clades, indicating effective V1/V2-mediated masking of several HIV-1 clades. The effect on the neutralization sensitivity of the residue at the crown of the V3 loop (position 18) was shown to be low for this Ab. Krachmarov *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2456: Full-length gp160 clones were derived from acute and early human HIV-1 infections and used as env-pseudotyped viruses in neutralization assays for their characterization as neutralization reference agents. 2 out of 19 pseudoviruses were sensitive to neutralization by 2456, as was the SF162.LS strain. Li *et al.* [2005a] (**neutralization**, **assay standardization/improvement**)
- 2456: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. The set that can cross-neutralize primary isolates (2182, 2191, 2219, 2412, 2442, 2456) bind V3 but are conformationally senstitive, suggesting some structural conservation despite sequence variation. These MAbs have distinct epitopes relative to 447-52D, a MAb directed at the tip of the V3 loop that also can neutralize many primary isolates. Interclade cross-neutralization by these anti-V3 MAbs is reduced. Gorny & Zolla-Pazner [2004] (**review**)
- 2456: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using a JR-CSF fusion protein, and could neutralize 4/12 B clade viruses. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 2456: Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated from cells of asymptomatic HIV-1-infected individuals by selection of heterhybridomas using a V3-fusion protein (V3-fp), the HIV-1 JRCSF V3 loop inserted into a truncated murine leukemia virus gp70 – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions of clades A(N=2), B(N=4), and F(N=2), limited binding to C(N=3) and D(N=3), and did not bind to CRF01(subtype E, N=2) – the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control), MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades) – 5/6 MAbs were derived from individuals infected in the US, presumably with clade B, and one, 2182, was derived from an individual who was infected abroad with clade A who is presently living in New York city – 2412 and 2456 were produced from cells obtained from the same individual, while the other MAbs were each generated from different subjects – 2456 bound to 12/16 of the diverse isolates. Gorny *et al.* [2002]

No. 1485
MAb ID 2483
HXB2 Location Env
Author Location Env (JR-CSF)
Epitope
Subtype B
Neutralizing P
Immunogen
Species (Isotype) human
Ab Type gp120 V3
Research Contact Dr. Zolla-Pazner, Veterans Affairs Center, NY, NY. zollas01@endeavor.med.nyu.edu
References Gorny *et al.* 2006; Gorny *et al.* 2004
Keywords antibody binding site definition and exposure, binding affinity, subtype comparisons, variant cross-recognition or cross-neutralization

- 2483: This MAb was derived from plasma from a patient with env clade B virus with the GPGR V3 motif. When cross-reactivity was tested, this Ab bound to the V3subtypeB-fusion protein containing GPGR motif but not to the V3subtypeA-fusion protein containing GPGQ motif. Gorny *et al.* [2006] (**variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)
- 2483: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This antibody was selected using a JRCSF fusion protein. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)

No. 1486
MAb ID 2497
HXB2 Location Env
Author Location Env (JR-CSF)
Epitope
Subtype B
Neutralizing P
Immunogen
Species (Isotype) human
Ab Type gp120 V3
Research Contact Dr. Zolla-Pazner, Veterans Affairs Center, NY, NY. zollas01@endeavor.med.nyu.edu
References Gorny *et al.* 2006; Gorny *et al.* 2004

B Cell

Keywords antibody binding site definition and exposure, binding affinity, neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- 2497: This MAb was derived from plasma from a patient with env clade B virus with the GPGR V3 motif. When cross-reactivity was tested, this Ab bound to both the V3subtypeB-fusion protein containing GPGR motif and the V3subtypeA-fusion protein containing GPGQ motif. This Ab was also shown to be able to neutralize both clade B psSF162 (GPGR) and clade C psMW965 (GPGQ) virus, and three of subtype B and three of non-B primary isolates. Gorny *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)
- 2497: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This antibody was selected using a JRCSF fusion protein. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)

No. 1487
MAb ID 2557
HXB2 Location Env
Author Location Env (JR-CSF)
Epitope
Subtype A, CRF02_AG
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V3
Research Contact Dr. Zolla-Pazner, Veterans Affairs Center, NY, NY. zollas01@endeavor.med.nyu.edu
References Krachmarov *et al.* 2006; Gorny *et al.* 2006; Krachmarov *et al.* 2005; Gorny *et al.* 2004
Keywords antibody binding site definition and exposure, binding affinity, neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- 2557: This MAb was derived from plasma from a patient with env clade A virus with the GPGQ V3 motif. When cross-reactivity was tested, this Ab bound to both the V3subtypeB-fusion protein containing GPGR motif and V3subtypeA-fusion protein containing GPGQ motif. This Ab was also shown to be able to neutralize both clade B psSF162 (GPGR) and clade C psMW965 (GPGQ) virus and the majority of subtype B and non-B primary isolates. Gorny *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)
- 2557: This Ab was shown to neutralize SF162 and the neutralization sensitivity increased in the SF162 variant with a JR-FL V3 loop, SF162(JR-FL V3). In contrast, a great reduction in sensitivity to neutralization was observed in the SF162(JR-FL V1/V2) variant and was somewhat restored in the SF162(JR-FL V1/V2/V3) variant, indicating that the masking of the V1/V2 loop plays a much greater role in restricting neutralization sensitivity than the variations in V3. This Ab was shown to neutralize viruses with V3 sequences from several different subtypes (B, F, A1, H, C, CRF02_AG and CRF01_AE). This Ab failed to neutralize SF162(JR-FL V1/V2) with V3 derived from different HIV-1 clades except A1, indicating effective V1/V2-mediated masking of several HIV-1 clades. The effect on the neutralization sensitivity of the residue at the crown of the V3 loop (position 18) was shown to be low for this Ab. Krachmarov *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2557: Sera from subtype A infected individuals from Cameroon have antibodies that react strongly with subtype A and subtype B V3 loops in fusion proteins, and neutralize SF162 pseudotypes, while sera from 47 subtype B infected individuals reacted only with subtype B V3s. Sera from Cameroon did not neutralize primary A or B isolates, due to indirect masking by the V1/V2 domain rather than due to loss of the target epitope. 2557 was derived from a person infected with a clade A or CRF02 virus, and binds to A and B V3 loops. Neutralization of JR-FL and SF162(UG V3) by anti-V3 MAbs 2557, 2558, 2601, but not subtype A primary isolates despite binding to the subtype A V3 loops, suggested masking by V1V2 blocking of neutralization by these antibodies. Krachmarov *et al.* [2005] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2557: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This antibody was selected using a JRCSF fusion protein. Gorny *et al.* [2004]

No. 1488
MAb ID 2558
HXB2 Location Env
Author Location Env (92UG037)
Epitope
Subtype A, CRF02_AG
Neutralizing P
Immunogen
Species (Isotype) human
Ab Type gp120 V3
Research Contact Dr. Zolla-Pazner, Veterans Affairs Center, NY, NY. zollas01@endeavor.med.nyu.edu
References Krachmarov *et al.* 2006; Gorny *et al.* 2006; Krachmarov *et al.* 2005; Gorny *et al.* 2004
Keywords antibody binding site definition and exposure, binding affinity, neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- 2558: This MAb was derived from plasma from a patient with env clade A virus with the GPGQ V3 motif. When cross-reactivity was tested, this Ab bound to both the V3subtypeB-fusion protein containing GPGR motif and V3subtypeA-fusion protein containing GPGQ motif. This Ab was also shown to be able to neutralize both clade B psSF162 (GPGR) and clade C psMW965 (GPGQ) virus and the majority of subtype B and non-B primary isolates. Gorny *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)

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- 2558: This Ab was shown to neutralize SF162 and the neutralization sensitivity increased in the SF162 variant with a JR-FL V3 loop, SF162(JR-FL V3). In contrast, no neutralization was observed of the SF162(JR-FL V1/V2) variant and was somewhat restored in the SF162(JR-FL V1/V2/V3) variant, indicating that the masking of the V1/V2 loop plays a much greater role in restricting neutralization sensitivity than the variations in V3. This Ab was shown to neutralize viruses with V3 sequences from several different subtypes (B, F, A1, H, C, CRF02_AG and CRF01_AE). This Ab failed to neutralize SF162(JR-FL V1/V2) with V3 derived from CRF02_AG but not A1 and C, indicating effective V1/V2-mediated masking of somel HIV-1 clades. The effect on the neutralization sensitivity of the residue at the crown of the V3 loop (position 18) was shown to be low for this Ab. Krachmarov *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2558: Sera from subtype A infected individuals from Cameroon have antibodies that react strongly with subtype A and subtype B V3 loops in fusion proteins, and neutralize SF162 pseudotypes, while sera from 47 subtype B infected individuals reacted only with subtype B V3s. Sera from Cameroon did not neutralize primary A or B isolates, due to indirect masking by the V1/V2 domain rather than due to loss of the target epitope. 2557 was derived from a person infected with a clade A or CRF02 virus, and binds to A and B V3 loops. Neutralization of JR-FL and SF162(UG V3) by anti-V3 MAbs 2557, 2558, 2601, but not subtype A primary isolates despite binding to the subtype A V3 loops, suggested masking by V1V2 blocking of neutralization by these antibodies. Krachmarov *et al.* [2005] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 2558: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This antibody was selected using an A clade fusion protein, 92UG037. It is unusual in that it is a V3 antibody selected for conformational aspects using an A clade virus, with a V3 GPGQ tip – clade B viruses are usually used and have GPGR tips. It cross-neutralizes and binds B clade HIV SF162. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)

No. 1489
MAb ID 2580
HXB2 Location Env
Author Location Env (JR-CSF)
Epitope
Subtype B
Neutralizing P
Immunogen
Species (Isotype) human
Ab Type gp120 V3
Research Contact Dr. Zolla-Pazner, Veterans Affairs Center, NY, NY. zollas01@endeavor.med.nyu.edu
References Gorny *et al.* 2006; Gorny *et al.* 2004
Keywords antibody binding site definition and exposure, binding affinity, subtype comparisons, variant cross-recognition or cross-neutralization

- 2580: This MAb was derived from plasma from a patient with env clade B virus with the GPGR V3 motif. When cross-reactivity was tested, this Ab bound to both the V3subtypeB-fusion protein containing GPGR motif and to the V3subtypeA-fusion protein containing GPGQ motif. Gorny *et al.* [2006] (**variant cross-recognition or cross-neutralization**, **binding affinity**, **subtype comparisons**)
- 2580: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This antibody was selected using a JRCSF fusion protein. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)

No. 1490
MAb ID 391/95-D
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V3
Research Contact S. Zolla-Pasner
References Guillon *et al.* 2002a
Keywords co-receptor, enhancing activity

- 391/95-D: This antibody was used to explore the sensitivity of chimeric envelope viruses to Ab-mediated enhancement or neutralization. V3 mediated enhancement and envelopes susceptible to enhancement used CCR5. Enhancement was CD4 dependent. Guillon *et al.* [2002a] (**co-receptor**, **enhancing activity**)

No. 1491
MAb ID 39F
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing no
Immunogen
Species (Isotype)
Ab Type gp120 V3
Research Contact James Robinson, Tulane University, New Orleans, LA, USA
References Vaine *et al.* 2008; Pugach *et al.* 2008; Pantophlet *et al.* 2008; Binley *et al.* 2008; Gao *et al.* 2007; Crooks *et al.* 2007; Yuan *et al.* 2006; Haynes *et al.* 2006; Liao *et al.* 2006; Xiang *et al.* 2005; Selvarajah *et al.* 2005; Pancera *et al.* 2005; Pancera & Wyatt 2005; Pantophlet *et al.* 2004; Kwong *et al.* 2002; Grundner *et al.* 2002; Yang *et al.* 2002

B Cell

Keywords antibody binding site definition and exposure, antibody interactions, binding affinity, co-receptor, enhancing activity, kinetics, neutralization, review, structure, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- 39F: 24 broadly neutralizing plasmas from HIV-1 subtype B and C infected individuals were investigated using a series of mapping methods to identify viral epitopes targeted by NAbs. V3 Ab activity was measured by the abilities of the plasmas to inhibit capture of JR-FL virus particles by 39F. Modest titers were exhibited by subtype B plasmas, while subtype C plasmas showed lower activities, suggesting subtype-specific V3 loop binding. Binley *et al.* [2008] (**neutralization**, **subtype comparisons**)
- 39F: 39F neutralized two of the 15 subtype B isolates tested, 93TH305 and 92BR020c. Binding affinity of MAb 39F to gp120 was strongly reduced upon substitutions of Lys305 or Ile307 to Ala, and was moderately reduced upon substitutions of Ser306 and Ile309. Substitutions of Arg298 or Arg304 also diminished binding but not substantially, indicating that 39F interacts principally with the N-terminal flank of the V3 loop. Of the 13 viruses that were not neutralized by 39F, the resistance of 6 viruses could be explained by substitutions at important contact residues, while neutralization resistance of 7 viruses could not be explained by this. The fine specificity of 39F was mapped onto V3 in the structural context of gp120. Residues Lys305, Ser306, Ile307, and Ile309 form a distinct binding site on the N-terminal flank of V3, supporting the indication that 39F interacts with the N-terminal part of V3. Pantophlet *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **variant cross-recognition or cross-neutralization**, **binding affinity**, **structure**)
- 39F: In order to assess whether small molecule CCR5 inhibitor resistant viruses were more sensitive to neutralization by NAbs, two escape mutant viruses, CC101.19 and D1/85.16, were tested for their sensitivity to neutralization by 39F, compared to the sensitivity of CC1/85 parental isolate and the CCcon.19 control isolate. The CC101.19 escape mutant has 4 sequence changes in V3 while the D1/85.16 has no sequence changes in V3 and relies on other sequence changes for its resistance. None of the control or resistant viruses were sensitive for neutralization by 39F, although 39F bound strongly to gp120 from CC1/85. These results indicate that V3-dependent and -independent changes responsible for CCR5 inhibitor resistance do not necessarily alter the exposure of V3 to some of the V3 Abs. Pugach *et al.* [2008] (**co-receptor**, **neutralization**, **binding affinity**)
- 39F: Sera from both gp120 DNA prime-protein boost immunized rabbits and from protein-only immunized rabbits competed for binding to 39F, indicating elicitation of 39F-like Abs by both immunization regimens. Competitive virus capture assay revealed higher titers of 39F-like Abs in animals immunized with DNA prime-protein boost than in protein-only immunized animals. Vaine *et al.* [2008] (**vaccine antigen design**)
- 39F: Guinea pigs were immunized with gp120 protein, or with three types of VLPs containing disulfide-shackled functional trimers (SOS-VLP), uncleaved nonfunctional Env (UNC-VLP), naked VLP bearing no Env. 39F was used in a capture assay showing that most of the SOS-VLP and UNC-VLP sera contained high titers of anti-V3 Abs. gp120 sera showed only moderate titers of V3 competing Abs. Crooks *et al.* [2007] (**neutralization**)
- 39F: This review summarizes data on the development of HIV-1 centralized genes (consensus and ancestral) for induction of neutralizing antibody responses. Functionality and conformation of native epitopes in proteins based on the centralized genes was tested and confirmed by binding to 39F and other MAbs. Gao *et al.* [2007] (**antibody binding site definition and exposure**, **review**)
- 39F: 29 subtype B V3 peptides were designed and used for immunization of guinea pigs. Peptides that induced Abs that neutralized more than 3 HIV isolates were shown to bind to this Ab better than peptides unable to induce neutralization of any of the HIV-1 primary isolates. Haynes *et al.* [2006] (**neutralization**, **binding affinity**)
- 39F: The gp140δCFI protein of CON-S M group consensus protein and gp140CFI and gp140CF proteins of CON6 and WT viruses from HIV-1 subtypes A, B and C were expressed in recombinant vaccinia viruses and tested as immunogens in guinea pigs. 39F was shown to bind specifically to all recombinant proteins except for the gp140δFI derived from subtype C virus. The specific binding of this Ab to CON-S indicated that its conformational epitope was intact. 39F also bound specifically to the two subtype B gp120 proteins tested. Liao *et al.* [2006] (**antibody binding site definition and exposure**, **vaccine antigen design**, **subtype comparisons**)
- 39F: Interactions of this Ab with gp120 monomer and two cleavage-defective gp140 trimers were studied. It was shown that 39F interactions with the soluble monomers and trimers were minimally affected by GA cross-linking of the proteins, indicating that the 39F epitope was maintained after cross-linking. This Ab was associated with a small entropy change upon gp120 binding. This Ab was shown to have a kinetic advantage as it bound to gp120 faster than other less neutralizing Abs. 39F sucsesfully recognized untreated trimers and monomer expressed on cell surfaces but this recognition was decreased by cross-linking indicating that differences exist between the soluble trimers and native proteins. Yuan *et al.* [2006] (**antibody binding site definition and exposure**, **antibody interactions**, **kinetics**, **binding affinity**)
- 39F: R-FL and YU2 HIV-1 strains were not neutralized by39F. 39F and other non-neutralizing Abs only recognized JR-FL cleavage-defective glycoproteins, while the neutralizing Abs (2G12 and IgG1b12) recognized both cleavage competent and cleavage-defective glycoproteins. It is suggested that an inefficient env glycoprotein precursor cleavage exposes non-neutralizing determinants, while only neutralizing regions remain accessible on efficiently cleaved spikes. For YU2, both cleavage-competent and -defective glycoproteins were recognized by both neutralizing and non-neutralizing Abs. 39F, along with other Abs able to neutralize lab-adapted isolates, displayed enhanced viral entry at higher Ab concentrations, whereas the Abs that cannot neutralize any virus did not display such enhancement. Pancera & Wyatt [2005] (**antibody**

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binding site definition and exposure, **enhancing activity**, **neutralization**, **binding affinity**)

- 39F: A stable trimerization motif, GCN4, was appended to the C terminus of YU2gp120 to obtain stable gp120 trimers (gp120-GCN4). Each trimer subunit was capable of binding IgG1b12, indicating that they were at least 85% active. D457V mutation in the CD4 binding site resulted in a decreased affinity of the gp120-GCN4 for CD4, but the mutation did not affect binding of 39F. 39F was able to bind to both wildtype gp120, gp120-GCN4, and to the respective corresponding mutant molecules D457Vgp120 and D457Vgp120-GCN4 with the similar affinities. Pancera *et al.* [2005] (**binding affinity**)
- 39F: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened, while not obscuring b12 binding. V3 MAbs (447-52D, 19b, F245-B4e8 and 39F) bound to the GDMR antigen, but either did not bind or had diminished binding to mCHO. Selvarajah *et al.* [2005] (**vaccine antigen design**, **vaccine-specific epitope characteristics**)
- 39F: CXCR4-using HXBc2 strain and CCR5-using YU2 strain differed from each other in amino acid residues 325 and 326 at the base of the V3 loop. Changing the residues 325 and 326 in the HXBc2 from the amino acids predominant in the CXCR4-using strains to amino acids predominant in the CCR5-using strains did not result in binding of 39F to HXBc2. Xiang *et al.* [2005] (**antibody binding site definition and exposure**, **co-receptor**)
- 39F: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 39F. To inhibit 39F binding, Arg 304 and Lys 305 had to be changed to Ala. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- 39F: HIV-1 gp160deltaCT (cytoplasmic tail-deleted) proteoliposomes (PLs) containing native, trimeric envelope glycoproteins from R5 strains YU2 and JRFL, and X4 strain HXBc2, were made in a physiologic membrane setting as candidate immunogens for HIV vaccines – 2F5 bound to gp160deltaCT with a reconstituted membrane ten-fold better than the same protein on beads – anti-CD4BS MAbs IgG1b12 and F105, A32 (C1-C4), C11 (C1-C5), and 39F (V3) MAbs bound gp160deltaCT PLs indistinguishably from gp160deltaCT expressed on the cell surface. Grundner *et al.* [2002]
- 39F: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-2999) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- 39F: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibritin – stabilized oligomer gp140 delta683(-FT) showed strong preferential recognition by NAbs IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAbs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002]

No. 1492
MAb ID 4148d
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 V3
Research Contact Abraham Pinter, Public Health Research Institute, Newark, NJ, 07103. pinter@phri.org
References Krachmarov *et al.* 2006; Pinter *et al.* 2004; Pinter *et al.* 1993b
Keywords antibody generation, variant cross-recognition or cross-neutralization

- 4148: This Ab was shown to neutralize SF162 and the neutralization sensitivity increased in the SF162 variant with a JR-FL V3 loop, SF162(JR-FL V3). In contrast, a great reduction in sensitivity to neutralization was observed in the SF162(JR-FL V1/V2) variant and was somewhat restored in the SF162(JR-FL V1/V2/V3) variant, indicating that the masking of the V1/V2 loop plays a much greater role in restricting neutralization sensitivity than the variations in V3. This Ab was shown to neutralize viruses with V3 sequences from several different subtypes (B, F, A1, C, CRF02_AG and H) except subtype CRF01_AE. This Ab failed to neutralize SF162(JR-FL V1/V2) with V3 derived from different HIV-1 clades indicating effective V1/V2-mediated masking of several HIV-1 clades. The effect on the neutralization sensitivity of the

residue at the crown of the V3 loop (position 18) was shown to be low for this Ab.
- 4148D: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neturalization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. 5/6 anti-V3 MAbs, including 4148D, had similar binding affinity to soluble SF162 and JR-FL rgp120s, although the V3 loop differs at three positions (HigpgrafyTtgE for JR-FL and TigpgrafyAtgD for SF162). Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 4148D: Pinter1993a first describes this MAb. Pinter *et al.* [1993b] (**antibody generation**)

No. 1493
MAb ID 55/68b
HXB2 Location Env
Author Location gp120 (300–315)
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 V3
References Peet *et al.* 1998

- 55/68b: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind, and anti-V3 MAb 55/68b binding was abrogated by V3 serine substitutions in the V3 loop – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]

No. 1494
MAb ID 5G11
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 V3
Research Contact S. Nigida and L. Arthur, NCI, Frederick, MD USA
References Moore & Sodroski 1996

- 5G11: Binds to conformation sensitive epitope in the V3 loop – reciprocal inhibition of other V3 loop MAbs – reciprocal enhancement of some C1-C5 MAbs (unusual for an anti-V3 MAb) and CD4 binding site MAbs – and enhances binding of V2 MAbs. Moore & Sodroski [1996]

No. 1495
MAb ID 6.1
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 V3
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords review

- 6.1: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. 6.1 was non-neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
- 6.1: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – 3/4 V3 MAbs bound a similar linear epitope between positions 11-30 of the MN V3 loop (8E11/A8, 6.1, and 6.7), but only 8E11/A8 could weakly neutralize autologous strain SF162. He *et al.* [2002]

No. 1496
MAb ID 6.7
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 V3
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, review

- 6.7: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. 6.7 was non-neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
- 6.7: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – 3/4 V3 MAbs bound a similar linear epitope between positions 11-30 of the MN V3 loop (8E11/A8, 6.1, and 6.7), but only 8E11/A8 could weakly neutralize autologous strain SF162. He *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**)

B Cell

No. 1497
MAb ID 8.27.3
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 V3
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords review, variant cross-recognition or cross-neutralization

- 8.27.3: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, like 8.27.3; a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**, **review**)
- 8.27.3: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – 1/4 V3 MAbs, 8.27.3, bound a discontinuous epitope that was broadly cross-reactive with B clade R5 and X4 strains (not E clade) and could neutralize autologous strain SF162. He *et al.* [2002]

No. 1498
MAb ID 8E11/A8
HXB2 Location Env
Author Location gp120 (SF162)
Epitope
Subtype B
Neutralizing L
Immunogen vaccine
Vector/Type: protein *Strain:* B clade SF162 *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) transgenic mouse (IgG2κ)
Ab Type gp120 V3
Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org
References Gorny & Zolla-Pazner 2004; He *et al.* 2002
Keywords antibody binding site definition and exposure, antibody generation, autologous responses, review

- 8E11/A8: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 8E11/A8: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – 3/4 V3 MAbs bound a similar linear epitope between positions 11-30 of the MN V3 loop (8E11/A8, 6.1, and 6.7), but only 8E11/A8 could weakly neutralize autologous strain SF162. He *et al.* [2002] (**antibody binding site definition and exposure**, **antibody generation**, **autologous responses**)

No. 1499
MAb ID 9305
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen
Species (Isotype) mouse
Ab Type gp120 V3
Research Contact Du Pont, Wilmington DE
References McDougal *et al.* 1996

No. 1500
MAb ID A1g8
HXB2 Location Env
Author Location gp120
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
Research Contact James Robinson, Tulane University Med School, New Orleans, LA, USA
References Cavacini *et al.* 2003; Cavacini *et al.* 2002
Keywords antibody interactions, co-receptor, variant cross-recognition or cross-neutralization

- A1g8: The MAb B4e8 binds to the base of the V3 loop, neutralizes multiple primary isolates and was studied for interaction with other MAbs. B4e8 enhanced binding of CD4i MAbs 4.8d, 1.7b, and A1g8 to R5X4 virus 92HT593, but only of 48d to the R5 virus 92US660, and there was only a modest impact of the combination of B4e8 and CD4i MAbs on neutralization. Cavacini *et al.* [2003] (**antibody interactions**, **co-receptor**)
- A1g8: This study examined antibody interactions, binding and neutralization with a B clade R5 isolate (92US660) and R5X4 isolate (92HT593). Abs generally bound and neutralized the R5X4 isolate better than the R5 isolate. Anti-V3 MAb B4a1 increased binding of CD4i MAbs 48d, 17b and A1g8, but only A1g8 binding was increased by B4a1 to the R5 isolate. Additive affects on neutralizaton of the R5X4 isolate with B4a1 and CD4i MAbs was observed, presumably due to increased exposure of the CD4i binding site, but not for the R5 isolate. Anti-gp41 MAb F240 had a synergistic effect on neutralization with CD4i MAbs 48d and 17b, but not with A1g8 for the R5X4 virus. Cavacini *et al.* [2002] (**antibody interactions**, **co-receptor**, **variant cross-recognition or cross-neutralization**)

No. 1501
MAb ID AG1121 (1121)
HXB2 Location Env
Author Location gp120

B Cell

Epitope
Neutralizing L
Immunogen
Species (Isotype)
Ab Type gp120 V3
Research Contact AGMED, Inc, Bedford, MA, USA or ImmunoDiagnostics, Inc, Woburn, MA, USA
References Pacheco *et al.* 2008; Yang *et al.* 2005c; Si *et al.* 2001; Cao *et al.* 1997b; Sullivan *et al.* 1995
Keywords neutralization

- 1121: Two HIV-1 isolates, NL4-3 and KB9, were adapted to replicate in cells using the common marmoset receptors CD4 and CXCR4. The adaptation resulted in a small number of changes of env sequences in both isolates. The adapted NL4-3 variants were generally more sensitive to neutralization by 1121 than the adapted KB9 variants. All of the NL4-3 exhibited similar sensitivity to neutralization by 1121 except for the viruses containing the V242I change, which exhibited a slight increase in neutralization sensitivity to 1121. Wildtype KB9 is resistant to neutralization by 1121 but the changes associated with adaptation to marmoset receptors resulted in variants with increased sensitivity to neutralization by 1121. Thus, adaptation to marmoset receptors resulted in an increase in sensitivity to neutralization by 1121 for KB9 but not for NL4-3. Pacheco *et al.* [2008] (**neutralization**)
- 1121: Ab neutralization of viruses with mixtures of neutralization-sensitive and neutralization-resistant envelope glycoproteins was measured. It was concluded that binding of a single Ab molecule is sufficient to inactivate function of an HIV-1 glycoprotein trimer. The inhibitory effect of the Ab was similar for neutralization-resistant and -sensitive viruses indicating that the major determinant of neutralization potency of an Ab is the efficiency with which it binds to the trimer. It was also indicated that each functional trimer on the virus surface supports HIV-1 entry independently, meaning that every trimer on the viral surface must be bound by an Ab for neutralization of the virus to be achieved. Yang *et al.* [2005c] (**neutralization**)
- AG1121: SHIV-HXBc2 is a neutralization sensitive non-pathogenic virus, and several *in vivo* passages through monkey's yielded highly pathogenic SHIV KU-1 – HXBc2 and the KU-1 clone HXBc2P3.2 differ in 12 amino acids in gp160 – substitutions in both gp120 and gp41 reduced the ability of sCD4, IgG1b12, F105 and AG1121 to Env achieve saturation and full occupancy, and neutralize KU-1 – 17b and 2F5 also bound less efficiently to HXBc2P3.2, although 2G12 was able to bind both comparably. Si *et al.* [2001]
- AG1121: Called 1121 – Virus with the V1-V2 loop deleted was viable and more susceptible to neutralization by CD4i MAb 17b, and anti-V3 MAbs 1121, 9284, and 110.4, but not to and CD4BS MAb F105 or sCD4. Cao *et al.* [1997b]
- AG1121: Recognizes monomeric gp120 from T-cell adapted line HXBc2 and primary isolate 89.6 equally well, but 89.6 was three-fold less sensitive to neutralization by AG1121 than HXBc2. Sullivan *et al.* [1995]

No. 1502
MAb ID Ag1211
HXB2 Location Env
Author Location gp120 (V3) (JRFL)
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 V3
References Kwong *et al.* 2002
Keywords antibody binding site definition and exposure

- Ag1211: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-2999) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)

No. 1503
MAb ID B4a1
HXB2 Location Env
Author Location gp120 (V3)
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V3
Research Contact James Robinson, Tulane University Med School, New Orleans, LA, USA
References Cavacini *et al.* 2003; Cavacini *et al.* 2002
Keywords antibody interactions, co-receptor, variant cross-recognition or cross-neutralization

- B4a1: The MAb B4e8 binds to the base of the V3 loop, neutralizes multiple primary isolates and was studied for interaction with other MAbs. The anti-V3 MAb B4a1 cross-competes with B4e8. Cavacini *et al.* [2003] (**antibody interactions**)
- B4a1: This study examined antibody interactions, binding and neutralization with a B clade R5 isolate (92US660) and R5X4 isolate (92HT593). Abs generally bound and neutralized the R5X4 isolate better than the R5 isolate. Anti-gp41 MAb F240 binding was not affected by the binding of the V3 loop MAb B4a1, but preincubation with F240 could enhance B4a1 binding of the R5 isolate. B4a1 reacts with many B clade isolates, and preincubation with sCD4 enhances binding to both the R5

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and R5X4 isolates. B4a1 increased binding of CD4i MAbs 48d, 17b and A1g8, as well as CD4BS MAbs IgG1b12 and F105 to R5X4 virions, but only A1g8 and IgG1b12 binding was increased by B4a1 to the R5 isolate. Additive affects on neutralizaton of the R5X4 isolate with B4a1 and CD4i MAbs was observed, presumably due to increased exposure of the CD4i binding site, but not for the R5 isolate. B4a1 had an additive affect on neutralization with 2G12 with the R5X4 virus but not the R5 virus, and did not impact 2F5 neutralization. Cavacini *et al.* [2002] (**antibody interactions**, **co-receptor**, **variant cross-recognition or cross-neutralization**)

No. 1504
MAb ID B4e8 (F425 B4e8)
HXB2 Location Env
Author Location gp120 (V3)
Epitope
Subtype B
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human (IgG2κ)
Ab Type gp120 V3
Research Contact Lisa Cavacini, Beth Isreal Deconess Medical Center, Boston MA, USA
References Pantophlet *et al.* 2008; Bell *et al.* 2008; Lusso *et al.* 2005; Zwick *et al.* 2003; Liu *et al.* 2003; Cavacini *et al.* 2003
Keywords antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, co-receptor, neutralization, structure, variant cross-recognition or cross-neutralization

- B4e8: The crystal structure of the B4e8 Fab fragment in complex with a 24-mer V3 peptide (RP142) at 2.8 A resolution is described. B4e8 recognizes a novel V3 loop conformation, featuring a five-residue alpha-turn around the conserved GPGRA apex of the beta-hairpin loop and interacts primarily with V3 through side-chain contacts with just two residues, Ile(P309) and Arg(P315), while the remaining contacts are to the main chain. The structure can explain how B4e8 can tolerate a certain degree of sequence variation within V3 and, hence, is able to neutralize different HIV-1 isolates. Bell *et al.* [2008] (**variant cross-recognition or cross-neutralization**, **structure**)
- B4e8: B4e8 neutralized 7 of the 15 subtype B isolates tested, of which 6 were resistant to neutralization by MAbs 19b, 39F, CO11, F2A3, F530, LA21 and LE311. Angle of interaction between B4e8 and V3 was shown by superimposing the Fab fragment of the Ab with V3. B4e8 was shown to interact with V3 from a slightly elevated angle relative to the MAbs 58.2 and 447-52D. Pantophlet *et al.* [2008] (**antibody binding site definition and exposure**, **neutralization**, **structure**)
- B4e8: The epitope for the MAb D19 is conserved and embedded in V3. D19 is unique in that for R5 viruses, it was cryptic and did not bind without exposure to sCD4, and for X4 and R5X4 isolates it was constitutively exposed. It had an overlapping binding region with MAbs 447-52D, B4e8, and 268-D, but different reactivity patterns and fine specificity. While B4e8 and 447-52D could bind to the R5 virus BaL in the absence of sCD4, treatment with sCD4 did increase the binding of both B4e8 and 447-52D, but did not impact their ability to neutralize BaL. Lusso *et al.* [2005] (**antibody binding site definition and exposure**)
- B4e8: This MAb binds to the base of the V3 loop, and binds and neutralizes multiple primary isolates. The anti-V3 MAb B4a1 cross-competes with B4e8. B4e8 and 2G12 enhanced each others binding, and gave synergistic neutralization. B4e8 could neutralize R5X4 virus 92HT593 better than 2G12, while 2G12 was better at neutralizing R5 virus 92US660. B4e8 enhanced binding of CD4i MAbs 4.8d, 1.7b, and A1g8 to 92HT593, but only of 48d to the 92US660, and there was only a modest impact of the combination of B4e8 and CD4i MAbs on neutralization. CD4BS MAb IgG1b12 had no effect on B4e8 binding. Anti-gp41 MAb F240 inhibited B4e8 neutralization. Cavacini *et al.* [2003] (**antibody binding site definition and exposure**, **antibody generation**, **antibody interactions**, **co-receptor**, **variant cross-recognition or cross-neutralization**)
- B4e8: The effect of isotype (IgG1 and IgG3) and subtype (IgA) switching of parental F425B4e8 (IgG2)on HIV-1 binding and neutralization was investigated. IgG1-and IgA-F425B4e8 mutants showed virus-specific binding levels and TCLA SF2 isolate compared to the parental IgG2. Comparable levels of neutralization of primary isolates 92HT593 (R5X4) and 92US660 (R5) was achieved by all isotypes and subtypes of F425B4e8. Liu *et al.* [2003] (**variant cross-recognition or cross-neutralization**, **antibody sequence variable domain**)
- B4e8: Called F425 B4e8. scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the V3 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)

No. 1505
MAb ID D27
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Otteken *et al.* 1996; Earl *et al.* 1994

- D27: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D27 is one of two MAbs labeled group Ca, that was type-specific for BH8 – D27 fully blocked

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CD4 binding, and the deletion of the V3 loop abrogated binding. Sugiura *et al.* [1999]
- D27: Pulse label experiments of 4 MAbs (D20, D27, T20, and T22) binding to noncleavable gp160 revealed that these anti-CD4 MAbs bound with a delay, and that the epitope formed with a t 1/2 of about 10 minutes. Otteken *et al.* [1996]
- D27: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1506
MAb ID D47
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* Env
Species (Isotype) mouse
Ab Type gp120 V3
Research Contact Patricia Earl, NIAID, NIH
References Zhang *et al.* 2008; Wright *et al.* 2008; Huang *et al.* 2005b; Salzwedel *et al.* 2000; Earl *et al.* 1997; Wyatt *et al.* 1997; Otteken *et al.* 1996; Richardson *et al.* 1996; Earl *et al.* 1994
Keywords antibody binding site definition and exposure, antibody generation, isotype switch, mucosal immunity, neutralization, variant cross-recognition or cross-neutralization

- D47: Several IgG MAbs were isotype switched to IgA and tested for their abilities to generate immune complexes with HIV-1 and be excreted from polarized epithelial cells from the basolateral to the apical surface via polymeric Ig receptor (pIgR) binding. IgA D47 showed robust excretion abilities which corresponded to increased binding of D47 to HIV, and, as immune complex with the virus, to pIgR. The excretion of the D47-HIV complex was IgA Ab concentration dependent, as well as time dependent, depending on on the duration of basolateral exposure of the immune complexes. Immune complexes with D10 plus D47 showed synergistic abilities, as the binding and excretion increased significantly with both Abs present than with only one of the Abs. D47 excreted non-infectious virus, correlating with it being a neutralizing Ab. These results show that IgA Abs have potential to excrete HIV from mucosal lamina propria thus decreasing the viral burden and access to susceptible cells. Wright *et al.* [2008] (**isotype switch**, **mucosal immunity**)
- D47: D47 did not compete with the newly defined neutralizing mAb m44 for binding to gp41. Zhang *et al.* [2008]
- D47: By isotype switching, IgG and IgA variants of D47 were produced. Both D47 IgA and IgG neutralized virus in conventional neutralization assays, however, IgA performed better. D47 IgA was also internalized into the cells by the polymeric Ig receptor (pIgR) and showed capability of intracellular neutralization of HIV-1, while D47 IgG showed no such activity. The extent of intracellular neutralization was shown to be dependent on the concentration of D47 IgA. D47 IgA also inhibited production of virus. Huang *et al.* [2005b] (**isotype switch**, **neutralization**, **mucosal immunity**)
- D47: sCD4 can activate fusion between effector cells expressing Env and target cells expressing coreceptor (CCR5 or CXCR4) alone without CD4 – V3 MAb D47 is strain specific and can inhibit sCD4 mediated infection, but only of the closely related LAV Env, while anti-CD4i MAbs were broadly cross-neutralizing. Salzwedel *et al.* [2000] (**variant cross-recognition or cross-neutralization**)
- D47: Used for comparison in a study of gp41 antibodies – D47 binds to a greater extent to cell surface expressed Env than any of 38 conformation dependent anti-gp41 MAbs. Earl *et al.* [1997]
- D47: Binds both gp120 and soluble gp120+gp41 complex efficiently, suggesting its gp120 epitope is not blocked by gp41 binding. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
- D47: Pulse label experiments of MAb binding to noncleavable gp160 revealed that this anti-V3 MAb bound immediately and binding stayed constant through chase period. Otteken *et al.* [1996]
- D47: Used for capture of oligomeric Env for antigen capture ELISA – binding of this antibody to oligomeric Env IIIB was not blocked by human sera from the US, consistent with a low prevalence of IIIB-like V3 strains. Richardson *et al.* [1996] (**antibody binding site definition and exposure**)
- D47: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994] (**antibody generation**)

No. 1507
MAb ID D56
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade IIIB *HIV component:* oligomeric gp140
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
Research Contact P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD
References Sugiura *et al.* 1999; Earl *et al.* 1994

- D56: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D56 is one of two MAbs labeled group Ca, that was type-specific for BH8 – D56 fully blocked CD4 binding, and the deletion of the V3 loop abrogated binding – 12.5 ug/ml of D56 was required to achieve 50% neutralization of HIV-1 NL4-3. Sugiura *et al.* [1999]
- D56: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1508
MAb ID F5.5
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen
Species (Isotype) mouse

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Ab Type gp120 V3
Research Contact Hybridolabs, Institute Pasteur
References Altmeyer *et al.* 1999

- F5.5: A Semliki Forest virus (SFV) expression system carrying BX08 env was used to study the conformation of gp120 Env – intracytoplasmic gp120 was recognized by the anti-V3 MAbs K24 and F5.5, while gp120 at the plasma membrane was detected only by conformation dependent MAbs 2G12, 670-D and 694/98D and not V3 MAbs – expression in rat brain also showed that surface-expressed Env was recognized only by the conformation-dependent antibodies and not by anti-V3 antibodies. Altmeyer *et al.* [1999]

No. 1509
MAb ID G3-1472
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 V3
Research Contact M. Fung
References Moore & Sodroski 1996

- G3-1472: Binds to carboxy-terminal side of the V3 loop – reciprocal binding inhibition with other anti-V3 and anti-C4 MAbs – reciprocal enhanced binding of some anti-V2 MAbs and anti-CD4 binding site MAbs – binding inhibited by anti-C4 MAbs. Moore & Sodroski [1996]

No. 1510
MAb ID K24
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen
Species (Isotype) mouse
Ab Type gp120 V3
Research Contact Hybridolabs, Institute Pasteur
References Altmeyer *et al.* 1999

- K24: A Semliki Forest virus (SFV) expression system carrying BX08 env was used to study the conformation of gp120 env – intracytoplasmic gp120 was recognized by the anti-V3 MAbs K24 and F5.5, while gp120 at the plasma membrane was detected only by conformation dependent MAbs 2G12, 670-D and 694/98D and not V3 MAbs – expression in rat brain also showed that surface-expressed Env was recognized only by the conformation-dependent antibodies and not by anti-V3 antibodies. Altmeyer *et al.* [1999]

No. 1511
MAb ID TH1
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L (MN, J)
Immunogen
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3
Research Contact Michael Fung, Tanox Biosystem, USA
References Gorny & Zolla-Pazner 2004; Yang *et al.* 1998; D'Souza *et al.* 1995
Keywords assay development, review, variant cross-recognition or cross-neutralization

- TH1: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. TH1 neutralizes some TCLA strains. Gorny & Zolla-Pazner [2004] (**review**)
- TH1: A neutralization assay was developed based on hemi-nested PCR amplification of the LTR (HNPCR) – LTR-HNPCR consistently revealed HIV DNA and was shown to be a rapid, specific and reliable neutralization assay based on tests with 6 MAbs and 5 isolates. Yang *et al.* [1998] (**assay development**)
- TH1: Found to neutralize MN and JRCSF, but not two B subtype primary isolates, nor a D subtype primary isolate, by most labs in a multi-laboratory study involving 11 labs. D'Souza *et al.* [1995] (**variant cross-recognition or cross-neutralization**)

No. 1512
MAb ID anti-gp120/V3
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein, virus-like particle (VLP) *Strain:* A clade 94UG018 *HIV component:* Gag, gp120, Nef, Pol
Species (Isotype) mouse (IgG)
Ab Type gp120 V3
Research Contact Intracel Co
References Buonaguro *et al.* 2001

- Anti-V3: HIV-1 pr55 gag-based virus-like particles (VLP) carrying Nef and Pol open reading frames as well as gp120 of the clade A isolate 94UG018 were created using a Baculovirus expression system to package additional ORFS into the VLP – anti-V3 and anti-p24 antibodies were used to assess the expression levels and Gag and gp120-TM were found to be expressed at comparable levels on the VLP. Buonaguro *et al.* [2001]

No. 1513
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: protein, virus-like particle (VLP) *Strain:* B clade LAI *HIV component:* CD4BS, Gag, V3
Species (Isotype) mouse
Ab Type gp120 V3
References Truong *et al.* 1996

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- Antibodies raised against recombinant anti-p55 virus-like particles with the p24 region 196-226 deleted, bearing inserts of either the V3 or the CD4BS regions of gp120 were studied – no neutralizing responses, weak Env, and strong Gag responses were elicited – the major homology region (MHR) and proximal sequences was found to be required for capsid assembly. Truong *et al.* [1996]

No. 1514
MAb ID polyclonal
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing yes
Immunogen vaccine
Vector/Type: canarypox prime with recombinant protein boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* Gag, gp120, gp41, Pol *Adjuvant:* MF59
Species (Isotype) human
Ab Type gp120 V3
References Verrier *et al.* 2000

- Serum Abs elicited by this vaccine reacted with V3 peptides from clades B, C, and F, reacted weakly with V3 peptides from clades A, D, G, and H, and did not react with V3 peptides from clades E and O – neutralizing activity against 5 of 14 primary isolates tested was observed, including one B clade X4 virus, two dualtropic B clade viruses (from clade B) and one clade B and one clade C R5 virus. Verrier *et al.* [2000]

No. 1515
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (303–325)
Epitope
Neutralizing no
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgM)
Ab Type gp120 V3
References Sidorova 1999

- Polyspecific anti-MN-24 antibodies were raised through V3 peptide, MN-24 stimulation of human cells, followed by EBV transformation: they react with homologous and heterologous peptides and may be autoantibodies. Sidorova [1999]

No. 1516
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
Ab Type gp120 V3
References Guevara *et al.* 2002

- Viral RNA in serum and high titers of subtype C consensus V3 peptide binding Abs were the best independent predictors of mother to infant transmission of HIV-1 subtype C – NAb to subtype B HIV-1 (MN) was also correlated. Guevara *et al.* [2002]

No. 1517
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype B
Neutralizing L
Immunogen vaccine
Vector/Type: HIV-1 captured on concavalin A-immobilized polystyrene nanospheres, Con A-NS *Strain:* B clade IIIB *HIV component:* gp120, heat-inactivated virus *Adjuvant:* concavalin A-immobilized polystyrene nanospheres
Species (Isotype) mouse (IgA)
Ab Type gp120 V3
References Kawamura *et al.* 2002

- Vaginal fluids were collected after intravaginal immunization of BALB/c mice and analyzed for their anti-HIV-1 antibody levels using a IIIB-V3 ELISA and IIIB neutralization assay – HIV-1 specific IgG was undetectable but anti-HIV IgA antibody response was identified in the vaginal fluids of immunized mice with HIV concavalin A-immobilized polystyrene nanosheres. Kawamura *et al.* [2002]

No. 1518
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype B
Neutralizing L
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade 89.6P, B clade MN *HIV component:* Env *Adjuvant:* aluminum hydroxide, Cholera toxin (CT), GM-CSF, IL-12, IL-18, IL-1α
Species (Isotype) human (IgA, IgG1, IgG2a)
Ab Type gp120 V3
References Bradney *et al.* 2002

- The cytokine-adjuvant combination IL-1alpha, IL-12 and IL-18 were found to stimulate potent mucosal antibody responses upon intranasal immunization of mice – cholera toxin is the most widely used adjuvant, but is not safe for use in humans. Bradney *et al.* [2002]

No. 1519
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Subtype C
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* multiple epitope immunogen *HIV component:* V3 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse
Ab Type gp120 V3

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References Hewer & Meyer 2002

- A synthetic peptide immunogen designated a multiple epitope immunogen (MEI) was generated by synthesizing peptides with mixtures of frequently found amino acids (>10%) from the C subtypes allowed in the synthetic peptide – when injected into mice, the C subtype MEI induced antibodies that recognized the immunogen and whole virus as an antigen in ELIZAs – sera from eight HIV positive South Africans recognized the MEI peptide in ELISA tests. Hewer & Meyer [2002]

No. 1520
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (V3)
Epitope
Subtype B, C, F
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
Ab Type gp120 V3
References Bongertz *et al.* 2003
Keywords rate of progression, subtype comparisons

- Ab responses at diluations above 1:1000 against the consensus V3 loops of subtypes A, B, C, D, F, and Brazilian B and F, were detected in only 6/60 individuals infected with HIV by sexual exposure, while a significantly higher (38/46) reactivity and frequency of peptide recognition was observed in the plasma of IDUs. High Ab titers (> 1:10,000) were directed against V3B, V3Bbr and V3F peptides. The IDU group also displayed broader NAb responses, in comparison to the sexually transmitted group. This may contribute to a slower disease progression in IDUs. Bongertz *et al.* [2003] (**subtype comparisons**, **rate of progression**)

No. 1521
MAb ID polyclonal
HXB2 Location Env
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: adenovirus *Strain:* B clade HXB2/Bal *HIV component:* gp140ΔCFI, gp140ΔV1V2ΔCFImodifiedV3
Species (Isotype) guinea pig (IgG)
Ab Type gp120 V3
References Yang *et al.* 2004
Keywords co-receptor

- Neutralizing antibodies against V3 with greater breadth among B clade viruses were created in vaccinated guinea pigs using a combination gp140ΔV1V2 and shortened V3 loop envelope than using intact Envelope. The interior V3 glycosylation site was removed in the modification of V3. This change also caused the virus to become CXCR4 tropic. Yang *et al.* [2004] (**co-receptor**)

No. 1522
MAb ID 11/75a/21/41
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 V3 discontinuous
References Peet *et al.* 1998; McKeating *et al.* 1992a

- 11/75a/21/41: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind, but anti-V3 MAb 11/75a/21/41 binding was dramatically diminished by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]

No. 1523
MAb ID 41.1 (ICR41.1i, ICR41. ICR 41.1i)
HXB2 Location Env
Author Location gp120 (HXB10)
Epitope
Neutralizing L (HXB2)
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* gp120
Species (Isotype) rat (IgG2a)
Ab Type gp120 CD4i, gp120 V3 discontinuous
Research Contact J. Cordell, Institute for Cancer Research, Sutton, Surrey, UK
References Heap *et al.* 2005a; Ugolini *et al.* 1997; Jeffs *et al.* 1996; Armstrong *et al.* 1996; Armstrong & Dimmock 1996; McLain & Dimmock 1994; Klasse *et al.* 1993a; McKeating *et al.* 1993b; McKeating *et al.* 1992a; Reitz *et al.* 1988

- 41.1: Called ICR 41.1i. Used as a positive control for enhanced MAb binding after sCD4 exposure – 41.1 binding to virions is increased 2-fold by sCD4. Heap *et al.* [2005a]
- 41.1: Viral binding inhibition by 41.1 was weakly correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5) Ugolini *et al.* [1997]
- 41.1: Called ICR41.1i – IgG2c? – Neutralization was affected if the Ab was added after the virus bound to the host cells at 24 degrees C or below. Armstrong & Dimmock [1996]
- 41.1: Called ICR41.1i – Neutralization occurs by blocking a post-fusion internalization event, in contrast to MAb F58. Armstrong *et al.* [1996]
- 41.1: Deletion of the V1V2 regions did not affect anti-V3 Abs ability to bind when compared to intact rec gp120. Jeffs *et al.* [1996]
- 41.1: Called ICR41.1i – Kinetics of neutralization studied – no lag for 39.3b, while ICR 39.13g and ICR 41.1i have lags of 5 and 15 min respectively – neutralization mediated by 3 molecules of IgG per virion – most efficient at neutralization of the three MAbs studied – acts with multi-hit kinetics. McLain & Dimmock [1994]

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- 41.1: The gp41 mutation 582(Ala to Thr) results in conformational changes in gp120 that confer neutralization resistance to conformationally sensitive neutralizing MAbs – neutralization efficiency of 41.1 is not affected. Klasse *et al.* [1993a]; Reitz *et al.* [1988]

No. 1524
MAb ID 55/45a/11
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen
Species (Isotype)
Ab Type gp120 V3 discontinuous
References Peet *et al.* 1998

- 55/45a/11: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind, and anti-V3 MAb 55/45a/11 binding was only marginally diminished by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]

No. 1525
MAb ID 1108
HXB2 Location Env
Author Location Env (987)
Epitope
Subtype B
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp120 V3 mimotope
References Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a
Keywords antibody binding site definition and exposure, antibody generation, mimotopes, review

- 1108: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 1108: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 1108: Selected with peptide 987, a mimotope of anti-V3 MAb 447-D – MAb peptide reactivity pattern clustered with immunological related MAbs: 1108, 386, 268, 311, 257, 694.8 – the amino acids HI tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**, **antibody generation**, **mimotopes**)
- 1108: The sequence of peptide 987, used to select MAb 1108, is ADGAWRSVHLGPGRGSGSGMGK. Zolla-Pazner *et al.* [1999a] (**antibody binding site definition and exposure**, **antibody generation**)

No. 1526
MAb ID polyclonal
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade MN *HIV component:* gp120 *Adjuvant:* Cholera toxin (CT)
Species (Isotype) rabbit
Ab Type gp120 V3-C4
References Zinckgraf *et al.* 1999

- Nasal mucosal immunization and boosting of HIV peptide and was superior for inducing serum IgG and vaginal secretory IgA compared to nasal immunization and vaginal boosting – vaginal immunization and boosting resulted low serum IgG and vaginal IgA and a high vaginal IgG response. Zinckgraf *et al.* [1999]

No. 1527
MAb ID polyclonal
HXB2 Location Env
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgA, IgG)
Ab Type gp120 V3, gp120 V4
References Skott *et al.* 1999

- IgA and IgG from 45 HIV+ individuals was studied – people with low CD4+ cell counts had decreased levels IgA in saliva – sera and saliva IgA was primarily directed toward Env – peptide ELISA studies indicated that teh dominant IgA epitopes were the V4 region (aa 385-409) and the C-term part of the V3 loop (aa 325-344), while the IgG response was directed towards the tip of the loop (aa 308-325). Skott *et al.* [1999]

No. 1528
MAb ID polyclonal
HXB2 Location Env
Author Location gp41
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* gp41
Species (Isotype) rabbit (IgG)
Ab Type gp41 alpha-helical hairpin intermediate
References Louis *et al.* 2003
Keywords vaccine antigen design

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- Polyclonal Abs raised against soluble trivalently linked N35CCG-N13 and N34CCG, the internal trimeric core of the coiled-coil ectodomain, inhibit HIV-1 Env-mediated cell fusion at levels comparable to 2G12. Louis *et al.* [2003] (**vaccine antigen design**)

No. 1529
MAb ID 1367 (1367-D)
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp41 cluster I
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Eda *et al.* 2006b; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Gorny *et al.* 2000; Gorny & Zolla-Pazner 2000; Nyambi *et al.* 1998
Keywords antibody binding site definition and exposure, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 1367: Called 1367-D. The neutralization potency of this Ab against 7 HIV-1 primary isolates was compared to the neutralization potency of the Ab KD-247. Higher concentrations of 1367-D were needed for the neutralization of all of the HIV-1 isolates suggesting a lower neutralization potency of this Ab. Eda *et al.* [2006b] (**variant cross-recognition or cross-neutralization**)
- 1367: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 1367: A cluster I epitope that binds to rgp41 567-647, recognizes a peptide N51-C43 complex trimer of heterodimers that approximates the core of the fusogenic form of gp41 – this MAb doesn't react with either of the peptides N51 or C43 individually – MAbs 50-69 and 1367 had similar properties. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
- 1367: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, but gp41 MAb 50-69 bound with a 5 fold preference for the oligomer, while other gp41 MAbs (1367, 98-6, 167-D, 1281, 1342, and 1379) did not show a preference. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)
- 1367: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 cluster I anti-gp41 MAbs which showed good cross clade reactivity – 1367 weakly bound to the majority of isolates – no neutralizing activity was observed when tested with 5 isolates, but 1367 did not bind well to these isolates. Nyambi *et al.* [2000] (**subtype comparisons**)
- 1367: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – anti-gp41 Abs 98-6, 1367 and 1342 were not able to bind detectably with any of the viruses from any clade. Nyambi *et al.* [1998] (**subtype comparisons**)

No. 1530
MAb ID 7B2
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing no
Immunogen
Species (Isotype) human
Ab Type gp41 cluster I
References Vaine *et al.* 2008; Nelson *et al.* 2008; Crooks *et al.* 2007; Moore *et al.* 2006; Robinson *et al.* 2005; Haynes *et al.* 2005a; Binley *et al.* 2003; Binley *et al.* 1999
Keywords antibody binding site definition and exposure, antibody generation, assay development, HAART, ART, neutralization, vaccine antigen design

- 7B2: 7B2 was shown to bind to Envs used in typical epitope binding assays, unlike the neutralizing Abs 8K8, DN9, and D5 used in this study. Nelson *et al.* [2008]
- 7B2: Sera from both gp120 DNA prime-protein boost immunized rabbits and from protein-only immunized rabbits did not compete for binding to 7B2, indicating no elicitation of 7B2-like Abs by either of the immunization regimens. Vaine *et al.* [2008] (**vaccine antigen design**)
- 7B2: Most of the sera from guinea pigs immunized with gp120 protein or with three types of VLPs containing disulfide-shackled functional trimers (SOS-VLP), uncleaved nonfunctional Env (UNC-VLP), and naked VLP bearing no Env, weakly or ineffectively inhibited 7B2. HIV-1 + plasma strongly inhibited this Ab, and high inhibition was also found in three of the VLP-sera. Crooks *et al.* [2007] (**neutralization**)
- 7B2: In addition to gp120-gp41 trimers, HIV-1 particles were shown to bear nonfunctional gp120-gp41 monomers and gp120-depleted gp41 stumps on their surface. 7B2 recognizes trimeric and monomeric gp41 stumps. Thus, it did not neutralize wildype virus particles but it could capture virus efficiently. It is hypothesized that the nonfunctional monomers on the HIV-1 surface serve to divert the Ab response, helping the virus to avoid neutralization. Moore *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**)
- 7B2: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 7B2 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)
- 7B2: A reverse capture assay was developed to asses what kind of human MAbs were produced in EBV B-cell transformation assays performed on PBMC sampled at different timepoints from three HIV-1 infected patients on HAART. The reverse capture assay was validated by the solid phase MAbs that could not capture biotin-MAbs of the same or overlapping specificity when reacted with patient virus envelope glycoproteins preincubated with or without sCD4. Detection of gp41

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Abs in the assay was based on the fact that they would capture cleaved gp41 and thus be detected by binding to biotin-labeled gp41 Abs recognizing non-competing sites. Reverse capture assay showed that the produced Abs from the patients were detected by biotin-labeled 7B2 in a mixture with 2.2B, indicating presence of gp41 Abs. Robinson *et al.* [2005] (**antibody generation**, **assay development**, **HAART, ART**)

- 7B2: The SOS mutant envelope protein introduces a covalent disulfide bond between gp120 surface and gp41 transmembrane proteins into the R5 isolate JR-FL by adding cysteines at residues 501 and 605. Pseudovirions bearing this protein bind to CD4 and co-receptor bearing cells, but do not fuse until treatment with a reducing agent, and are arrested prior to fusion after CD4 and co-receptor engagement. gp41 Abs 7B2 and 2.2B did not neutralize in any format, WT, SOS, nor when added postbinding. Binley *et al.* [2003] (**vaccine antigen design**)
- 7B2: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999] (**antibody binding site definition and exposure**)

No.	1531
MAb ID	126-6 (SZ-126.6)
HXB2 Location	Env
Author Location	gp41 (HXB2)
Epitope	
Subtype	B
Neutralizing	no
Immunogen	HIV-1 infection
Species (Isotype)	human (IgG2κ)
Ab Type	gp41 cluster II
Research Contact	Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU Med Center, NY, NY
References	Alam *et al.* 2008; Holl *et al.* 2006a; Gorny & Zolla-Pazner 2004; Finnegan *et al.* 2002; Nyambi *et al.* 2000; Gorny & Zolla-Pazner 2000; Hioe *et al.* 1997b; Earl *et al.* 1997; Binley *et al.* 1996; Chen *et al.* 1995; Eddleston *et al.* 1993; Xu *et al.* 1991; Robinson *et al.* 1991; Robinson *et al.* 1990b
Keywords	antibody binding site definition and exposure, antibody interactions, dendritic cells, enhancing activity, kinetics, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 126-6: NIH AIDS Research and Reference Reagent Program: 1243.
- 126-6: 126-6 blocked 2F5 and 13H11 binding to gp41 epitopes to variable degrees. MAb 126-6 showed strong binding to HIV-1-positive infected cells. Alam *et al.* [2008] (**antibody interactions**)
- 126-6: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**, **dendritic cells**)
- 126-6: One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- 126-6: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I MAbs 50-69, F240, 240-D,3D6, and 246-D recognize a nonhelical hydrophobic region, positions 598-604, that forms a disulfide loop in the six-helix bundle. Cluster II MAbs 98-6 and 126-6 recognized residues 644-663 of gp41, a portion of the second heptad repeat. These MAbs were found to behave similarly, so 50-69 and 98-6 were used as representatives. Exposure of cluster I and cluster II epitopes required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor. Binding to CD4 exposed hidden cluster I and II epitopes. The MAbs were found to bind to gp120/gp41 complexes, not to gp41 after shedding of gp120, and were localized to at fusing-cell interfaces. Kinetic and binding results indicate that these MAbs are exposed in transitional structures during the fusion process, possibly the prehairpin intermediate prior to co-receptor binding, although other intermediate structures may be involved. They do not bind once syncytia begin to show extensive cyotplasmic mixing. These MAbs failed to inhibit fusion. The NAb 2F5 has a very different behavior in this study. Finnegan *et al.* [2002] (**antibody binding site definition and exposure**, **kinetics**)
- 126-6: This cluster II MAb binds to a conformational epitope in the region 644-663 – like most cluster II MAbs (126-6, 167-D, 1281, 1342, and 1379 all reacted similarly) it binds to a peptide N51-C43 complex trimer of heterodimers that approximates the core of the fusogenic form of gp41, but not to C43 nor to N51 alone – MAb 126-6 was biotinylated and used as a probe to determine that anti-gp41 MAb 50-69 bound the fusogenic form of the protein in liquid phase. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
- 126-6: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 cluster II anti-gp41 MAbs – of these 2F5, 167-D, 126-6, and 1281 bound across clades, but usually weakly, while 98-6 and 1342 had poor cross reactivity – Clade D isolates bound most consistently to cluster II MAbs. Nyambi *et al.* [2000] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)
- 126-6: Discontinuous epitope recognizing residues between 649-668 – designated cluster II – Fabs D5, D11, G1, T3, M12, M15, S6, S8, S9, S10 block binding. Binley *et al.* [1996] (**antibody binding site definition and exposure**)

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- 126-6: One of several anti-gp41 MAbs that bind to a gp41-maltose binding fusion protein designed to study the leucine zipper domain of gp41, showing that the construct has retained aspects of normal gp41 conformation. Chen *et al.* [1995] (**antibody binding site definition and exposure**)
- 126-6: Called SZ-126.6. Eddleston *et al.* [1993]
- 126-6: No enhancing or neutralizing activity. Robinson *et al.* [1991] (**enhancing activity**)
- 126-6: Specific for a conformational epitope. Xu *et al.* [1991] (**antibody binding site definition and exposure**)
- 126-6: No enhancing activity for HIV-1 IIIB. Robinson *et al.* [1990b] (**enhancing activity**)

No. 1532
MAb ID 1342
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp41 cluster II
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Gorny *et al.* 2000; Gorny & Zolla-Pazner 2000; Nyambi *et al.* 1998
Keywords antibody binding site definition and exposure, review, subtype comparisons

- 1342: One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- 1342: This cluster II MAb is a conformational epitope that binds in the region 644-663 – like most cluster II MAbs (126-6, 167-D, 1281, 1342, and 1379 all reacted similarly) it binds to a peptide N51-C43 complex trimer of heterodimers that approximates the core of the fusogenic form of gp41, but not to C43 nor to N51 alone. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
- 1342: Binds within the region gp41 647-682 – binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, but gp41 MAb 50-69 bound with a 5 fold preference for the oligomer, while other gp41 MAbs (1367, 98-6, 167-D, 1281, 1342, and 1379) did not show a preference. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)
- 1342: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 cluster II anti-gp41 MAbs – of these 2F5, 167-D, 126-6, and 1281 bound across clades, but usually weakly, while 98-6 and 1342 had poor cross reactivity – Clade D isolates bound most consistently to cluster II MAbs – no neutralizing activity was observed when tested with 5 isolates, but 1342 did not bind to these isolates. Nyambi *et al.* [2000] (**subtype comparisons**)
- 1342: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – anti-gp41 Abs 98-6, 1367 and 1342 were not able to bind detectably with any of the viruses from any clade. Nyambi *et al.* [1998] (**subtype comparisons**)

No. 1533
MAb ID 1379
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp41 cluster II
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Gorny & Zolla-Pazner 2004; Gorny *et al.* 2000; Gorny & Zolla-Pazner 2000
Keywords antibody binding site definition and exposure, review

- 1379: One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- 1379: This cluster II MAb binds to a conformational epitope in the region 644-663 – like most cluster II MAbs (126-6, 167-D, 1281, 1342, and 1379 all reacted similarly) it binds to a peptide N51-C43 complex trimer of heterodimers that approximates the core of the fusogenic form of gp41, but not to C43 nor to N51 alone. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
- 1379: Binds within the region gp41 647-682 – binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, but gp41 MAb 50-69 bound with a 5 fold preference for the oligomer, while other gp41 MAbs (1367, 98-6, 167-D, 1281, 1342, and 1379) did not show a preference. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)

No. 1534
MAb ID 2.2B
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing no
Immunogen
Species (Isotype) human
Ab Type gp41 cluster II
Research Contact James Robinson, Tulane University, Tulane, LA
References Moore *et al.* 2006; Robinson *et al.* 2005; Haynes *et al.* 2005a; Binley *et al.* 2003; Schulke *et al.* 2002; Binley *et al.* 1999
Keywords antibody binding site definition and exposure, antibody generation, assay development, HAART, ART, neutralization, vaccine antigen design

- 2.2B: In addition to gp120-gp41 trimers, HIV-1 particles were shown to bear nonfunctional gp120-gp41 monomers and gp120-depleted gp41 stumps on their surface. 2.2B recognizes trimeric and monomeric gp41 stumps. 2.2B did not neutralize wildype virus particles but it was able to capture the virus efficiently. It is hypothesized that the nonfunctional monomers on the HIV-1 surface serve to divert the Ab response, helping the virus to avoid neutralization. Moore *et al.* [2006] (**antibody binding site definition and exposure**, **neutralization**)
- 2.2B: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. Haynes *et al.* [2005a] (**antibody binding site definition and exposure**)
- 2.2B: A reverse capture assay was developed to asses what kind of human MAbs were produced in EBV B-cell transformation assays performed on PBMC sampled at different timepoints from three HIV-1 infected patients on HAART. The reverse capture assay was validated by the solid phase MAbs that could not capture biotin-MAbs of the same or overlapping specificity when reacted with patient virus envelope glycoproteins preincubated with or without sCD4. Detection of gp41 Abs in the assay was based on the fact that they would capture cleaved gp41 and thus be detected by binding to biotin-labeled gp41 Abs recognizing non-competing sites. Reverse capture assay showed that the produced Abs from the patients were detected by biotin-labeled 2.2B in a mixture with 7B2, indicating presence of gp41 Abs. Robinson *et al.* [2005] (**antibody generation**, **assay development**, **HAART, ART**)
- 2.2B: The SOS mutant envelope protein introduces a covalent disulfide bond between gp120 surface and gp41 transmembrane proteins into the R5 isolate JR-FL by adding cysteines at residues 501 and 605. Pseudovirions bearing this protein bind to CD4 and co-receptor bearing cells, but do not fuse until treatment with a reducing agent, and are arrested prior to fusion after CD4 and co-receptor engagement. gp41 Abs 7B2 and 2.2B did not neutralize in any format, WT, SOS, nor when added postbinding. Binley *et al.* [2003] (**vaccine antigen design**)
- 2.2B: Ab binding characteristics of SOS gp140 were tested using SPR and RIPA – SOS gp140 is gp120-gp41 bound by a disulfide bond – NAbs 2G12, 2F5, IgG1b12, CD4 inducible 17b, and 19b bound to SOS gp140 better than uncleaved gp140 (gp140unc) and gp120 – non-neutralizing MAbs 2.2B (binds to gp41 in gp140unc) and 23A (binds gp120) did not bind SOS gp140. Schulke *et al.* [2002] (**vaccine antigen design**)
- 2.2B: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999] (**vaccine antigen design**)

No. 1535
MAb ID Fab D11 (D11)
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster II
References Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody sequence variable domain, review

- Fab D11: Called D11. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab D11: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody sequence variable domain**)

No. 1536
MAb ID Fab D5 (D5)
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster II
References Hrin *et al.* 2008; Eckert *et al.* 2008; Phogat *et al.* 2007; Lin & Nara 2007; Gustchina *et al.* 2007; Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, neutralization, review

- D5: D5 scFv and D5 IgG, along with C-peptide inhibitors of different sizes, were used to determine if the pocket region of the gp41 N-trimer is specifically protected by a steric block. The smaller D5 scFv was 4 times more potent than the larger D5 IgG in inhibiting HIV entry. In contrast, in an in vitro binding assay, 5-10 fold more IgG than scFv bound to target. This disparity indicates that there is a steric block at the

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pocket region. N-trimer was shown to be sterically protected from inhibitors and NAbs approaching from both the cell side and the virus side, and that the N-trimer block is present also on a CD4-activated virus. It is suggested that the source of the steric block is derived from viral factors, such as gp120. Eckert *et al.* [2008] (**antibody binding site definition and exposure**)
- D5: Synergy of 2F5 with MAbs 2G12, D5, and peptide C34 was examined. 2F5 exhibited synergy in inhibition of HIV-1 89.6 with MAb 2G12, D5 and peptide C34. In combination with a matured D5 variant (2-75), the synergistic effect was increased. D5 and 2F5 contributed equally to the observed synergy. It is suggested that 2F5 and D5 have complementary roles, binding to distinct but adjacent Env trimers on the same virion, thereby synergistically preventing formation of fusion pores. Hrin *et al.* [2008] (**antibody interactions**)
- D5: The potency of D5 was 2-3 times lower than the potency of new neutralizing Fab 3674 in neutralization of laboratory and primary strains of HIV-1. Gustchina *et al.* [2007] (**neutralization**)
- D5: D5 structure, binding, neutralization, and strategies that can be used for vaccine antigen design to elicit anti-gp41 Abs, are reviewed in detail. Lin & Nara [2007] (**review**)
- D5: This review provides information on the HIV-1 glycoprotein properties that make it challenging to target with neutralizing Abs. D5 neutralization properties and binding to HIV-1 envelope, and current strategies to develop versions of the Env spike with functional trimer properties for elicitation of broadly neutralizing Abs, are discussed. In addition, approaches to target cellular molecules, such as CD4, CCR5, CXCR4, and MHC molecules, with therapeutic Abs are reviewed. Phogat *et al.* [2007] (**review**)
- Fab D5: Called D5. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab D5: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody sequence variable domain**)

No. 1537
MAb ID Fab G1
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster II
References Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody sequence variable domain, review

- Fab G1: Called G1. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab G1: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody sequence variable domain**)

No. 1538
MAb ID Fab M10
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster II
References Parren *et al.* 1997b; Binley *et al.* 1996

- Fab M10: Does not bind to MN native oligomer, but does bind to both LAI and MN rgp120 and rgp140. Parren *et al.* [1997b]
- Fab M10: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996]

No. 1539
MAb ID Fab M12 (M12)
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster II
References Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody sequence variable domain, review

- M12 database comment: There is a p15 and a gp120 mouse MAb both called M12 and a human gp41 Fab M12.
- Fab M12: Called M12. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab M12: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody sequence variable domain**)

No. 1540
MAb ID Fab M15
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster II

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References Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords review

- Fab M15: Called M15. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab M15: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996]

No. 1541
MAb ID Fab S10 (S10)
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster II
References Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab S10: Called S10. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab S10: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody generation**, **antibody sequence variable domain**)

No. 1542
MAb ID Fab S6 (S6)
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster II
References Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, review

- Fab S6: Called S6. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab S6: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody interactions**, **antibody sequence variable domain**)

No. 1543
MAb ID Fab S8 (S8)
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster II
References Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, review

- Fab S8: Called S8. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab S8: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody generation**, **antibody interactions**, **antibody sequence variable domain**)

No. 1544
MAb ID Fab S9 (S9)
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster II
References Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, review

- Fab S9: Called S9. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab S9: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody generation**, **antibody interactions**, **antibody sequence variable domain**)

No. 1545
MAb ID Fab T3 (T3)
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection

Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster II
References Nelson *et al.* 2008; Crooks *et al.* 2008; Moore *et al.* 2006; Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, binding affinity, neutralization, review

- T3: The study compared Ab neutralization against the JR-FL primary isolate and trimer binding affinities judged by native PAGE. There was direct quantitative relationship between monovalent Fab-trimer binding and neutralization, implying that neutralization begins as each trimer is occupied by one Ab. In BN-PAGE, neutralizing Fabs and sCD4 were able to shift JR-FL trimers, In contrast, most non-neutralizing Fabs, T3 in particular, bound to monomer, but their epitopes were conformationally occluded on trimers, confirming the exclusive relationship of trimer binding and neutralization. Crooks *et al.* [2008] (**neutralization**, **binding affinity**)
- T3: T3 bound to N35ccg-N13 peptide, which is a soluble homotrimer corresponding to the HIV-1 gp41 NHR region, and to recombinant r-gp41 (HXB2), indicating that the T3 epitope is present on the N35ccg-N13 peptide. T3 did not neutralize HXB2. As other human-derived Abs in this study, T3 has a long CDR H3 (19 residues), and it was shown to bind to Envs used in typical epitope binding assays, unlike the neutralizing Abs in this study. While T3 had no observable reactivity with a peptide corresponding to the C-heptad repeat of gp41 (C34), low nanomolar concentrations of C34 were sufficient to induce recognition of IZN36 (another mimetic peptide) by T3. The neutralizing Abs in this study were, however, able to recognize IZN36 without C34. T3 was able to inhibit mAb D5 binding to immobilized 5-Helix, but it did not have any effect on the neutralization potency of D5 against HXB2, indicating that T3 cannot bind to the fusogenic NHR trimers. Nelson *et al.* [2008] (**neutralization**, **binding affinity**, **antibody sequence variable domain**)
- T3: In addition to gp120-gp41 trimers, HIV-1 particles were shown to bear nonfunctional gp120-gp41 monomers and gp120-depleted gp41 stumps on their surface. T3 did not bind to trimers nor monomers but it did recognize gp41 stumps from which gp120 had dissociated. T3 was able to capture wildtype virus particles. The capture occurs with moderate efficiency, probably through gp41 stumps on viral surface. It is hypothesized that the nonfunctional monomers on the HIV-1 surface serve to divert the Ab response, helping the virus to avoid neutralization. Moore *et al.* [2006] (**antibody binding site definition and exposure**)
- Fab T3: Called T3. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab T3: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody generation**, **antibody sequence variable domain**)

No. 1546

MAb ID Md-1 (MD-1, Md1)
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing no
Immunogen
Species (Isotype) human (IgG1λ)
Ab Type gp41 cluster II
Research Contact R. A. Myers State of Maryland Dept. of Health
References Vincent *et al.* 2008; Kalia *et al.* 2005; Gorny & Zolla-Pazner 2004; Binley *et al.* 1996; Chen *et al.* 1995; Myers *et al.* 1993
Keywords antibody binding site definition and exposure, binding affinity, review

- Md-1: NIH AIDS Research and Reference Reagent Program: 1223.
- Md1: Md1 reacted with maltose-binding proteins MBP30 and MBP32, containing both HR1 and HR2 domains of gp41, but did not react with MBP37 and MBP44, containing only the HR2 domain, nor with MBP-HR1, containing only the HR1 domain. In addition, Md1 bound to MBP44/N36 and MBP-HR1/C34 complexes reaching a plateau at a concentration of $\sim$ 1 µg/ml. In ELISA, Md1 reacted with the complex formed between MBP-HR1 and H44 (His-targeted protein) and C34, but failed to recognize the mixture of MBP-HR1 and T20, MBP3 and C34, and MBP3 and H44. In addition, Md1 recognized the peptide complex N36/C34 but not the peptides individually. Vincent *et al.* [2008] (**antibody binding site definition and exposure**)
- Md-1: Point mutations in the highly conserved structural motif LLP-2 within the intracytoplasmic tail of gp41 resulted in conformational alternations of both gp41 and gp120. The alternations did not affect virus CD4 binding, coreceptor binding site exposure, or infectivity of the virus, but did result in decreased binding and neutralization by certain MAbs and human sera. Md-1 bound with similar levels to both the LLP-2 mutant and wildtype viruses, indicating that the ologomeric potential of the LLP-2 mutanat Env was not altered. Kalia *et al.* [2005] (**antibody binding site definition and exposure**, **binding affinity**)
- Md-1: One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Md-1: Discontinuous epitope recognizing residues between 563-672, does not recognize cluster I disulfide bridge region – reacts almost exclusively with trimers and tetramers on WB – designated cluster II – Fabs D5, D11, G1, T3, M12, M15, S6, S8, S9, S10 block binding. Binley *et al.* [1996] (**antibody binding site definition and exposure**)
- Md-1: Called MD-1 – one of several anti-gp41 MAbs that bind to a gp41-maltose binding fusion protein designed to study the leucine zipper domain of gp41, showing that the construct has retained aspects of normal gp41 conformation. Chen *et al.* [1995] (**antibody binding site definition and exposure**)

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- Md-1: Called MD-1 – discontinuous epitope that binds in the N-terminal region – reacts exclusively with oligomer. Myers *et al.* [1993] (**antibody binding site definition and exposure**)

No. 1547
MAb ID Fab A9 (A9)
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster III
References Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab A9: Called A9. One of six Fabs in this database that bind to the gp41 cluster III region (a conformational epitope involving aa 619-648); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab A9: Binds to cluster III region – competes with MAb Md-1, but not MAbs 126-6 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody generation**, **antibody sequence variable domain**)

No. 1548
MAb ID Fab G15 (G15)
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster III
References Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab G15: Called G15. One of six Fabs in this database that bind to the gp41 cluster III region (a conformational epitope involving aa 619-648); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab G15: Binds to cluster III region – competes with MAb Md-1, but not MAbs 126-6 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody generation**, **antibody sequence variable domain**)

No. 1549
MAb ID Fab G5
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster III
References Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab G5: Called G5. One of six Fabs in this database that bind to the gp41 cluster III region (a conformational epitope involving aa 619-648); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab G5: Binds to cluster III region – competes with MAb Md-1, but not MAbs 126-6 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody generation**, **antibody sequence variable domain**)

No. 1550
MAb ID Fab L1 (L1)
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster III
References Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab L1: Called L1. One of six Fabs in this database that bind to the gp41 cluster III region (a conformational epitope involving aa 619-648); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab L1: Binds to cluster III region – competes with MAb Md-1, but not MAbs 126-6 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody generation**, **antibody sequence variable domain**)

No. 1551
MAb ID Fab L11 (L11)
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster III
References Gorny & Zolla-Pazner 2004; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab L11: Called L11. One of six Fabs in this database that bind to the gp41 cluster III region (a conformational epitope involving aa 619-648); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab L11: Binds to cluster III region – competes with MAb Md-1, but not MAbs 126-6 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody generation**, **antibody sequence variable domain**)

No. 1552
MAb ID Fab L2 (L2)
HXB2 Location Env
Author Location gp41 (LAI)
Epitope
Subtype B
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgG1κ)
Ab Type gp41 cluster III
Research Contact P. Perrin and D. Burton (Scripps Research Institute, La Jolla, California
References Gorny & Zolla-Pazner 2004; Earl *et al.* 1997; Binley *et al.* 1996
Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab L2: Called L2. One of six Fabs in this database that bind to the gp41 cluster III region (a conformational epitope involving aa 619-648); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab L2: Binds to cluster III region – competes with MAb Md-1, but not MAbs 126-6 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure**, **antibody generation**, **antibody sequence variable domain**)

No. 1553
MAb ID 1281 (1281-D)
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG1λ)
Ab Type gp41 cluster II, gp41six-helix bundle
Research Contact Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)
References Gorny & Zolla-Pazner 2004; Follis *et al.* 2002; Golding *et al.* 2002b; Verrier *et al.* 2001; Gorny *et al.* 2000; Gorny & Zolla-Pazner 2000; Hioe *et al.* 1997b
Keywords antibody binding site definition and exposure, antibody interactions, review, variant cross-recognition or cross-neutralization

- 1281: One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- 1281: Alanine mutations were introduced into the N- and C-terminal α-helices of gp41 to destabilize interhelical packing interactions in order to study their inhibitory effect on viral infectivity. These mutations were shown to inhibit viral replication though affecting the conformational transition to the fusion-active form of gp41, and allow increased inhibition by gp41 peptides. 2F5 senstivity is increased in the mutated viruses, presumably because 2F5s neutralization activity is focused on the transition to the fusion active state. No other gp41 MAb against tested, including NC-1, 50-69D, 1281, 98-6D, 246-D and F240, neutralized the parental or the fusion-deficient mutated viruses. Follis *et al.* [2002] (**antibody binding site definition and exposure**)
- 1281: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – 98-6 binds to a C-HR hairpin epitope and blocks fusion when added to a 2 hour E/T preincubation at 31.5 C, but if added after 1 hour, doesn't inhibit – this is in contrast to six-helix bundle Abs 167-D and 1281 that inhibit more efficiently when added after one hour of incubation. Golding *et al.* [2002b] (**antibody binding site definition and exposure**)
- 1281: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001] (**antibody interactions**)
- 1281: This cluster II MAb binds to a conformational epitope in the region 644-663 – like most cluster II MAbs (126-6, 167-D, 1281, 1342, and 1379 all reacted similarly) it binds to a peptide N51-C43 complex trimer of heterodimers that approximates the core of the fusogenic form of gp41, but not to C43 nor to N51 alone. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
- 1281: Binds within the region gp41 647-682 – binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, but gp41 MAb 50-69 bound with a 5 fold preference for the oligomer, while other gp41 MAbs (1367, 98-6, 167-D, 1281, 1342, and 1379) did not show a preference. Gorny *et al.* [2000] (**antibody binding site definition and exposure**, **variant cross-recognition or cross-neutralization**)
- 1281: Called 1281-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D)and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal

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sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)

No. 1554
MAb ID Chessie 8
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing
Immunogen
Species (Isotype) mouse (IgG)
Ab Type gp41 cytoplasmic domain
Research Contact G. Lewis
References Usami *et al.* 2005; Smith-Franklin *et al.* 2002; Rovinski *et al.* 1995; Poumbourios *et al.* 1995; Lewis *et al.* 1991
Keywords antibody binding site definition and exposure

- Chessie 8: Chessie 8 was found to bind to both monomeric and oligomeric gp41. Usami *et al.* [2005] (**antibody binding site definition and exposure**)
- Chessie 8: This Ab was used in an *in vitro* study demonstrating that HIV-1 antibody and Fcgamma receptors can trap virus on the surface of follicular dendritic cells (FDC)'s and extend the period of infectivity – blocking the FDC-Fcgamma receptor killing the FDC cell reduced their ability to maintain infectivity, and FDC cells seemed to stabilize viral particles and decrease gp120 shedding. Smith-Franklin *et al.* [2002]
- Chessie 8: Used to precipitate gp160 in immunoblots in a study examining the feasibility of using unprocessed gp160 glycoprotein as an immunogen. Rovinski *et al.* [1995]

No. 1555
MAb ID 8F102
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120
Species (Isotype) mouse (IgG)
Ab Type gp120-CD4 complex
References DeVico *et al.* 1995

- 8F102: MAbs specifically reactive to crosslinked gp120 and CD4 were derived (8F101, 8F102) – conformation dependent – competition studies indicate the epitope is immunogenic in infected humans. DeVico *et al.* [1995]

No. 1556
MAb ID CG-10 (CG10)
HXB2 Location Env
Author Location gp120 (IIIB)
Epitope
Subtype B
Neutralizing L
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *Strain:* B clade IIIB *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120-CD4 complex
Research Contact Jonathan Gershoni, Tel Aviv University, Isreal
References Srivastava *et al.* 2005; Enshell-Seijffers *et al.* 2003; Finnegan *et al.* 2001; Oscherwitz *et al.* 1999a; Sullivan *et al.* 1998b; Rizzuto *et al.* 1998; Lee *et al.* 1997; Wu *et al.* 1996; Gershoni *et al.* 1993
Keywords antibody binding site definition and exposure, computational epitope prediction, neutralization, review, structure, vaccine antigen design

- CG10: This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **review**)
- CG10: Using 17b MAb to select peptides from a combinatorial library, and analyzing the peptides using a novel discontinuous epitope reconstruction program, enabled epitope prediction. Segments of gp120 were reconstructed as an antigenic protein mimetic recognized by 17b. Comparisons then were made with a similar prediction of contact residues for CG10, a CD4i MAb that competes with 17b, but has a distinct binding site. Enshell-Seijffers *et al.* [2003] (**antibody binding site definition and exposure**, **computational epitope prediction**, **structure**)
- CG-10: Called CG10. Using a cell-fusion system, it was found CD4i antibodies 17b, 48d, and CG10 reacted faintly with Env expressing HeLA cells even in the absence of sCD4 or CD4 expressing target cells. Reactivity increased after sCD4 addition, but not after CD4 expressing target cell addition, and binding was not increased at the cell-to-cell CD4-Env interface. This suggests the CD4i co-receptor binding domain is largely blocked at the cell-fusion interface, and so CD4i antibodies would not be able access this site and neutralize cell-mediated viral entry. Finnegan *et al.* [2001] (**antibody binding site definition and exposure**)
- CG-10: Called CG10 – disrupts gp120-CCR5 interaction and competes with MAb 17b –binds near the conserved bridging sheet of gp120 – mutations in positions K/D 121, T/D 123, K/D 207, K/D 421, Q/L 422, Y/S 435, M/A 434, K/A 432 and I/S 423 result in a 70% reduction in CG10 binding. Rizzuto *et al.* [1998]
- CG-10: Called CG10 – CD4BS MAb 15e competes with CG-10 binding, probably due to the disruption of CD4-gp120 by 15e – CD4i MAbs 17b and 48d compete and the binding sites may overlap – MAb A32 enhances binding of 17b, 48d and CG10 – MAbs C11, 2G12 and 212A do not affect CG10 binding – CG-10 can bind gp120 with V1/V2 and V3 deleted – HXBc2 mutations Delta 119-205, 314 G/W, 432 K/A, 183,184

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PI/SG decrease CG-10 recognition, HXBc2 mutations Delta 298-327 (V3), 384 Y/E, 298 R/G, 435 Y/S enhance recognition – the CD4 contribution to the CG10 epitope maps to the CD4 CDR2-like loop – CG10 can neutralize HIV-1 in the presence of sCD4 even though it does not do so in the context of cell surface CD4 binding to gp120. Sullivan *et al.* [1998b]
- CG-10: Called CG10 – Promotes envelope mediated cell fusion between CD4+ cells and cells infected with either T-cell and macrophage tropic viruses – infection of HeLa CD4+ (MAGI) cells by HIV-1 LAI, ELI1, and ELI2 strains was increased two-to four-fold in the presence of CG10. Lee *et al.* [1997]
- CG-10: Called CG10 – MIP-1alpha binding to CCR-5 expressing cells can be inhibited by gp120-sCD4, and MAb CG10 does not block this inhibition. Wu *et al.* [1996]
- CG-10: Reacts exclusively with sCD4-gp120 complex, not with sCD4 or gp120 alone. Gershoni *et al.* [1993]

No. 1557
MAb ID CG-25
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120-CD4 complex
References Gershoni *et al.* 1993
- CG-25: Reacts preferentially with sCD4-gp120, also with sCD4, not with gp120. Gershoni *et al.* [1993]

No. 1558
MAb ID CG-4 (CG4)
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120-CD4 complex
Research Contact Jonathan Gershoni, Tel Aviv University, Isreal
References Gershoni *et al.* 1993
- CG-4: Reacts with gp120 and sCD4-gp120 complex, not with sCD4. Gershoni *et al.* [1993]

No. 1559
MAb ID CG-76
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120-CD4 complex
References Gershoni *et al.* 1993
- CG-76: Reacts equally well with sCD4-gp120 and sCD4, but not with purified gp120. Gershoni *et al.* [1993]

No. 1560
MAb ID CG-9
HXB2 Location Env
Author Location gp120
Epitope
Neutralizing L
Immunogen vaccine
Vector/Type: sCD4-gp120 complex *HIV component:* gp120
Species (Isotype) mouse (IgG1)
Ab Type gp120-CD4 complex
References Gershoni *et al.* 1993
- CG-9: Reacts preferentially with sCD4-gp120, also with sCD4, not with gp120. Gershoni *et al.* [1993]

No. 1561
MAb ID 105-518
HXB2 Location Env
Author Location gp41 (608–637 HAM112, O group)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* O group HAM112 *HIV component:* gp160
Species (Isotype) mouse (IgG1κ)
Ab Type immunodominant region
References Scheffel *et al.* 1999
- 101-518: Overlapping peptides based on group O HAM112 Env were tested for MAb reactivity. Scheffel *et al.* [1999]

No. 1562
MAb ID 31A1
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing no
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgMκ/λ)
Ab Type p24+gp41
References Pollock *et al.* 1989
- 31A1: Denatured virus was used for *in vitro* stimulation to generate Abs – Reacts with both p24 and gp41. Pollock *et al.* [1989]

No. 1563
MAb ID 39A64
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing no
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgMκ/λ)
Ab Type p24+gp41
References Pollock *et al.* 1989

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- 39A64: Denatured virus was used for *in vitro* stimulation to generate Abs – Reacts with both p24 and gp41. Pollock *et al.* [1989]

No. 1564
MAb ID 39B86
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing no
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgMκ/λ)
Ab Type p24+gp41
References Pollock *et al.* 1989

- 39B86: Denatured virus was used for *in vitro* stimulation to generate Abs – Reacts with both p24 and gp41. Pollock *et al.* [1989]

No. 1565
MAb ID 9303
HXB2 Location Env
Author Location gp41
Epitope
Neutralizing no
Immunogen
Species (Isotype) mouse
Ab Type p24+gp41
Research Contact Du Pont
References McDougal *et al.* 1996

No. 1566
MAb ID NC-1
HXB2 Location Env
Author Location gp41 (IIIB)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide *Strain:* B clade IIIB *HIV component:* gp41
Species (Isotype) mouse (IgG2a)
Ab Type gp41 NHR (N-heptad repeat), gp41six-helix bundle, gp41 five-helix bundle (one CHR peptide of six helix bundle is missing)
Research Contact S. Jiang, New York Blood Center, NY, NY
References Zhang *et al.* 2008; Nelson *et al.* 2008; Gustchina *et al.* 2008; Ye *et al.* 2006; Kim *et al.* 2007; de Rosny *et al.* 2004a; de Rosny *et al.* 2004b; Follis *et al.* 2002; Yang *et al.* 2002; Yang *et al.* 2000; Jiang *et al.* 1998
Keywords antibody binding site definition and exposure, antibody generation, antibody interactions, binding affinity, kinetics, neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- NC-1: NC-1 failed to inhibit HXB2 and SF162 infectivity in the Env-pseudotyped virus neutralization assay, and did not enhance the inhibitory activity of N36Mut(e,g) peptide, which is a class 3 inhibitor that disrupts trimerization of the N-heptad repeat (N-HR) in the prehairpin intermediate by sequestering the N-HR into N-HR/N36Mut(e,g) heterodimers. Gustchina *et al.* [2008] (**neutralization**, **kinetics**)
- NC-1: NC-1 bound to N35ccg-N13 peptide, which is a soluble homotrimer corresponding to the HIV-1 gp41 NHR region, and to recombinant r-gp41 (HXB2), indicating that the NC-1 epitope is present on the N35ccg-N13 peptide. NC1 recognized gp140HXB2(-), in which the cleavage site has been knocked out, but it did not recognize cleavage competent gp160 HXB2 (+) that had been detergent-liberated from infectious virions. While NC-1 had no observable reactivity with a peptide corresponding to the C-heptad repeat of gp41 (C34), low nanomolar concentrations of C34 were sufficient to induce recognition of IZN36 (another mimetic peptide) by NC-1. The neutralizing Abs in this study were, however, able to recognize IZN36 without C34. Nelson *et al.* [2008]
- NC-1: NC-1 did not compete with the newly defined neutralizing mAb m44 for binding to gp41. NC-1 bound strongly to 5HB, 6HB and recombinant gp140. NC-1 bound to 5HB and 6HB in a way similar to mAb T3. Zhang *et al.* [2008] (**binding affinity**)
- NC-1: This Ab was used to verify that the constructed HA/gp41 chimeric protein expressed on cell surfaces did not form post-fusion six-helix bundle structure since this Ab is specific for HIV gp41 in this conformation. No interaction between the HA/gp41 and NC-1 was observed indicating that the chimeric protein did not assume the post-fusion conformation, which is thought to be ineffective in eliciting neutralizing Abs. Ye *et al.* [2006] (**antibody binding site definition and exposure**, **binding affinity**)
- NC-1: The MAb 2F5 binds to the C-heptad and is neutralizing, but the MAb D50 binds to the C-heptad and is not neutralizing. 2F5 binds preferentially to native gp41 prior to receptor activation. Trapped fusion-intermediates suggest 2F5 remains present shortly after gp120 triggering by CD4, but may be lost by the time the six-helix bundle is formed. 2F5 neutralization seems to block a later step of the fusion process, but it does not inhibit binding of NC-1, a MAb specific for the six-helix bundle, so it does not prevent formation of the six-helix bundle. The results are most consistent with 2F5 inhibiting a post-fusion-intermediate step. de Rosny *et al.* [2004b] (**antibody binding site definition and exposure**, **antibody interactions**)
- NC-1: The mechanism of 2F5 neutralization was explored, and experiments suggest it is due to interference with a late step in viral entry. 2F5 does not block six-helix bundle formation, as 2F5 prebinding does not inhibit NC-1 binding, a MAb that binds specifically to the six-helix bundle. de Rosny *et al.* [2004a] (**antibody binding site definition and exposure**)
- NC-1: Alanine mutations were introduced into the N- and C-terminal alpha-helices of gp41 to destabilize interhelical packing interactions in order to study their inhibitory effect on viral infectivity. These mutations were shown to inhibit viral replication though affecting the conformational transition to the fusion-active form of gp41, and allow increased inhibition by gp41 peptides. 2F5 senstivity is increased in the mutated viruses, presumably because 2F5s neutralization activity is focused on the transition to the fusion active state. No other gp41 MAb against tested, including NC-1, 50-69D, 1281, 98-6D, 246-D and F240, neutralized the parental or the fusion-

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deficient mutated viruses. Follis *et al.* [2002] (**antibody binding site definition and exposure**)

- NC-1: Uncleaved soluble gp140 can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif (gp140delta683(-/GCN4)) or using a T4 trimeric motif derived from T4 bacteriophage fibritin (gp140delta683(-/FT)) – NC-1 binds to 15% of the GCN4 motif trimers, but this was significantly reduced for the T4 fibritin stabilized structures, indicating little is in the six-helix bundle, fusogenic conformation. Yang *et al.* [2002] (**antibody binding site definition and exposure**)
- NC-1: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) – approximately 16% of the gp140(-GNC4) stabilized trimer recognized by pooled sera was precipitated by NC-1, indicating that at a fraction assumes a fusogenic gp41 six-helix bundle conformation – gp140(-) monomers were not able to bind to the NC-1, nor was gp130(-/GCN4) glycoprotein, consistent with the expectation that the absence of C34 helices would preclude formation of the six-helix bundle. Yang *et al.* [2000] (**antibody binding site definition and exposure**)
- NC-1: Ab elicited in response to immunization with N36(L6)C34, a peptide that folds into a six helix bundle like gp41 – NC-1 binds to the surface of HIV-1 infected cells only in the presence of sCD4, recognizing the fusogenic core structure – binding affinity was decreased by point mutations that disrupt core formation and abolish membrane fusion activity, (I573P and I573A) – NC-1 can recognize discontinuous epitopes from B clade isolate SC, but not E clade strain N243, O group strain GAB, or HIV-2 ROD. Jiang *et al.* [1998] (**antibody binding site definition and exposure**, **antibody generation**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

IV-C-18 Nef Antibodies

No. 1567
MAb ID 4H4
HXB2 Location Nef (1–33)
Author Location Nef (1–33 IIIB)
Epitope MGGKWSKSSVVGWPTVRERMRRAPTVRERMRR-AEPAADGVGAA
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade IIIB *HIV component:* Nef
Species (Isotype) human (IgG1)
References Otake *et al.* 1994

- 4H4: This MAb, elicited by vaccination with a Nef fusion protein, could not detect Nef protein on the cell surface – C-term anti-Nef Abs could. Otake *et al.* [1994]

No. 1568
MAb ID polyclonal
HXB2 Location Nef (9–24)
Author Location Nef (9–24)
Epitope SVIGWLTVRERMRRAE
Neutralizing no
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade BRU *HIV component:* Nef
Species (Isotype) mouse (IgG)
References Tahtinen *et al.* 2001

- BALB/c mice were immunized with a pBN-vector expressing HIV-1 nef, rev, or tat genes – DNA loaded onto gold microparticles was delivered using a gene gun, and DNA dissolved in saline was given intradermally or intramuscularly – Nef gene gun immunized mice showed the strongest and most long-lasting (6 months) Ab, CTL and proliferative responses – the highest IgG1/IgG2a ratio was observed in the gene gun immunized mice – three Ab binding sites were found in Nef using peptide mapping, although some sera reacted only to complete Nef – Rev- or-Tat immunized mice did not generate an Ab response. Tahtinen *et al.* [2001]

No. 1569
MAb ID 13/042
HXB2 Location Nef (11–20)
Author Location Nef (11–24 BH10)
Epitope VGWPTVRERM
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Nef
Species (Isotype) mouse
References Kanduc *et al.* 2008; Schneider *et al.* 1991

- 13/042: Similarity level of the 13/042 binding site pentapeptide VGWPT to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- 13/042: Epitope mapped by overlapping decapeptides – core: TVRERM. Schneider *et al.* [1991]

No. 1570
MAb ID 13/035
HXB2 Location Nef (15–24)
Author Location Nef (11–24 BH10)
Epitope TVRERMRRAE
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Nef
Species (Isotype) mouse
References Schneider *et al.* 1991

- 13/035: Epitope mapped by overlapping decapeptides – core: TVRERM. Schneider *et al.* [1991]

No. 1571
MAb ID A6
HXB2 Location Nef (18–26)
Author Location Nef (18–26 NL-432)
Epitope ERMRRAEPA?
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43 *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)

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Species (Isotype) mouse (IgM)
References Otake *et al.* 1997
Keywords antibody binding site definition and exposure, antibody generation

- A6: BALB/c mice were immunized with Nef protein to create a series of anti-Nef antibodies. A6 bound to the peptide spanning amino acids 18-26; we inferred the amino acids from the positions in the NL-43 strain. A6 also bound to the complete Nef protein. Otake *et al.* [1997] (**antibody binding site definition and exposure**, **antibody generation**)

No. 1572
MAb ID AM5C6
HXB2 Location Nef (28–43)
Author Location Nef (28–43 BH10)
Epitope `DGVGAASRDLEKHGAI+KAAVDLSHFLK`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Nef
Species (Isotype) mouse
References Maksiutov *et al.* 2002; Schneider *et al.* 1991

- AM5C6: This epitope is similar to a fragment of the human protein vascular endothelial growth factor C, AEPDAGEATAYASKDLE. Maksiutov *et al.* [2002]
- AM5C6: Epitope mapped by overlapping decapeptides – core: SRDL – also reacts with Nef(78-92). Schneider *et al.* [1991]

No. 1573
MAb ID AM5C6
HXB2 Location Nef (28–43)
Author Location Nef (28–43 BH10)
Epitope `DGVGAASRDLEKHGAI+KAAVDLSHFLK`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Nef
Species (Isotype) mouse
References Maksiutov *et al.* 2002; Schneider *et al.* 1991

- AM5C6: This epitope is similar to a fragment of the human protein vascular endothelial growth factor C, AEPDAGEATAYASKDLE. Maksiutov *et al.* [2002]
- AM5C6: Epitope mapped by overlapping decapeptides – core: KAAVDL – also reacts with Nef(28-43). Schneider *et al.* [1991]

No. 1574
MAb ID A7
HXB2 Location Nef (28–45)
Author Location Nef (28–45 NL-432)
Epitope `DGVGAVSRDLEKHGAITS?`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43 *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse (IgG1)
References Otake *et al.* 1997
Keywords antibody binding site definition and exposure, antibody generation

- A7: BALB/c mice were immunized with Nef protein to create a series of anti-Nef antibodies. A7 bound to the peptide spanning amino acids 28-45; we inferred the amino acids from the positions in the NL-43 strain. A7 did not bind to the complete Nef protein. Otake *et al.* [1997] (**antibody binding site definition and exposure**, **antibody generation**)

No. 1575
MAb ID 25/03
HXB2 Location Nef (30–43)
Author Location Nef (30–43 BH10)
Epitope `VGAASRDLEKHGAI`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Nef
Species (Isotype) mouse
References Maksiutov *et al.* 2002; Schneider *et al.* 1991

- 25/03: This epitope is similar to a fragment of the human protein vascular endothelial growth factor C, AEPDAGEATAYASKDLE. Maksiutov *et al.* [2002]
- 25/03: Epitope mapped by overlapping decapeptides – core: ASRDLEK. Schneider *et al.* [1991]

No. 1576
MAb ID 26/76
HXB2 Location Nef (30–43)
Author Location Nef (30–43 BH10)
Epitope `VGAASRDLEKHGAI`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Nef
Species (Isotype) mouse
References Maksiutov *et al.* 2002; Schneider *et al.* 1991

- 26/76: This epitope is similar to a fragment of the human protein vascular endothelial growth factor C, AEPDAGEATAYASKDLE. Maksiutov *et al.* [2002]
- 26/76: Epitope mapped by overlapping decapeptides – core: SRDLEK. Schneider *et al.* [1991]

No. 1577
MAb ID 3F2
HXB2 Location Nef (31–40)
Author Location Nef (31–40 BRU)
Epitope `GAASRDLEKH`
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU *HIV component:* Nef
Species (Isotype) mouse (IgG1)
References Maksiutov *et al.* 2002; Ranki *et al.* 1995; Saito *et al.* 1994; Ovod *et al.* 1992

- 3F2: UK Medical Research Council AIDS reagent: EVA3067.1.
- 3F2: This epitope is similar to a fragment of the human protein vascular endothelial growth factor C, AEPDAGEATAYASKDLE. Maksiutov *et al.* [2002]
- 3F2: Faintly cross-reactive with astrocytes of uninfected control samples. Ranki *et al.* [1995]
- 3F2: Reacted with Nef from different HIV-1 strains (BRU, IIIB, RF, MN). Ovod *et al.* [1992]

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No. 1578
MAb ID 3D12
HXB2 Location Nef (31–50)
Author Location Nef (31–50 BRU)
Epitope GAASRDLEKHGAITSSNTAA
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU *HIV component:* Nef
Species (Isotype) mouse (IgG1)
References Maksiutov *et al.* 2002; Ranki *et al.* 1995; Saito *et al.* 1994; Ovod *et al.* 1992

- 3D12 database comment: There is an anti-RT MAb that also has this name.
- 3D12: UK Medical Research Council AIDS reagent: EVA3067.2.
- 3D12: This epitope is similar to a fragment of the human protein vascular endothelial growth factor C, AEPDAGEATAYASKDLE. Maksiutov *et al.* [2002]
- 3D12: One of four antibodies used in combination to show HIV Nef protein expressed in astrocytes from 7/14 brain samples from HIV+ individuals – Nef expression associated with dementia. Ranki *et al.* [1995]
- 3D12: Over-expression of Nef in astrocytes from postmortem pediatric CNS tissues. Saito *et al.* [1994]
- 3D12: Reacted with Nef from different HIV-1 strains (BRU, IIIB, RF, MN). Ovod *et al.* [1992]

No. 1579
MAb ID polyclonal
HXB2 Location Nef (33–65)
Author Location Nef (32–64 LAI, BRU)
Epitope ASRDLEKHGAITSSNTAATNAACAWLEAQEEEE
Subtype B
Neutralizing
Immunogen HIV-1 infection, vaccine
Vector/Type: protein, PLG microparticle *Strain:* B clade BRU, B clade LAI *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA), PLG
Species (Isotype) mouse (IgG1)
References Maksiutov *et al.* 2002; Moureau *et al.* 2002

- This epitope is similar to a fragment of the human protein vascular endothelial growth factor C, AEPDAGEATAYASKDLE. Maksiutov *et al.* [2002]
- Nef encapsulated in poly(DL-lactide-co-glycolide) (PLG) had a more prolonged Ab response than Nef in PBS or in Freund's adjuvant (CFA), still strong after 7 months – the response was predominantly IgG1, a Th2 immune response – three linear epitopes, Nef 32-64, 118-167, and 185-205, were frequently recognized by the sera of mice immunized with NefPLG or Nef-CFA, but not after immunization with Nef in PBS, which seemed to preferentially stimulate an Ab response to conformational epitopes. Moureau *et al.* [2002]

No. 1580
MAb ID polyclonal
HXB2 Location Nef (49–64)
Author Location Nef (49–64)
Epitope AATNAACAWLEAQEEE
Neutralizing no
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade BRU *HIV component:* Nef
Species (Isotype) mouse (IgG)
References Tahtinen *et al.* 2001

- BALB/c mice were immunized with a pBN-vector expressing HIV-1 nef, rev, or tat genes – DNA loaded onto gold microparticles was delivered using a gene gun, and DNA dissolved in saline was given intradermally or intramuscularly – Nef gene gun immunized mice showed the strongest and most long-lasting (6 months) Ab, CTL and proliferative responses – the highest IgG1/IgG2a ratio was observed in the gene gun immunized mice – three Ab binding sites were found in Nef using peptide mapping, although some sera reacted only to complete Nef – Rev- or-Tat immunized mice did not generate an Ab response. Tahtinen *et al.* [2001]

No. 1581
MAb ID 3G12
HXB2 Location Nef (51–71)
Author Location Nef (51–71 BRU)
Epitope TNAACAWLEAQEEEEVGFPVT
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU *HIV component:* Nef
Species (Isotype) mouse (IgG2a)
References Ovod *et al.* 1992

- 3G12: Reacted with Nef from different HIV-1 strains (BRU, IIIB, RF, MN). Ovod *et al.* [1992]

No. 1582
MAb ID 13/058
HXB2 Location Nef (60–73)
Author Location Nef (60–73 BH10)
Epitope AQEEEEVGFPVTPQ
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Nef
Species (Isotype) mouse
References Schneider *et al.* 1991

- 13/058: Epitope mapped by overlapping decapeptides – core: EEVGFP. Schneider *et al.* [1991]

No. 1583
MAb ID 26/028
HXB2 Location Nef (60–73)
Author Location Nef (60–73 BH10)
Epitope AQEEEEVGFPVTPQ
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Nef
Species (Isotype) mouse
References Schneider *et al.* 1991

- 26/028: Epitope mapped by overlapping decapeptides – core: EEVGFPV. Schneider *et al.* [1991]

No. 1584
MAb ID polyclonal

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HXB2 Location Nef (61–71)
Author Location Nef
Epitope QEEEEVGFPVT
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* Env, Gag, Nef, Pol
Species (Isotype) rabbit
References Li *et al.* 2005b
Keywords mimics

- In early HIV-1 infection, patients develop autoimmune thrombocytopenia, with Ab directed against beta3 integrin, GPIIIa49-66. Panning with a 7-mer phage display library using rabbit anti-GPIIIa49-66 (CAPESIEFPVSEARVLED), the immunodominant epitope of the identified potential molecular mimicry epitopes with HIV-1 Env (sklFDeGLFn, elfnkTIIFP), Pol (geAPEFPskq), Gag (gktHyMINPl) and Nef (qeeeeVgFPVt, qeeeeVgFPVt, edeGigFPVr, fkLVPVSEae, ssnTPTTNaa) proteins. Pools of these peptides elicted Ab in rabbits that induce platelet oxidation in vitro and thrombocytopenia in vivo upon passive transfer. Nef (qeeeeVgFPVt), Gag (gktHyMINPl), and Nef (fkLVPVSEae) all overlap with known HIV-1 epitopes. Li *et al.* [2005b] (**mimics**)

No. 1585
MAb ID 2E3
HXB2 Location Nef (61–80)
Author Location Nef (61–80 BRU)
Epitope QEEEEVGFPVTPQVPLRPMT
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU *HIV component:* Nef
Species (Isotype) mouse (IgG1)
References Nilsen *et al.* 1996; Ovod *et al.* 1992

- 2E3: There are two MAbs with the name 2E3 – the other one binds to integrase. Nilsen *et al.* [1996]
- 2E3: Two isomorphic forms of Nef were identified, 2E3 reacted with the p24 but not p27 form, and was strain specific (MN and BRU reactive, not IIIB or RF). Ovod *et al.* [1992]

No. 1586
MAb ID polyclonal
HXB2 Location Nef (66–97)
Author Location Nef (66–97 LAI)
Epitope VGFPVTPQVPLRPMTYKAAVDLSHFLKEKGGL
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Nef *Adjuvant:* QS21
Species (Isotype) human (IgG)
References Pialoux *et al.* 2001

- 28 subjects were vaccinated with six HIV-1 peptides that were selected to be particularly rich in CTL epitopes, presented in lipopeptides with or without adjuvant QS21 – HIV-specific Ab responses were detected in 10/28, proliferative in 11/14, and CTL in 13/24 (54%) of testable volunteers – 10/28 had Ab responses to this peptide (N1), 11/24 had proliferative responses, and CTL responses were detected. Pialoux *et al.* [2001]

No. 1587
MAb ID F14.11
HXB2 Location Nef (83–88)
Author Location Nef (83–88)
Epitope AAVDLS
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* Nef
Species (Isotype) mouse (IgG2aκ)
References Chang *et al.* 1998; De Santis *et al.* 1991

- F14.11: Used as a control in a study of Nef-specific single chain Abs constructed from AG11 and EH1. Chang *et al.* [1998]
- F14.11: The MAb was made to a six aa region of Nef that is similar to a region found in thymosin alpha 1 protein – the MAb binds to the natural Nef protein. De Santis *et al.* [1991]

No. 1588
MAb ID 31/03
HXB2 Location Nef (83–103)
Author Location Nef (82–103 BH10)
Epitope AAVDLSHFLKEKGGLEGLIHS
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Nef
Species (Isotype) mouse
References Schneider *et al.* 1991

- 31/03: Epitope mapped by overlapping decapeptides – mapping suggests complex epitope in this region. Schneider *et al.* [1991]

No. 1589
MAb ID polyclonal
HXB2 Location Nef (90–98)
Author Location Nef (NL43)
Epitope FLKEKGGLE
Neutralizing
Immunogen HIV-1 infection, vaccine
Species (Isotype) human, rabbit
References Yamada & Iwamoto 1999
Keywords ADCC, antibody binding site definition and exposure, antibody generation, complement, rate of progression

- Antibody responses to overlapping 9-mers from the Nef protein were mapped in a set of HIV+ Japanese hemophiliacs. Long term non-progressors among the group were significantly more likely to react to Nef peptide 31 (FLKEKGGLE) ($p=0.008$). Rabbit polyclonal Abs were raised against this peptide. These Abs bound Nef, could kill infected cells in a complement dependent manner, and the domain near peptide 31 was exposed on the surface of infected T-cells. Yamada & Iwamoto [1999] (**ADCC**, **antibody binding site definition and exposure**, **antibody generation**, **complement**, **rate of progression**)

No. 1590

B Cell

MAb ID polyclonal
HXB2 Location Nef (90–98)
Author Location Nef
Epitope FLKEKGGLE
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Yamada *et al.* 2004
Keywords ADCC, rate of progression

- Plasma and PBMC from long term non-progressors can mediate ADCC against Nef infected target cells. Addition of the peptide FLKEKGGLE reduces this activity by half. Patients who were LTNPs were found to make antibodies against this peptide in an earlier study. Anti-Gag antibodies do not elicit ADCC, and Pol proteins are not expressed on the cell surface, in contrast to this Nef epitope. Yamada *et al.* [2004] (**ADCC**, **rate of progression**)

No. 1591
MAb ID F4
HXB2 Location Nef (115–126)
Author Location Nef (115–126 NL-432)
Epitope YHTQGYFPDWQN?
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43 *HIV component:* Nef
Species (Isotype) mouse (IgG1)
References Kanduc *et al.* 2008; Otake *et al.* 1997
Keywords antibody binding site definition and exposure, antibody generation

- F4: Similarity level of the F4 binding site pentapeptide FPDWQ to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- F4: BALB/c mice were immunized with Nef protein to create a series of anti-Nef antibodies. F4 bound to the peptide spanning amino acids 115-126; we inferred the amino acids from the positions in the NL-43 strain. A6 also bound to the complete Nef protein. Otake *et al.* [1997] (**antibody binding site definition and exposure**, **antibody generation**)

No. 1592
MAb ID F2
HXB2 Location Nef (115–136)
Author Location Nef (115–137 NL-432)
Epitope YHTQGYFPDWQNYTPGPGVRYP?
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43 *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse (IgG1)
References Otake *et al.* 1997
Keywords antibody binding site definition and exposure, antibody generation

- F2: BALB/c mice were immunized with Nef protein to create a series of anti-Nef antibodies. F2 bound to the peptide spanning amino acids 115-137; we inferred the amino acids from the positions in the NL-43 strain. F2 also bound to the complete Nef protein. Otake *et al.* [1997] (**antibody binding site definition and exposure**, **antibody generation**)

No. 1593
MAb ID polyclonal
HXB2 Location Nef (117–147)
Author Location Nef (117–147 LAI)
Epitope TQGYFPDWQNYTPGPGVRYPLTFGWCYKLVP
Subtype B
Neutralizing no
Immunogen vaccine
Vector/Type: lipopeptide *Strain:* B clade LAI *HIV component:* Nef *Adjuvant:* QS21
Species (Isotype) human (IgG)
References Pialoux *et al.* 2001

- 28 subjects were vaccinated with six HIV-1 peptides that were selected to be particularly rich in CTL epitopes, presented in lipopeptides with or without adjuvant QS21 – HIV-specific Ab responses were detected in 25/28, proliferative in 3/24, and CTL in 13/24 (54%) of testable volunteers – 20/28 had antibody responses to this particular peptide (N2), 3/24 had proliferative responses, and CTL responses were detected. Pialoux *et al.* [2001]

No. 1594
MAb ID polyclonal
HXB2 Location Nef (118–133)
Author Location Nef (118–133)
Epitope QGYFPDWQNYTPGPGV
Neutralizing no
Immunogen vaccine
Vector/Type: DNA *Strain:* B clade BRU *HIV component:* Nef
Species (Isotype) mouse (IgG)
References Tahtinen *et al.* 2001

- BALB/c mice were immunized with a pBN-vector expressing HIV-1 nef, rev, or tat genes—DNA loaded onto gold microparticles was delivered using a gene gun, and DNA dissolved in saline was given intradermally or intramuscularly—Nef gene gun immunized mice showed the strongest and most long-lasting (6 months) Ab, CTL and proliferative responses—the highest IgG1/IgG2a ratio was observed in the gene gun immunized mice—three Ab binding sites were found in Nef using peptide mapping, although some sera reacted only to complete Nef—Rev- or Tat-immunized mice did not generate an Ab response. Tahtinen *et al.* [2001]

No. 1595
MAb ID polyclonal
HXB2 Location Nef (119–168)
Author Location Nef (118–167 LAI, BRU)
Epitope GYFPDWQNYTPGPGVRYPLTFGWCYKLVPVEP-DKVEEANKGENTSLLHPV
Subtype B
Neutralizing

B Cell

Immunogen HIV-1 infection, vaccine
Vector/Type: protein, PLG microparticle *Strain:* B clade BRU, B clade LAI *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA), PLG
Species (Isotype) mouse (IgG1)
References Maksiutov *et al.* 2002; Moureau *et al.* 2002

- This epitope is similar to a fragment of the human protein Bone-derived growth factor, PLEPAKLEE, and to Hematopoietic progenitor cell antigen CD34, TSLHPVSQHG. Maksiutov *et al.* [2002]
- Nef encapsulated in poly(DL-lactide-co-glycolide) (PLG) had a more prolonged Ab response than Nef in PBS or in Freund's adjuvant (CFA), still strong after 7 months – the response was predominantly IgG1, a Th2 immune response – three linear epitopes, Nef 32-64, 118-167, and 185-205, were frequently recognized by the sera of mice immunized with NefPLG or Nef-CFA, but not after immunization with Nef in PBS, which seemed to preferentially stimulate an Ab response to conformational epitopes. Moureau *et al.* [2002]

No. 1596
MAb ID F3
HXB2 Location Nef (128–137)
Author Location Nef (128–137 NL-432)
Epitope `TPGPGVRYPL?`
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43 *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse (IgG1)
References Kawai *et al.* 2003; Otake *et al.* 1997
Keywords antibody binding site definition and exposure, antibody generation, complement

- F3: Used as a control for Nef binding in a study designed to elicit anti-Nef IgM human Abs in trans-chromosome mice that carry human chromosomes responsible for Ig production. These mice were immunized with recombinant Nef protein. Human heavy chain, mouse light chain anti-Nef IgM were obtained. The hope was that these human IgM anti-Nef chimeric Abs would activate complement mediated cytolysis; C3 deposition was induced but not at high enough levels to induce lysis. Kawai *et al.* [2003] (**complement**)
- F3: BALB/c mice were immunized with Nef protein to create a series of anti-Nef antibodies. F3 bound to the peptide spanning amino acids 128-137; we inferred the amino acids from the positions in the NL-43 strain. F3 also bound to the complete Nef protein. Otake *et al.* [1997] (**antibody binding site definition and exposure**, **antibody generation**)

No. 1597
MAb ID F8
HXB2 Location Nef (128–137)
Author Location Nef (128–137 NL-432)
Epitope `TPGPGVRYPL?`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43 *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse (IgM)
References Otake *et al.* 1997
Keywords antibody binding site definition and exposure, antibody generation

- F8: BALB/c mice were immunized with Nef protein to create a series of anti-Nef antibodies. F8 bound to the peptide spanning amino acids 128-137; we inferred the amino acids from the positions in the NL-43 strain. F8 also bound to the complete Nef protein. Otake *et al.* [1997] (**antibody binding site definition and exposure**, **antibody generation**)

No. 1598
MAb ID polyclonal
HXB2 Location Nef (143–151)
Author Location Nef
Epitope `FKLVPVSEAE`
Neutralizing
Immunogen vaccine
Vector/Type: peptide *HIV component:* Env, Gag, Nef, Pol
Species (Isotype) rabbit
References Li *et al.* 2005b
Keywords mimics

- In early HIV-1 infection, patients develop autoimmune thrombocytopenia, with Ab directed against beta3 integrin, GPIIIa49-66. Panning with a 7-mer phage display library using rabbit anti-GPIIIa49-66 (CAPESIEFPVSEARVLED), the immunodominant epitope of the identified potential molecular mimicry epitopes with HIV-1 Env (sklFDeGLFn, elfnkTIIFP), Pol (geAPEFPskq), Gag (gktHyMINPl) and Nef (qeeeeVgFPVt, qeeeeVgFPVt, edeGigFPVr, fkLVPVSEae, ssnTPTTNaa) proteins. Pools of these peptides elicted Ab in rabbits that induce platelet oxidation in vitro and thrombocytopenia in vivo upon passive transfer. Nef (qeeeeVgFPVt), Gag (gktHyMINPl), and Nef (fkLVPVSEae) all overlap with known HIV-1 epitopes. Li *et al.* [2005b] (**mimics**)

No. 1599
MAb ID F1
HXB2 Location Nef (148–157)
Author Location Nef (148–157 IIIB)
Epitope `VEPDKVEEAN`
Neutralizing
Immunogen
Species (Isotype) mouse (IgM)
References Haynes *et al.* 2005a; Fujii *et al.* 1996b; Fujii *et al.* 1996c; Otake *et al.* 1994; Fujii *et al.* 1993

- F1: There is a Nef (Fujii1993) and a CD4BS (Haynes2005) MAb that are called F1. Fujii *et al.* [1993]; Haynes *et al.* [2005a]
- F1: Insect cells expressing myristylated Nef proteins on their cell surface can induce cytolysis of unstimulated CD4+ cells – this response is not due to MHC restricted CTL activity – the cell surface of Nef expressing insect cells carry Nef that can be recognized by MAbs E7 and E9 but not F1. Fujii *et al.* [1996c]

B Cell

- F1: A carboxy-terminal domain of Nef on the cell surface induces cytolysis of CD4+ T cells. Fujii *et al.* [1996b]
- F1: The C-term end of Nef is accessible to Abs at the cell surface – stained IIIB/M10, but not MN/M10, cells. Fujii *et al.* [1993]; Otake *et al.* [1994]

No. 1600
MAb ID 2F2
HXB2 Location Nef (151–170)
Author Location Nef (151–170 BRU)
Epitope DKVEEANKGENTSLLHPVSL
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Nef
Species (Isotype) mouse (IgG1)
References Maksiutov *et al.* 2002; Ranki *et al.* 1995; Saito *et al.* 1994; Ovod *et al.* 1992

- 2F2: UK Medical Research Council AIDS reagent: EVA3067.3.
- 2F2: This epitope is similar to a fragment of the human protein Hematopoietic progenitor cell antigen CD34, TSLHPVSQHG. Maksiutov *et al.* [2002]
- 2F2: One of four antibodies used in combination to show HIV Nef protein expressed in astrocytes from 7/14 brain samples from HIV+ individuals – Nef expression associated with dementia. Ranki *et al.* [1995]
- 2F2: Over-expression of Nef in astrocytes from postmortem pediatric CNS tissue. Saito *et al.* [1994]
- 2F2: Strain specific (MN and BRU reactive, not IIIB or RF). Ovod *et al.* [1992]

No. 1601
MAb ID E9
HXB2 Location Nef (158–181)
Author Location Nef (158–206 IIIB)
Epitope KGENTSLLHPVSLHGMDDPEREVL
Neutralizing
Immunogen
Species (Isotype) mouse (IgM)
References Maksiutov *et al.* 2002; Fujii *et al.* 1996b; Fujii *et al.* 1996c; Otake *et al.* 1994; Fujii *et al.* 1993

- E9: This epitope is similar to a fragment of the human protein Hematopoietic progenitor cell antigen CD34, TSLHPVSQHG. Maksiutov *et al.* [2002]
- E9: A carboxy-terminal domain of Nef on the cell surface induces cytolysis of CD4+ T cells. Fujii *et al.* [1996b]
- E9: Insect cells expressing myristylated Nef proteins on their cell surface can induce cytolysis of unstimulated CD4+ cells – this response is not due to MHC restricted CTL activity – the cell surface of Nef expressing insect cells carry Nef that can be recognized by MAbs E7 and E9 but not F1. Fujii *et al.* [1996c]
- E9: The C-term end of Nef is accessible to Abs at the cell surface – stained IIIB/M10, but not MN/M10, cells. Fujii *et al.* [1993]; Otake *et al.* [1994]

No. 1602
MAb ID 3E6
HXB2 Location Nef (161–180)
Author Location Nef (161–180 BRU)
Epitope NTSLLHPVSLHGMDDPEREV
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU
HIV component: Nef
Species (Isotype) mouse (IgG1)
References Maksiutov *et al.* 2002; Ranki *et al.* 1995; Saito *et al.* 1994; Ovod *et al.* 1992

- 3E6: UK Medical Research Council AIDS reagent: EVA3067.4.
- 3E6: This epitope is similar to a fragment of the human protein Hematopoietic progenitor cell antigen CD34, TSLHPVSQHG. Maksiutov *et al.* [2002]
- 3E6: Faintly cross-reactive with astrocytes of uninfected control samples. Ranki *et al.* [1995]
- 3E6: Reacted with Nef from different HIV-1 strains (BRU, IIIB, RF, MN). Ovod *et al.* [1992]

No. 1603
MAb ID E5
HXB2 Location Nef (170–181)
Author Location Nef (170–181)
Epitope LHGMDDPEREVL?
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade NL43
HIV component: Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) mouse (IgM)
References Kanduc *et al.* 2008; Otake *et al.* 1997
Keywords antibody binding site definition and exposure, antibody generation

- E5: Similarity level of the E5 binding site pentapeptide GMDDP to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 1 time, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- E5: BALB/c mice were immunized with Nef protein to create a series of anti-Nef antibodies. E5 bound to the peptide spanning amino acids 170-181; we inferred the amino acids from the positions in the NL-43 strain. E5 also bound to the complete Nef protein. Otake *et al.* [1997] (**antibody binding site definition and exposure**, **antibody generation**)

No. 1604
MAb ID 2A3
HXB2 Location Nef (171–190)
Author Location Nef (171–190 BRU)
Epitope HGMDDPEREVLEWRFDSRLA
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU
HIV component: Nef
Species (Isotype) mouse (IgG1)
References Ovod *et al.* 1992

- 2A3: Reacted with Nef from different HIV-1 strains (BRU, IIIB, MN, but not RF). Ovod *et al.* [1992]

No. 1605
MAb ID 2E4
HXB2 Location Nef (171–190)
Author Location Nef (171–190 BRU)
Epitope HGMDDPEREVLEWRFDSRLA
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU *HIV component:* Nef
Species (Isotype) mouse (IgG1)
References Ovod *et al.* 1992

- 2EA: Reacted with Nef from different HIV-1 strains (BRU, IIIB, MN but not RF). Ovod *et al.* [1992]

No. 1606
MAb ID 2H12
HXB2 Location Nef (171–190)
Author Location Nef (171–190 BRU)
Epitope HGMDDPEREVLEWRFDSRLA
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU *HIV component:* Nef
Species (Isotype) mouse (IgG1)
References Ranki *et al.* 1995; Saito *et al.* 1994; Ovod *et al.* 1992

- 2H12: One of four antibodies used in combination to show HIV Nef protein expressed in astrocytes from 7/14 brain samples from HIV+ individuals – Nef expression associated with dementia. Ranki *et al.* [1995]
- 2H12: Over-expression of Nef in astrocytes from postmortem pediatric CNS tissue. Saito *et al.* [1994]
- 2H12: Reacted with Nef from different HIV-1 strains (BRU, IIIB, RF, MN). Ovod *et al.* [1992]

No. 1607
MAb ID 3A2
HXB2 Location Nef (171–190)
Author Location Nef (171–190 BRU)
Epitope HGMDDPEREVLEWRFDSRLA
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BRU *HIV component:* Nef
Species (Isotype) mouse (IgG1)
References Ranki *et al.* 1995; Saito *et al.* 1994; Ovod *et al.* 1992

- 3A2: UK Medical Research Council AIDS reagent: EVA3067.5.
- 3A2: One of four antibodies used in combination to show HIV Nef protein expressed in astrocytes from 7/14 brain samples from HIV+ individuals – Nef expression associated with dementia. Ranki *et al.* [1995]
- 3A2: Over-expression of Nef in astrocytes from postmortem pediatric CNS tissue. Saito *et al.* [1994]
- 3A2: Reacted with Nef from different HIV-1 strains (BRU, IIIB, RF, MN). Ovod *et al.* [1992]

No. 1608
MAb ID NF1A1
HXB2 Location Nef (173–206)
Author Location Nef (173–206)
Epitope MDDPEREVLEWRFDSRLAFHHVARELHPEYFK-NC
Neutralizing
Immunogen
Species (Isotype) mouse
References Kaminchik *et al.* 1990

- NF1A1: Recognizes the Nef protein of the two isolates BH10 and LAV1 – low affinity. Kaminchik *et al.* [1990]

No. 1609
MAb ID polyclonal
HXB2 Location Nef (186–206)
Author Location Nef (185–205 LAI, BRU)
Epitope DSRLAFHHVARELHPEYFKNC
Subtype B
Neutralizing
Immunogen HIV-1 infection, vaccine
Vector/Type: protein, PLG microparticle *Strain:* B clade BRU, B clade LAI *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA), PLG
Species (Isotype) mouse (IgG1)
References Moureau *et al.* 2002

- Nef encapsulated in poly(DL-lactide-co-glycolide) (PLG) had a more prolonged Ab response than Nef in PBS or in Freund's adjuvant (CFA), still strong after 7 months – the response was predominantly IgG1, a Th2 immune response – three linear epitopes, Nef 32-64, 118-167, and 185-205, were frequently recognized by the sera of mice immunized with NefPLG or Nef-CFA, but not after immunization with Nef in PBS, which seemed to preferentially stimulate an Ab response to conformational epitopes. Moureau *et al.* [2002]

No. 1610
MAb ID E7
HXB2 Location Nef (192–206)
Author Location Nef (192–206 IIIB)
Epitope HHVARELHPEYFKNC
Neutralizing
Immunogen
Species (Isotype) mouse (IgM)
References Fujii *et al.* 1996d; Fujii *et al.* 1996b; Fujii *et al.* 1996a; Fujii *et al.* 1996c; Otake *et al.* 1994; Fujii *et al.* 1993

- E7: Insect cells expressing myristylated Nef proteins on their cell surface can induce cytolysis of unstimulated CD4+ cells – this response is not due to MHC restricted CTL activity – the cell surface of Nef expressing insect cells carry Nef that can be recognized by MAbs E7 and E9 but not F1. Fujii *et al.* [1996c]
- E7: Nef forms a homomeric oligomerizing structure, and using E7 and membrane immunofluorescence or immunoelectron microscopy, was shown to clusters on the surface of HIV-1 infected CD4+ cells. Fujii *et al.* [1996a]
- E7: A carboxy-terminal domain of Nef on the cell surface induces cytolysis of CD4+ T cells. Fujii *et al.* [1996b]

B Cell

- E7: Soluble Nef inhibits proliferation of CD4+ cells, and Nef cross-linking by MAbs may induce anti-CD4 cytocidal activity – sera from HIV+ individuals contain soluble Nef, thus this may be important for immune dysfunction and disease progression. Fujii *et al.* [1996d]
- E7: The C-term end of Nef is accessible to Abs at the cell surface – stained IIIB/M10, but not MN/M10, cells. Fujii *et al.* [1993]; Otake *et al.* [1994]

No. 1611
MAb ID AE6
HXB2 Location Nef (194–206)
Author Location Nef (LAI)
Epitope `VARELHPEYFKNC`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Nef
Species (Isotype) mouse (IgG1κ)
Ab Type C-term
Research Contact Frank Jirik, Centre for Molecular Med and Therapeutics, U. B. C., Vancouver, B. C. Canada
References Kanduc *et al.* 2008; Chang *et al.* 1998

- AE6: Similarity level of the AE6 binding site pentapeptide HPEYF to the host proteome was low, with the low-similarity 5-mer occurring in the host proteome 0 times, indicating that this peptide can be used to elicit Abs for active/passive immunotherapy with low risk of cross-reaction with the host proteome. Kanduc *et al.* [2008]
- AE6: The light and heavy chains of three MAbs (AG11, AE6, EH1) specific to C-terminus of NEF were cloned and variable regions sequenced – the complementarity determining regions (CDR) of AG11 and AE6 were highly related (95.1% at the DNA level) and bound LAI Nef, but not SF2 Nef – EH1 bound to SF2 and LAI and cross-competed AG11 and AE6 but had a distinctive CDR (57.9% similar to AG11) – single chain Abs were constructed from AG11 and EH1. Chang *et al.* [1998]

No. 1612
MAb ID AG11
HXB2 Location Nef (194–206)
Author Location Nef (LAI)
Epitope `VARELHPEYFKNC`
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Nef
Species (Isotype) mouse (IgG1κ)
Ab Type C-term
Research Contact Frank Jirik, Centre for Molecular Med and Therapeutics, U. B. C., Vancouver, B. C. Canada
References Chang *et al.* 1998

- AG11: The light and heavy chains of three MAbs (AG11, AE6, EH1) specific to C-terminus of NEF were cloned and variable regions sequenced – the complementarity determining regions (CDR) of AG11 and AE6 were highly related (95.1% at the DNA level) and bound LAI Nef, but not SF2 Nef – EH1 bound to SF2 and LAI and cross-competed AG11 and AE6 but had a distinctive CDR (57.9% similar to AG11) – single chain Abs were constructed from AG11 and EH1 and subcloned into a eukaryotic expression vector with a green fluorescent protein marker to allow intracellular expression – the single chain Abs bind Nef intracellularly and may be useful to better understand the role of Nef and as a gene therapy model. Chang *et al.* [1998]

No. 1613
MAb ID EH1
HXB2 Location Nef (194–206)
Author Location Nef (SF2)
Epitope `MARELHPEYYKDC`
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Nef
Species (Isotype) mouse (IgG1κ)
Ab Type C-term
Research Contact Frank Jirik, Centre for Molecular Med and Therapeutics, U. B. C., Vancouver, B. C. Canada
References Chang *et al.* 1998

- EH1: The light and heavy chains of three MAbs (AG11, AE6, EH1) specific to C-terminus of NEF were cloned and variable regions sequenced – the complementarity determining regions (CDR) of AG11 and AE6 were highly related (95.1% at the DNA level) and bound LAI Nef, but not SF2 Nef – EH1 bound to SF2 and LAI and cross-competed AG11 and AE6 but had a distinctive CDR (57.9% similar to AG11) – single chain Abs were constructed from AG11 and EH1 and subcloned into a eukaryotic expression vector with a green fluorescent protein marker to allow intracellular expression – the single chain Abs bind Nef intracellularly and may be useful to better understand the role of Nef and as a gene therapy model. Chang *et al.* [1998]

No. 1614
MAb ID 3B4B
HXB2 Location Nef
Author Location Nef
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Nef
Adjuvant: Incomplete Freund's Adjuvant (IFA)
Species (Isotype) transgenic mouse (IgM)
References Kawai *et al.* 2003
Keywords antibody generation, complement

- 3B4B: The goal of this study was to elicit anti-Nef IgM human Abs in trans-chromosome mice that carry human chromosomes responsible for Ig production. These mice were immunized with recombinant Nef protein. Two human heavy chain, mouse light chain anti-Nef IgM were obtained, 3B4B and 3H3E; 3B4B was able to stain MOLT4/IIIB cells with greater intensity. The hope was that these human IgM anti-Nef chimeric Abs would activate complement mediated cytolysis; C3 deposition was induced but not at high enough levels to induce lysis. Kawai *et al.* [2003] (**antibody generation**, **complement**)

B Cell

No. 1615
MAb ID 3H3E
HXB2 Location Nef
Author Location Nef
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) transgenic mouse (IgM)
References Kawai *et al.* 2003
Keywords antibody generation, complement

- 3H3E: The goal of this study was to elicit anti-Nef IgM human Abs in trans-chromosome mice that carry human chromosomes responsible for Ig production. These mice were immunized with recombinant Nef protein. Two human heavy chain, mouse light chain anti-Nef IgM were obtained, 3B4B and 3H3E; 3B4B was able to stain MOLT4/IIIB cells with greater intensity. The hope was that these human IgM anti-Nef chimeric Abs would activate complement mediated cytolysis; C3 deposition was induced but not at high enough levels to induce lysis. Kawai *et al.* [2003] (**antibody generation**, **complement**)

No. 1616
MAb ID 6.1
HXB2 Location Nef
Author Location Nef (JRCSF)
Epitope
Subtype B
Neutralizing
Immunogen
Species (Isotype) mouse
References Ranki *et al.* 1995

- 6.1: Raised against CNS primary isolates, stains astrocytes more densely than other Nef MAbs – Nef expression associated with dementia. Ranki *et al.* [1995]
- 6.1: NIAID Repository number 1123. Ranki *et al.* [1995]

No. 1617
MAb ID NF2B2
HXB2 Location Nef
Author Location Nef (20–78 BH10)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* Nef
Species (Isotype) mouse
References Kaminchik *et al.* 1990

- NF2B2: NIH AIDS Research and Reference Reagent Program: 456.
- NF2B2: Recognizes the Nef protein of the two isolates BH10 and LAV1. Kaminchik *et al.* [1990]

No. 1618
MAb ID NF3A3
HXB2 Location Nef
Author Location Nef (20–78 BH10)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* Nef
Species (Isotype) mouse
References Kaminchik *et al.* 1990

- NF3A3: Recognizes the Nef protein of the two isolates BH10 and LAV1 – low affinity. Kaminchik *et al.* [1990]

No. 1619
MAb ID NF8B4
HXB2 Location Nef
Author Location Nef (BH10)
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10 *HIV component:* Nef
Species (Isotype) mouse
References Kaminchik *et al.* 1990

- NF8B4: Does not recognize Nef CNBr cleavage products – recognizes intact BH10 Nef but not LAV1 Nef. Kaminchik *et al.* [1990]

No. 1620
MAb ID polyclonal
HXB2 Location Nef
Author Location Nef
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI, SIV *HIV component:* gp120, Nef, Tat *Adjuvant:* AS02A (oil-in-water emulsion, 3D-monophosphoryl lipid A, QS21), AS06 (CpG, aluminum hydroxide)
Species (Isotype) macaque (IgG)
References Voss *et al.* 2003
Keywords adjuvant comparison, variant cross-recognition or cross-neutralization

- Monkeys were immunized with different combinations of gp120/NefTat/SIV-Tat three times over a three-month time period and intravenously challenged with SHIV 89.6P four weeks after the last immunzation. Vaccination induced anti-Tat, -Nef and -gp120 Ab responses that decreased until challenge. Neutralizing Ab responses against HIV-1 MN and HIV-1 W61D were observed. Vaccination with the combination of all three proteins reduced viral load and kept animals from a CD4+ T cell decline, preventing AIDS for more than 2.5 years. The adjuvant AS02A elicited NAbs and protected from disease, while AS06 did not. gp120 alone or TatNef/SIV-Tat without gp120 could not protect from disease. Voss *et al.* [2003] (**adjuvant comparison**, **variant cross-recognition or cross-neutralization**)

No. 1621
MAb ID AE6
HXB2 Location Nef

B Cell

Author Location Nef
Epitope
Neutralizing
Immunogen
Species (Isotype) mouse
Ab Type C-term
Research Contact James Hoxie, Div of AIDS, NIAID, NIH
References Tornatore *et al.* 1994; Greenway *et al.* 1994

- AE6: NIH AIDS Research and Reference Reagent Program: 709.

IV-C-19 HIV-1 Antibodies

No. 1622
MAb ID
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype)
References Goepfert 2003
Keywords review

- A general review of anti-HIV human immune responses and the implications of these responses for vaccines, summarizing neutralizing antibodies, CD4+ and CD8+ T cell responses. A general overview of methods used to study these responses is presented. Goepfert [2003] (**review**)

No. 1623
MAb ID
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen vaccine
Adjuvant: CD40, CD80, CD86, Complete Freund's Adjuvant (CFA), GM-CSF, IFNγ, IL-12, IL-15, IL-18, IL-1α, IL-2, IL-2/Ig, IL-4, IL-7, CpG immunostimulatory sequence (ISS), Tumor Necrosis Factor α (TNFα), Tumor Necrosis Factor β (TNFβ), M-CSF, IL-8, RANTES
Species (Isotype)
References Mitchison & Sattentau 2005
Keywords adjuvant comparison, review, Th1, Th2

- Review summarizes mechanisms of immunoregulation relevant for new vaccine development, with a brief summary of adjuvant triggering innate immunity through Toll-like receptors (TLRs), Nod molecules, and other activators. DNA encoded adjuvants that have been tested in DNA vaccines are summarized. The balance between Th1 (CTL activating) and Th2 (B cell activating) responses is discussed, and it is noted that BALB/c mice are predominately Th2 responders, C57BL Th1. Mitchison & Sattentau [2005] (**adjuvant comparison**, **Th1**, **Th2**, **review**)

No. 1624
MAb ID
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) human
References Piontkivska & Hughes 2006
Keywords escape

- The greatest amino acid diversity is found in sites in the HIV genome that are spanned by antibody epitopes. Sites spanned by CTL epitopes, not but not by antibody epitopes, showed reduced amino acid diversity even in comparison to non-epitope sites. However, mutations within CTL epitopes were more likely to be convergent than mutations within antibody epitopes. These patterns were consistent both in Gag and Env. Piontkivska & Hughes [2006] (**escape**)

No. 1625
MAb ID 1G12
HXB2 Location HIV-1
Author Location Env
Epitope
Subtype C
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* C clade 97CN54 *HIV component:* Other
Species (Isotype) mouse (IgG1)
References Chen *et al.* 2008a
Keywords neutralization, variant cross-recognition or cross-neutralization

- 1G12: Mice were immunized with a construct of the outer domain (OD) of gp120 of subtype C fused with Fc, and MAbs specific for the CN54 OD were derived by exhaustive screening of the mice sera. The OD-specific 1G12 MAb cross-competed with three other newly identified OD-specific MAbs: 4E1, 3F9, 1H8, but did not cross-compete with 4D3 (bridging sheet) or the V3-specific 2B7 and 4E5. 1G12 showed no neutralization of the three isolates tested, CN54, MN, and 93MW965.26. Chen *et al.* [2008a] (**neutralization**, **variant cross-recognition or cross-neutralization**)

No. 1626
MAb ID 1H8
HXB2 Location HIV-1
Author Location Env
Epitope
Subtype C
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* C clade 97CN54 *HIV component:* Other
Species (Isotype) mouse (IgG1)
References Chen *et al.* 2008a
Keywords neutralization, variant cross-recognition or cross-neutralization

B Cell

- 1H8: Mice were immunized with a construct of the outer domain (OD) of gp120 of subtype C fused with Fc, and MAbs specific for the CN54 OD were derived by exhaustive screening of the mice sera. The OD-specific 1H8 MAb cross-competed with three other newly identified OD-specific MAbs: 4E1, 1G12, 3F9, but did not cross-compete with 4D3 (bridging sheet) or the V3-specific 2B7 and 4E5. 1H8 showed no neutralization of the three isolates tested, CN54, MN, and 93MW965.26. Chen *et al.* [2008a] (**neutralization**, **variant cross-recognition or cross-neutralization**)

No. 1627
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Fournier *et al.* 2002b

- Purified B lymphocytes secret only a fraction of Ig and anti-HIV-1 Ab compared with unfractionated cells because monocytes and natural killer cells enhance both secretions by cell-to-cell contacts, involving adhesion and CD27, CD80 costimulatory molecules and IL-6 – cell-to-cell contacts and soluble factors induce maturation of activated B cells *in vitro* to allow prolonged survival and terminal differentiation. Fournier *et al.* [2002b]

No. 1628
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Fournier *et al.* 2002a

- An early and sustained fall in plasma viral load to below detection was observed in 17 HAART responders while HIV-1 RNA remained detectable in 13 incomplete responders – HIV-1 specific Ab secretion decreased in parallel with plasma viral load – HIV-1 specific Abs became negative in only six responders, and was correlated with greater increases of CD4 T-cell counts and higher levels of HIV-specific IgA secretion at baseline – persistent immune activation may be due to residual HIV antigen. Fournier *et al.* [2002a]

No. 1629
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Subbramanian *et al.* 2002

- Sera from 39 patients were used to study the relative prevalence of neutralizing Abs (NAbs), ADCC-Abs and enhancing Abs – 69% of the sera were positive for NAbs but only 39% could neutralize in the presence of complement – 60% had ADCC Abs – 72% mediated the enhancement of infection in the presence of complement. Subbramanian *et al.* [2002]

No. 1630
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgA, IgG1)
References Battle-Miller *et al.* 2002

- In a study of HIV-1 infected women, ADCC Abs were detected in 16% (12/51) of cervicovaginal fluids, and 56% (25/45) of serum samples – 3 women had ADCC in cervical lavage fluids, but not sera, suggesting local production. Battle-Miller *et al.* [2002]

No. 1631
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgA1, IgA2, IgM)
References Wu & Jackson 2002

- IgA1 accounted for the majority of anti-HIV-1 IgA in the saliva in HIV-1 infected individuals – there was no anti-gp41 IgA in saliva, in contrast to plasma – lower levels of IgA and IgM were found in saliva than in plasma. Wu & Jackson [2002]

No. 1632
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgA, IgG)
References Oelemann *et al.* 2002

- A urine based commercial EIA kit from Calypte Biomedical Corporation, Berkeley, CA was found to work well as a primary screening for HIV in Brazilian samples – 76 HIV+ samples were correctly identified (100% sensitivity), and 278/284 negative samples 97.9% specificity. Oelemann *et al.* [2002]

No. 1633
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing no
Immunogen HIV-1 infection
Species (Isotype) human (IgE)

References Pellegrino *et al.* 2002; Secord *et al.* 1996

- Pediatric long term survivors (LTS) have been found to carry HIV-1 specific IgE – serum from these children inhibit HIV-1 production in culture, but this inhibition did not seem to be due to neutralization, rather due to a cytoxic event – serum lost the HIV-1 inhibitory effect when depleted of IgE. Pellegrino *et al.* [2002]
- HIV-specific IgE found in clinically healthy HIV-1 infected children. Secord *et al.* [1996]

No. 1634
MAb ID polyclonal
HXB2 Location HIV-1
Author Location gp120 and p55
Epitope
Neutralizing no
Immunogen vaccine
Vector/Type: vaccinia *Strain:* B clade 89.6 *HIV component:* Env, Gag-Pol *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
Species (Isotype) macaque
References Ambrose *et al.* 2003
Keywords genital and mucosal immunity

- Systemic priming with rVVs expressing HIV-1 Env and SHIV Gag-Pol followed by intragastric and intranasal mucosal boosting of LT(R192G) and aldrithiol-2 (AT-2)-inactiviated SHIV induced SHIV-specific IgA and IgG plasma and mucosal Abs. Viral loads in vaccinated animals were reduced after vaginal challenge with SHIV 89.6. Ambrose *et al.* [2003] (**genital and mucosal immunity**)

No. 1635
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Subtype B
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
References Binley *et al.* 2004
Keywords subtype comparisons, variant cross-recognition or cross-neutralization

- 93 viruses from different clades were tested for their neutralization cross-reactivity using a panel of HIV monoclonal antibodies, and a plasma from an HIV-1 + donor infected with a B clade virus. The plasma antibodies broadly neutralized viruses from many clades, with a slight preference for B clade. Binley *et al.* [2004] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1636
MAb ID polyclonal
HXB2 Location HIV-1
Author Location (HXB2)
Epitope
Subtype B
Neutralizing yes
Immunogen vaccine
Vector/Type: vesicular stomatitis virus (VSV) with protein boost *Strain:* B clade HXB2 *HIV component:* gp41 MPER *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)
Species (Isotype) rabbit
References Luo *et al.* 2006
Keywords vaccine antigen design

- gp41 and p15E of the porcine endogenous retrovirus (PERV) share structural and functional similarities, and epitopes in the membrane proximal region of p15E are able to elicit NAbs upon immunization with soluble p15E. Rabbits immunized with a VSV recombinant expressing an HIV-1 membrane-proximal external region (MPER) fused to PERV p15E, with a fusion p15E-HIV MPER protein boost, elicted HIV specific NAbs in 3/9 rabbits each for two different constructs, with and without the E2 region of p15E. Luo *et al.* [2006] (**vaccine antigen design**)

No. 1637
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Subtype multiple
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Parekh & McDougal 2005
Keywords acute/early infection, assay development, assay standardization/improvement

- This paper describes IgG-Capture BED-EIA, which detects the increasing proportion of HIV-1-IgG relative to total IgG and can be used to detect early infection and incidence data in cross-sectional and sentinel surveillance studies, and is robust for use with multiple HIV-1 subtypes. Parekh & McDougal [2005] (**assay development**, **acute/early infection**, **assay standardization/improvement**)

No. 1638
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *HIV component:* Env, Gag-Pol
Species (Isotype) macaque
References Sadagopal *et al.* 2005
Keywords vaccine-induced epitopes

- 22/23 macaques vaccinated with a DNA Gag-Pol_Env prime and vaccinia virus Ankara boost controlled SHIV viremia until euthanasia at 200 weeks post-challenge. All animals had low or undetectable viral loads, normal CD4 counts, and high titers of neutralizing antibodies. Most animals recognized 2 CD8 epitopes and 1 CD4 epitope, with up to 3 CD8 and 5 CD4 epitopes. Most T-cell epitopes were in Gag, though some were in Env. Sadagopal *et al.* [2005] (**vaccine-induced epitopes**)

No. 1639
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Haynes & Montefiori 2006
Keywords antibody binding site definition and exposure, co-receptor, escape, genital and mucosal immunity, neutralization, optimal epitope, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- This review describes the effectiveness of the current HIV-1 immunogens in eliciting neutralizing antibody responses to different clades of HIV-1. It also summarizes different evasion and antibody escape mechanisms, as well as the most potent neutralizing MAbs and their properties. MAbs reviewed in this article are: 2G12, IgG1b12, 2F5, 4E10, A32, 447-52D and, briefly, D50. Novel immunogen design strategies are also discussed. Haynes & Montefiori [2006] (**antibody binding site definition and exposure**, **co-receptor**, **genital and mucosal immunity**, **neutralization**, **optimal epitope**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **escape**, **review**, **subtype comparisons**)

No. 1640
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (Isotype) human (IgA, IgG)
References Holl *et al.* 2006b
Keywords dendritic cells, kinetics, neutralization

- Inhibition of R5 HIV replication by monoclonal and polyclonal IgGs and IgAs in immature monocyte-derived dendritic cells (iMDDCs) was evaluated. It was shown that anti-HIV IgG was able to inhibit HIV-1 replication more efficiently in iMDDCs than in PBLs, while no such activity was observed for polyclonal IgA. The kinetics of IgG addition suggested that the inhibition occurred early in HIV infection. No induction of maturation was observed. Two mechanisms of HIV inhibition in iMDDCs by IgG are described: i) neutralization of HIV infectivity by Fab parts of IgG, and ii) inhibition of HIV infection via FcγRII or FcγRI expressed on target cells. Holl *et al.* [2006b] (**neutralization**, **kinetics**, **dendritic cells**)

No. 1641
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Subtype C
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
References Lakhashe *et al.* 2007
Keywords subtype comparisons, variant cross-recognition or cross-neutralization

- Plasma samples collected from HIV-1 infected individuals in India showed extensive cross-neutralizing response against a panel of primary subtype C isolates, suggesting presence of shared neutralization determinants among subtype C in India. Sequence analysis showed limited genetic diversity of Indian subtype C compared to subtype C from Africa. Lakhashe *et al.* [2007] (**variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1642
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing L, P
Immunogen HIV-1 infection, HIV-2 infection
Species (Isotype) human
References Rodriguez *et al.* 2007
Keywords HIV-2, neutralization, variant cross-recognition or cross-neutralization

- Neutralizing Ab responses against 7 heterologous primary isolates and 1 laboratory strain were compared in HIV-1 and HIV-2 infections. HIV-2 infection was found to be charaterized by a broad, low magnitude neutralization response, while HIV-1 infection was charaterized by a more narrow, higher magnitude response. A significant positive association between the magnitude of neutralization response and viremia was observed for both HIV-1 and HIV-2. Cross-neutralization of HIV-2 by HIV-1 plasma and vice versa was very rare. Rodriguez *et al.* [2007] (**HIV-2**, **neutralization**, **variant cross-recognition or cross-neutralization**)

No. 1643
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Humbert & Dietrich 2006
Keywords antibody binding site definition and exposure, assay standardization/improvement, escape, immune evasion, neutralization, vaccine antigen design

- This review discusses different mechanisms of Ab mediated neutralization and different mechanisms of NAb viral escape and immune evasion. Furthermore, recent research on the protective role of NAbs in HIV-1 infection, as well as preliminary vaccines and immunogens are summarized. Detection of NAbs by neutralization assays and the importance and requirements of assay standardization are highlighted. Humbert &

Dietrich [2006] (**antibody binding site definition and exposure**, **immune evasion**, **neutralization**, **vaccine antigen design**, **escape**, **assay standardization/improvement**)

No. 1644
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Killian *et al.* 2006
Keywords acute/early infection, dynamics, early treatment, HAART, ART

- The influence of ART on the HIV-specific antibody titers during primary HIV-1 infection was examined in treated and untreated individuals as well as individuals that discontinued ART. It was found that the Ab levels gradually increased in untreated patients, and continued to increase after the viral load set point, until approximattely 40 weeks postinfection when an Ab plateau was reached. Early ART-treated patients had low Ab titers associated with an early and substantial reduction in virus replication. Patients that discontinued early ART experienced a rebound of virus replication associated with a rapid rise in Ab titer. The results indicate that early ART influences typical evolution of HIV-1 specific Ab response. Killian *et al.* [2006] (**acute/early infection**, **dynamics**, **early treatment**, **HAART, ART**)

No. 1645
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG, IgG1, IgG3, IgG2, IgG4)
References Adalid-Peralta *et al.* 2006
Keywords acute/early infection, dynamics, early treatment, HAART, ART

- This study examined the impact of early HAART on antibody quality and production in patients with primary HIV-1 infection by comparing traeted and untreated patients. Responses against pol, env and gag were analysed. HAART affected the concentration of all anti-HIV IgG subclasses studied, as treated patients showed lower Ab responses. However, HAART did not change the ratio between the Ab subclasses. Furthermore, the avidity of anti-HIV-1 IgG did not differ between the two patient groups, indicating that the effect of HAART is only quantitative and limited to the final stages of the anti-HIV B-cell response. Adalid-Peralta *et al.* [2006] (**acute/early infection**, **dynamics**, **early treatment**, **HAART, ART**)

No. 1646
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing L, P
Immunogen HIV-1 infection
Species (Isotype) human
References Deeks *et al.* 2006
Keywords acute/early infection, autologous responses, neutralization, variant cross-recognition or cross-neutralization

- Neutralizing Ab responses were measured against autologous and heterologous isolates in acutely and chronically HIV-1 infected patients. Individuals with acute infection showed lower neutralizing Ab response against both autologous and heterologous viruses than the chronically infected patients, and had a higher neutralizing titers directed against earlier viruses than against contemporaneous viruses. In chronically infected patients, the level of neutralizing Abs against heterologous viruses was positivelly correlated with the level of viremia, indicating that HIV replication continuously drives the production of of Abs that cross-neutralize primary isolates. Furthermore, the correlation of neutralizing Abs against autologous viruses and viremia was negative, indicating that these Abs may contribute to the control of HIV-1 replication. In addition, neutralizing Ab response against contemporaneous viruses in chronic infection could be detected, although it was low. These results suggest that there might exist limits to the capacity of HIV-1 to evolve continuously in response to neutralizing Abs. Deeks *et al.* [2006] (**autologous responses**, **neutralization**, **variant cross-recognition or cross-neutralization**, **acute/early infection**)

No. 1647
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing P
Immunogen HIV-1 infection
Species (Isotype) human
References Barin *et al.* 2006
Keywords mother-to-infant transmission, neutralization, variant cross-recognition or cross-neutralization

- The association between mother-to-child-transmission (MTCT) and maternal neutralizing Abs to heterologous primary isolates of HIV-1 clades B, F, CRF01_AE and CRF02_AG was examined. An association between higher titer of maternal neutralizing Abs to heterologous HIV-1 strain of the same clade (CRF01_AE) and lower rate of MTCT was observed, but only for the intrapartum transmission. No association was found for in utero transmission or for any of the other clades tested. These results indicate that neutralizing Abs might have a role in the natural prevention of late perinatal HIV transmission. Barin *et al.* [2006] (**neutralization**, **variant cross-recognition or cross-neutralization**, **mother-to-infant transmission**)

No. 1648
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope

B Cell

Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Dickover *et al.* 2006
Keywords autologous responses, escape, mother-to-infant transmission, neutralization

- The role of maternal autologous NAbs in selective transmission of HIV-1 escape variants to their infants was examined. In utero transmitting mothers were significantly less likely to have autologous NAbs at delivery than nontransmitting mothers, while no difference between intrapartum transmitters and nontransmitters was observed. In addition, the infecting HIV-1 strains found in the infants were more closely related to maternal autologous NAb escape variants, suggesting that neutralizing Abs may have both protective and selective effects. However, sequence analyses of these HIV-1 strains, transmitted in the presence of maternal NAbs, showed that they had features of both sensitive and escape maternal HIV-1 strains. It is suggested that NAb sensitive strains were transmitted from the mothers to their children, and that these strains rapidly evolved to acquire escape mutations due to the presence of maternal NAbs in the infants. These results suggest that neutralizing Abs can promote rapid evolution of HIV-1 in infected children. Dickover *et al.* [2006] (**autologous responses**, **neutralization**, **escape**, **mother-to-infant transmission**)

No. 1649
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Bailey *et al.* 2006a
Keywords autologous responses, HAART, ART, neutralization

- The amount of env gene diversity, the lengths of variable loops, and the number of N-linked glycosylation sites were observed lower in elite supressors (ES) than in patients on HAART and in untreated chronically infected individuals. Also, the titers of NAbs against two HIV-1 lab strains was shown to be lower in ES and HAART-treated patients than in untreated viremic individuals. However, despite these differences, the titers of NAb against autologous virus did not differ significantly between the three groups of patients. In addition, there was no difference in the titer of NAbs against plasma viruses and against proviral variants in the ES. These results suggest that NAb do not play a dominant role in the maintainance of viral supression in elite supressors. Bailey *et al.* [2006a] (**autologous responses**, **neutralization**, **HAART, ART**)

No. 1650
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Le Guillou-Guillemette *et al.* 2006
Keywords binding affinity, HAART, ART, memory cells

- The avidity of anti-HIV-1 IgG during HAART was observed to progressively decrease in patients, however, the B-cell subset depleted at the chronic stage of infection was shown to increase during the treatment. The increase concerned the naive B-cells secreting new antibodies with low affinity as the HIV antigen levels are lower under HAART. Investigation of the cellular, humoral and innate immune responses showed that HAART induced different immune restoration patterns in patients. It is suggested that the IgG avidity index is a weak marker of the restoration of humoral immune function in HIV-1 infected patinents under HAART. Le Guillou-Guillemette *et al.* [2006] (**memory cells**, **binding affinity**, **HAART, ART**)

No. 1651
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgA, IgE, IgG, IgM)
References Hasson *et al.* 2006
Keywords HAART, ART, rate of progression, Th2

- Treatment of HIV-1 infected patients with the entry inhibitor ENF induced no change in patient's total IgM, IgG and IgA, however, a significant increase of IgE was observed in all the patients. A high proporton of the patients with elevated levels of IgE were characterized by advanced disease. However, the positive outcome of ENF treatment increasing the level of CD4 was observed in the patients irrespectively of their IgE levels. Hasson *et al.* [2006] (**HAART, ART**, **Th2**, **rate of progression**)

No. 1652
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Titanji *et al.* 2006
Keywords acute/early infection, HAART, ART, memory cells

- The precentage of memory B-cells was shown to progressively decrease during the course of HIV-1 infection, and was correlated to the CD4+ T-cell counts, thus suggested to represent a marker of disease progression. In addition, patients with primary and chronic HIV-1 infection showed a decrease in the Ab titers to other viral and bacterial pathogens, indicating early occurence of a defect in the B-cell compartment leading to a decline of serologic memory and immune response. However, this was not observed for LTNPs. Antiretroviral therapy did not restore serologic memory irrespectively of when the treatment was initiated. Titanji *et al.* [2006] (**memory cells**, **acute/early infection**, **HAART, ART**)

No. 1653
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: adenovirus type 5 (Ad5) *Strain:* B clade HXB2, B clade NL43, B clade BaL, A clade 92RW020, C clade 97ZA012 *HIV component:* Env, Gag-Pol
Species (Isotype) human
References Catanzaro *et al.* 2006
Keywords neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- 18 of 30 patients immunized with rAd5 vector HIV-1 clade B gag-pol and clade A, B and C Env vaccine had vaccine-induced Ab response detected by ELISA, which also was shown to be dose-dependent. 28 of 30 patients were positive for an EnvB-specific Ab response by Western-blot 4 weeks after immunization. A greater magnitude of response was detected to EnvC and EnvA than to EnvB. Weak responses to Gag were detected. No neutralizing Abs were detected. Catanzaro *et al.* [2006] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1654
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide, protein *Strain:* B clade SF2 *HIV component:* gp120, p24 Gag *Adjuvant:* Immune stimulating complexes (ISCOM)
Species (Isotype) macaque (IgA, IgG)
References Koopman *et al.* 2007
Keywords genital and mucosal immunity, neutralization

- Macaques were immunized intranasally (IN) or via targeted lymph node immunization (TLNI) with gp120 and gp24 proteins and V2 and V3 peptides, with ISCOM as adjuvant. Animals immunized via TLNI route had greater gp120-specific IgG and IgA responses, including mucosal responses. Two out of four TLNI-immunized animals were able to neutralize the homologous virus strain while no neutralization of a heterologous strain was observed. Koopman *et al.* [2007] (**genital and mucosal immunity**, **neutralization**)

No. 1655
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen HIV-1 exposed seronegative
Species (Isotype) human (IgA, IgG)
References Nguyen *et al.* 2006
Keywords HIV exposed persistently seronegative (HEPS)

- HIV-1 exposed uninfected individuals were tested for HIV-1 specific Abs. It was found that IgA anti-gp41 and IgG anti-CD4-gp120-complex Abs were significantly higher in the exposed uninfected persons than in unexposed controls. Nguyen *et al.* [2006] (**HIV exposed persistently seronegative (HEPS)**)

No. 1656
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen
Species (Isotype) (IgA, IgG, IgM)
References Mestecky 2007
Keywords genital and mucosal immunity, HIV exposed persistently seronegative (HEPS), mucosal immunity, review

- This review describes data on humoral immune responses to HIV-1 in mucosal sites comparing male and female genital tract immune responses and responses in vaccinated and HIV exposed but seronegative individuals. Mestecky [2007] (**genital and mucosal immunity**, **mucosal immunity**, **HIV exposed persistently seronegative (HEPS)**, **review**)

No. 1657
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype B
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) (IgA, IgE, IgG, IgM)
References He *et al.* 2006
Keywords antibody generation, isotype switch

- A subset of B cells was shown to bind gp120 through mannose C-type lectin receptors (MCLRs), mainly DC-SIGN. In the presence of gp120, these B cells proliferated and up-regulated AID, which induced class switching from IgM to IgG and IgA. Presence of IL-10 and IL-4 further augmented the class switching and IL4 also elicited class switching to IgE. The Ab secretion is managed by BAFF, which was up-regulated by gp120 interaction with CD4, CCR5 and CXCR4. Thus, gp120 can initiate polyclonal IgG, IgA and IgE responses. gp120-reactive Abs did not interfere with the ability of gp120 to bind and activate B-cells, while anti-gp120 Abs against the CD4bs augmented B-cell binding by increasing the exposure of CXCR4-binding sites on gp120. He *et al.* [2006] (**antibody generation**, **isotype switch**)

No. 1658
MAb ID polyclonal

HXB2 Location HIV-1
Author Location gp120
Epitope
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) (IgG)
References Pashov *et al.* 2006
Keywords mimotopes

- A carbohydrate mimetic peptide with central motif versions RYRY and YPYRY was shown to precipitate human IgG Ab that bind to gp120 and to immunoprecipitate gp120 from transfected cells. Thus, these motifs can mimic multiple carbohydrate epitopes found on HIV-1. Pashov *et al.* [2006] (**mimotopes**)

No. 1659
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Draenert *et al.* 2006
Keywords acute/early infection, autologous responses, neutralization, variant cross-recognition or cross-neutralization

- Adult monozygotic twins simultaneously infected with the same HIV-1 strain showed strikingly similar humoral immune responses. Neutralizing Abs to early autologous virus were detected 6 months after infection and reached a peak 34 months after infection. The neutralization profiles were similar in both twins. The twin's plasma also showed similar profiles of cross-neutralization of each other's viruses. A brother to the twins, infected with the same strain of HIV-1 13 months after the twins, did not develop potent cross-neutralization Abs to twins' isolates. Draenert *et al.* [2006] (**autologous responses**, **neutralization**, **variant cross-recognition or cross-neutralization**, **acute/early infection**)

No. 1660
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgA, IgE, IgG)
References Qiao *et al.* 2006
Keywords antibody generation, isotype switch

- Nef was found to penetrate uninfected B-cells both in vitro and in vivo. There it would suppress CD40-dependent IgG, IgA and IgE class-switching by inducing IκBα and SOCS proteins. These are negative feedback proteins, which block CD154 and cytokine signaling via NF-κB and STAT, thereby preventing Ab class switching. In addition, Nef inhibited IL10 signaling through Jak and STAT, thereby preventing differentiation of class-switched B-cells into Ab-secreting cells. Qiao *et al.* [2006] (**antibody generation**, **isotype switch**)

No. 1661
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Moore *et al.* 2006
Keywords antibody binding site definition and exposure, immunodominance

- In addition to gp120-gp41 trimers, HIV-1 particles were shown to bear nonfunctional gp120-gp41 monomers and gp120-depleted gp41 stumps on their surface. It was shown that Ab binding to trimers predicts neutralization, while non-neutralizing Abs bind to the nonfunctional forms of Env. HIVIG prepared from HIV-positive donor plasma targeted mainly monomers, suggesting that the monomers elicit strong Ab responses during natural infection. It is hypothesized that the nonfunctional monomers on the HIV-1 surface serve to divert the Ab response, helping the virus to avoid neutralization. Moore *et al.* [2006] (**antibody binding site definition and exposure**, **immunodominance**)

No. 1662
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype A, B, C
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with gp120 boost *Strain:* B clade, Other, A clade UG37, C clade 96ZM651 *HIV component:* Gag, gp120
Species (Isotype) macaque
References Pal *et al.* 2005
Keywords neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- Macaques immunized with multivalent DNA encoding gp120 from subtypes A, B and E and p55 gag of subtype C followed by boost with homologous gp120 proteins developed strong humoral responses. The elicited anti-gp120 Abs were capable of neutralizing homologous and, to a lesser extent, heterologous HIV-1 isolates of subtypes A, B and C but not E. The Abs elicited during the primary immunization phase decayed but the responses could easily be boosted back to the original level with limited additional immunizations. One of the six immunized animals was protected from challenge by SHIV while the rest showed significant containment of plasma viremia compared to the control animals. The neutralization titer of anti-Env Abs to the challenge virus was not correlated to the challenge outcome. Pal *et al.* [2005] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1663

MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype A, CRF02_AG, G, multiple
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Kelly *et al.* 2005
Keywords autologous responses, escape, neutralization, rate of progression, subtype comparisons

- Sequentially sampled plasma from eight chronically non-subtype B infected patients showed an increasing capacity to neutralize early autologous viruses and a low capacity to neutralize contemporaneous and later time-point autologous viruses. In two individuals, the capcity to neutralize early, contemporaneous and later time-point viruses was conserved. There was a low or weak capacity of Abs in plasma to neutralize heterologous viruses. Although the ten patients showed different rates of CD4 T-cell decline, this decline was independent of the generation of NAbs in these patients. Kelly *et al.* [2005] (**autologous responses**, **neutralization**, **escape**, **subtype comparisons**, **rate of progression**)

No. 1664
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Crooks *et al.* 2005
Keywords antibody binding site definition and exposure, assay standardization/improvement, neutralization

- Several anti-HIV MAbs were investigated in differnt neutralization formats, including the standard format that measures activity over the entire infection period and several formats that emphasize various stages of infection. The neutralization formats were then used to analyze neutralization mechanism of several HIV+ donor plasmas. All plasmas mediated high-levels of post-CD4 neutralization indicating presence of b12 and 2G12 -like Abs. None of the plasmas neutralized in the post-CD4/CCR5 format indicating absence of 2F5 and 4E10 - like Abs. Crooks *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **assay standardization/improvement**)

No. 1665
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Slobod *et al.* 2005
Keywords review, vaccine antigen design

- This review summarizes data from past and present vaccine strategies including vaccine studies in the non-human primates, and data relevant for development of cocktail vaccines. Three different sampling strategies for formulation of vaccine cocktail are suggested: sampling from HIV-infected individuals, antibody binding studies, and sequence analyses. Slobod *et al.* [2005] (**vaccine antigen design**, **review**)

No. 1666
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype A, B, C
Neutralizing
Immunogen vaccine
Vector/Type: DNA *Strain:* A clade, B clade, Other *HIV component:* gp160, Rev, RT, Other *Adjuvant:* GM-CSF, Other
Species (Isotype) mouse (IgA, IgG, IgG1, IgG2a)
References Bråve *et al.* 2005
Keywords Th1, Th2, vaccine antigen design

- Strong cellular and humoral responses in mice were induced by intradermal immunization with an HIV-1 vaccine containing seven plasmids encoding nine HIV-1 proteins from three subtypes, A, B and C. Together with GM-CSF adjuvant, the vaccine induced high levels of gp160-, gp120- and p24-specific Abs, while no anti-RT responses were observed. SImilar levels of IgG1 and IgG2a indicated a balanced Th1/Th2 response. In addition to high IgG responses, high levels of gp160-specific IgA were induced. Bråve *et al.* [2005] (**vaccine antigen design**, **Th1**, **Th2**)

No. 1667
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Mc Cann *et al.* 2005
Keywords acute/early infection, ADCC, antibody binding site definition and exposure, antibody interactions, autologous responses, co-receptor, escape, immunotherapy, neutralization, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- This review focuses on the importance of neutralizing Abs in protecting against HIV-1 infection, including mechanisms of Ab interference with the viral lifecycle, Ab responses elicited during natural HIV infection, and use of monoclonal and polyclonal Abs in passive immunization. In addition, vaccine design strategies for eliciting of protective broadly neutralizing Abs are discussed. Mc Cann *et al.* [2005] (**ADCC**, **antibody binding site definition and exposure**, **antibody interactions**, **autologous responses**, **co-receptor**, **neutralization**,

B Cell

vaccine antigen design, **variant cross-recognition or cross-neutralization**, **acute/early infection**, **escape**, **immunotherapy**, **review**, **subtype comparisons**)

No. 1668
MAb ID polyclonal
HXB2 Location HIV-1
Author Location gp120
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA, protein, DNA prime with protein boost *Strain:* B clade JRFL *HIV component:* gp120 *Adjuvant:* QS21
Species (Isotype) guinea pig
Ab Type gp120 CD4i
References Varadarajan *et al.* 2005
Keywords antibody binding site definition and exposure, neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- gp120 alone and gp120 bound to CD4D12 (the first two domains of human CD4) or to M9 (a 27-residue CD4 analog) were used to immunize guinea pigs. Only sera from the gp120-CD4D12 immunized animals showed broadly neutralizing activity. This activity was shown to be exclusively due to anti-CD4D12 Abs. Abs targeting the CD4i epitope were generated by the gp120-CD4D12, but they were nonneutralizing. Varadarajan *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1669
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype C
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Zhang *et al.* 2005b
Keywords mother-to-infant transmission, neutralization, responses in children

- In a mother-child HIV-1 infected pair, neutralization of infant HIV-1 isolates was analyzed by contemporaneous and non-contemporaneous infant and maternal plasma. Neutralization assays suggested that most of the neutralizing Abs in the infant during the first months of life were of maternal origin, however, these were just a subset of maternal NAbs, since maternal plasma more effectively neutralized early infant virus than infant plasma did. The maternal humoral component in the child decreased over time, and increasing titers of NAbs were detected in non-contemporaneous child plasma after 12 months, indicating development of effective humoral immune responses in the infant. The de novo humoral responses in the child corresponded with an increase in Env diversity. Zhang *et al.* [2005b] (**neutralization**, **responses in children**, **mother-to-infant transmission**)

No. 1670
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Vincent *et al.* 2005
Keywords antibody interactions

- The levels of Abs directed to the HR2 region of gp41 decreased following treatment of HIV-1 infected patients with T20. The depletion of these Abs by T20 suggests formation of T20-Ab complexes that may interfere with T20 treatment. Upon cessation of T20-treatment, the Abs to HR2 region returned to pre-treatment levels. The levels of Abs directed to other regions of gp41 and to gp120 remained stable after treatment with T20. Both sera from T20-treated and from T20-untreated patients did not recognize peptides representing the HR1-region of gp41. Vincent *et al.* [2005] (**antibody interactions**)

No. 1671
MAb ID polyclonal
HXB2 Location HIV-1
Author Location gp140
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade YU2 *HIV component:* gp140
Species (Isotype) mouse
References Yuan *et al.* 2005
Keywords neutralization, variant cross-recognition or cross-neutralization

- A substantial fraction of soluble envelope glycoprotein trimers contained inter-subunit disulfide bonds. Sera from mice immunized with soluble gp140 trimers with or without inter-disulfide bonds contained similar titers of Abs reactive to gp120. The sera also exhibited very mild neutralization activity to either homologous YU2 virus or heterologous HXBc2 virus. Yuan *et al.* [2005] (**neutralization**, **variant cross-recognition or cross-neutralization**)

No. 1672
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype A
Neutralizing P
Immunogen HIV-2 infection
Species (Isotype) human (IgG)
References Shi *et al.* 2005
Keywords autologous responses, co-receptor, escape, HIV-2, neutralization, rate of progression, variant cross-recognition or cross-neutralization

B Cell

- IgG purified from HIV-2 infected patient sera was shown to neutralize the majority of autologous viruses, including those isolated years later, indicating that neutralization escape is rare in HIV-2 infection. All HIV-2 sera also neutralized the majority of heterologous primary HIV-2 isolates, including an isolate of subtype B, suggesting that HIV-2 infection induces broadly neutralizing Ab responses. The neutralization sensitivity of HIV-2 isolates did not correlate with the number of N-linked glycosylation sites or the absence or presence of specific glycosylation sites. Shi *et al.* [2005] (**autologous responses**, **co-receptor**, **HIV-2**, **neutralization**, **variant cross-recognition or cross-neutralization**, **escape**, **rate of progression**)

No. 1673
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Srivastava *et al.* 2005
Keywords ADCC, antibody binding site definition and exposure, assay standardization/improvement, immunotherapy, neutralization, review, structure, vaccine antigen design, variant cross-recognition or cross-neutralization

- This review summarizes data on the role of NAb in HIV-1 infection and the mechanisms of Ab protection, data on challenges and strategies to design better immunogens that may induce protective Ab responses, and data on structure and importance of mAb epitopes targeted for immune intervention. The importance of standardized assays and standardized virus panels in neutralization and vaccine studies is also discussed. Srivastava *et al.* [2005] (**ADCC**, **antibody binding site definition and exposure**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **immunotherapy**, **review**, **structure**, **assay standardization/improvement**)

No. 1674
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Popovic *et al.* 2005
Keywords HAART, ART, neutralization

- Viral structural proteins and glycoproteins were present in the germinal centers of lymphoid tissue in HIV-1 infected patients and persisted in these patients during HAART. Antibodies to HIV-1 IIIB p17, p24 and gp120/160 were detected in these patients before and during HAART, however, treatment resulted in ∼4-fold decrease of Ab titers. Sera from the patients neutralized HIV-1 MN and to a lesser extent HIV-1 193BR020, and HAART treatment resulted in the same patterns of decrease of NAb titers. Popovic *et al.* [2005] (**neutralization**, **HAART, ART**)

No. 1675
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype A, B, C, CRF01_AE, F, G
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Rusert *et al.* 2005
Keywords acute/early infection, autologous responses, HAART, ART, neutralization

- Ab titers to gp120 and to p24 were significantly lower in the acutely infected HIV-1 patients compared to the chronically infected patients. The anti-gp120 response in acutely infected patients was a low-avidity response while it was medium- to high-avidity response in chronically infected patients. Abs directed to CD4BS were not detectable in the majority of acute patients while they were present in chronic infection. Also, there was no observed difference in the susceptibility of acute and chronic viruses to inhibitors targeting the CD4BS, CCR5, fusion, or MAb 2G12, while MAbs 2F5 and 4E10 were more potent at inhibiting viruses from acute infection. Rusert *et al.* [2005] (**autologous responses**, **neutralization**, **acute/early infection**, **HAART, ART**)

No. 1676
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Reeves *et al.* 2005
Keywords antibody binding site definition and exposure, drug resistance, escape, HAART, ART, neutralization

- Escape mutations in HR1 of gp41 that confer resistance to Enfuvirtide reduced infection and fusion efficiency and also delayed fusion kinetics of HIV-1. They also conferred increased neutralization sensitivity to a subset of neutralizing MAbs that target fusion intermediates or with epitopes exposed following receptor interactions. Enhanced neutralization correlated with reduced fusion kinetics, indicating that the mutations result in Env proteins remaining in the CD4-triggered state for a longer period of time. Viruses with escape mutations in HR1 were also more readily neutralized by sera from HIV-1 infected individuals than wildtype viruses, indicating that ENF therapy resulting in escape may lead to viruses with enhanced sensitivity to the immune response in vivo. Reeves *et al.* [2005] (**antibody binding site definition and exposure**, **drug resistance**, **neutralization**, **escape**, **HAART, ART**)

No. 1677
MAb ID polyclonal

HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: Venezuelan equine encephalitis virus (VEE), Other *Strain:* B clade R2 *HIV component:* Env *Adjuvant:* QS21, Ribi adjuvant (MPL+TDM) (RIBI)
Species (Isotype) macaque
References Quinnan *et al.* 2005
Keywords neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- The HIV-1 Env protein used in the immunizations was suggested to exhibit a conformation that HIV-1 proteins have after binding to the primary receptor, and was derived from a patient with broadly cross-reactive neutralizing Abs. Immunizations induced NAbs with broad cross-reactivity against heterologous strains of HIV-1 of the same subtype (B) and against other subtypes such as C, A/G and F, but not against subtypes E or D. NAbs also displayed cross-reactivity against a heterologous SHIV. Animals with higher levels of serum neutralizing activity were protected against infection by a heterologous SHIV challenge. Immunization was also associated with a reduction in the magnitude and duration of virus load in animals that got infected. Quinnan *et al.* [2005] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1678
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: inactivated HIV *Strain:* B clade *HIV component:* heat-inactivated virus *Adjuvant:* QS21
Species (Isotype) rabbit, mouse
References Poon *et al.* 2005
Keywords neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Formaldehyde-stabilized, heat-inactivated virus, with a single point mutation in gp41 enabling increased incorporation of oligomeric Env into virions, was used to immunize mice and rabbits. The vaccine was capable of inducing high-titer neutralizing Abs in the animals. The Abs could neutralize heterologous viruses, including those of clades A and C, but did not neutralize virus bearing an SIV Env. Poon *et al.* [2005] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1679
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Martinez *et al.* 2005
Keywords rate of progression, Th1

- HIV-1 specific CD4 T helper 1 and CD8 T cell responses were analyzed in a cohort of long-term non-progressors and their relationships to viral and host factors and to IgG2 antibody responses to HIV-1 were measured. IgG2 Abs against HIV-1 p55, p24, p68, gp160, gp120 and gp41 were analyzed but only IgG2 Abs against gp41 were shown to be independent predictors of long-term non-progression (LTNP). The probability of maintaining LTNP was 4.2-fold higher in patients with anti-HIV-1 gp41-specific IgG2 Abs than in those without. Persistence of CD4 Th1 cell counts was predicted by high HIV-1 p24-specific cell counts and anti-HIV-1 gp41 IgG2 Abs. Martinez *et al.* [2005] (**Th1**, **rate of progression**)

No. 1680
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Mello *et al.* 2005
Keywords co-receptor, neutralization

- Sera of HIV-1 infected individuals did not inhibit the infection of some primary HIV-1 isolates. There was no evidence that the level of sensitivity of primary HIV-1 isolates to neutralization by the sera was correlated to the virus co-receptor preference. Anti-carbohydrate mAbs, however, could neutralize seven primary isolates of HIV-1 irrespective of the preferential co-receptor usage of the isolates. The Abs were raised against the egg antigen of Shistosoma mansoni. Mello *et al.* [2005] (**co-receptor**, **neutralization**)

No. 1681
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Mascola *et al.* 2005a
Keywords assay standardization/improvement, neutralization, vaccine-induced epitopes

- Design of standardized panels of Env-pseudotyped viruses is recommended to asses the potencies and breadths of NAb responses elicited by vaccine immunogens. Also the use of well-characterized, genetically and geographically diverse reference strains of HIV-1 is suggested. For the evaluation of novel immunogens, a three-tier algorithm is proposed. Mascola *et al.* [2005a] (**neutralization**, **vaccine-induced epitopes**, **assay standardization/improvement**)

No. 1682
MAb ID polyclonal
HXB2 Location HIV-1

B Cell

Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: adenovirus type 5 (Ad5), DNA prime with Ad5 boost *Strain:* B clade 89.6P, B clade HXB2, B clade BaL *HIV component:* Env
Species (Isotype) macaque (IgG)
References Mascola *et al.* 2005b
Keywords neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- A boost with recombinant serotype 5 adenoviral vector (rAd5) in DNA-primed macaques resulted in a rapid rise of Ab titers, in contrast to little rise in Ab titers in sequentially rAd5-immunized animals. The neutralizing activity of plasma derived from the DNA-prime rAd5-boost animals was moderate. After a SHIV89.6P challenge, the animals developed a secondary NAb response to several heterologous viruses. These viruses belonged to the same subset of viruses that were neutralized after the primary immunization, indicating that the breadth of immunity elicited by the original vaccine immunogen is a limiting factor during the secondary Ab response. Mascola *et al.* [2005b] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1683
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Pancera & Wyatt 2005
Keywords antibody binding site definition and exposure, binding affinity, neutralization

- JR-FL and YU2 HIV-1 strains were neutralized by IgG pooled sera from HIV-1 infected patients. Lab-adapted isolate-neutralizing Abs and other non-neutralizing Abs only recognized JR-FL cleavage-defective glycoproteins, while the neutralizing Abs (2G12 and IgG1b12) recognized both cleavage competent and cleavage-defective glycoproteins. The pooled sera recognized cleavage-competent glycoproteins at high concentrations, consistent with its lower neutralizing potency. It is suggested that an inefficient env glycoprotein precursor cleavage exposes non-neutralizing determinants, while only neutralizing regions remain accessible on efficiently cleaved spikes. For YU2, both cleavage-competent and -defective glycoproteins were recognized by both neutralizing and non-neutralizing Abs. Pancera & Wyatt [2005] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)

No. 1684
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with peptide boost
Species (Isotype) mouse
References Pashov *et al.* 2005a
Keywords mimotopes, vaccine antigen design

- Sera from mice immunized with 911 mimotope (mimicking carbohydrate structures) encoded DNA and boosted with peptide itself displayed Abs that blocked the adhesion of infected cells to DCs. Cyclic MAPD002 peptide induced serum Abs that specifically bound to gp120 expressed on cells and inhibited gp120 binding to human DCs. Pashov *et al.* [2005a] (**mimotopes**, **vaccine antigen design**)

No. 1685
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Louder *et al.* 2005
Keywords assay standardization/improvement, neutralization

- Pseudoviruses expressing HIV-1 envelope glycoproteins from BL01, BR07 and 89.6 strains were compared in neutralization assays to replication competent clone derived from transfection of 293T cells (IMC-293T) and to the IMC-293T derived from a single passage through PBMC (IMC-PBMC). The neutralization responses of pseudoviruses and corresponding IMC-293T were similar while a significant decrease in viral neutralization sensitivity was observed for the IMC-PBMC BL01 virus. The decrease was associated with an increase in average virion envelope glycoprotein content on the PBMC-derved virus. Louder *et al.* [2005] (**neutralization**, **assay standardization/improvement**)

No. 1686
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: measles virus (MV) *HIV component:* gp140, Other
Species (Isotype) humanized mouse
References Lorin *et al.* 2005b
Keywords neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Humanized mice were immunized with MV-gp140, MV-ΔV3gp140 and MV-ΔV1V2V3gp140 viruses. Titers of cross-neutralizing Abs induced by the MV-ΔV1V2V3gp140 were the highest, followed by the titers induced by MV-ΔV3gp140 and by MV-gp140. In addition to cross-neutralizing Abs, MV-ΔV1V2V3gp140 induced effective CTL responses. Lorin *et al.* [2005b] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

B Cell

No. 1687
MAb ID polyclonal
HXB2 Location HIV-1
Author Location Env
Epitope
Subtype B, C
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with protein boost *Strain:* B clade SF162, Other *HIV component:* gp140, gp140ΔV2, gp160, Other *Adjuvant:* MF59
Species (Isotype) macaque, rabbit
References Lian *et al.* 2005
Keywords neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Rabbits were immunized with DNA-prime protein-boost with gp140, gp140ΔV1V2, and gp140ΔV2 of subtypes C and B. gp140ΔV1V2, and gp140ΔV2 elicited higher titers of homologous neutralizing Abs than gp140 alone. In addition, immunization with subtype B or C gp140ΔV2 yielded high titers of env-binding and neutralizing Abs against both subtypes. Macaques immunized with subtype C gp140ΔV2 developed high titers of env-binding Abs and neutralizing Abs against both B and C subtypes. Lian *et al.* [2005] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1688
MAb ID polyclonal
HXB2 Location HIV-1
Author Location Env
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Li *et al.* 2005a
Keywords assay standardization/improvement, neutralization

- Full-length gp160 clones were derived from acute and early human HIV-1 infections and used as env-pseudotyped viruses in neutralization assays for their characterization as neutralization reference agents. Most of the env-pseudotyped viruses were relatively insensitive to neutralization by individual serum samples from both HIV-1 infected subjects and from non-infected subjects immunized with gp120. Env-pseudotyped viruses were, in many cases, as insensitive to neutralization by serum and plasma from infected individuals as were their uncloned parental PBMC-grown viruses. Li *et al.* [2005a] (**neutralization**, **assay standardization/improvement**)

No. 1689
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Kalia *et al.* 2005
Keywords antibody binding site definition and exposure, binding affinity, neutralization

- Point mutations in the highly conserved structural motif LLP-2 within the intracytoplasmic tail of gp41 resulted in conformational alternations of both gp41 and gp120. The alternations did not affect virus CD4 binding, coreceptor binding site exposure, or infectivity of the virus, but did result in decreased binding of certain MAbs and increased neutralization resistance to MAbs as well as to human polyclonal HIV-Ig and pooled human sera. LLP-2 mutant virus was neutralized 25% by HIV-Ig while wildtype virus was neutralized 50%. Kalia *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)

No. 1690
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-2 infection
Species (Isotype) human
References Joos *et al.* 2005
Keywords autologous responses, HAART, ART, neutralization, rate of progression, supervised treatment interruptions (STI)

- HIV-1 sequences derived from plasma from patients prior to ART exhibited significantly lower diversity in those patients that were able to control their viremia when subjected to structured treatment interruptions (STI) after years of ART treatment. Patients with pre-ART lower viral diversity also had higher plasma neutralizing activity against autologous virus during STI. Joos *et al.* [2005] (**autologous responses**, **neutralization**, **HAART, ART**, **supervised treatment interruptions (STI)**, **rate of progression**)

No. 1691
MAb ID polyclonal
HXB2 Location HIV-1
Author Location Env
Epitope
Subtype B, C, HIV-2
Neutralizing
Immunogen HIV-1 infection, vaccine
Vector/Type: peptide *Strain:* Other *HIV component:* V3 *Adjuvant:* Complete Freund's Adjuvant (CFA)
Species (Isotype) human, rabbit, mouse (IgG)
References Hewer & Meyer 2005
Keywords assay standardization/improvement, HIV-2, mimics, neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- MEIV3b8, a branched peptide representing multiple sequences and allowing 1.8x10^{16} possible premutations, was constructed to mimic V3 loops of subtype C. Mice and rabbits immunized with the peptide developed strong immune responses. MEIV3b8 induced Abs reacted strongly to gp120,

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gp140 and gp160 and showed broad-range reactivity to HIV-1 subtypes B and C, and to HIV-2. These Abs also effectively neutralized two lab-adapted HIV-1 strains. MEIV3b8 showed 100% specificity and 100% sensitivity to subtypes B and C in the HIV-1 ELISA assays. Hewer & Meyer [2005] (**HIV-2**, **mimics**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **assay standardization/improvement**)

No. 1692
MAb ID polyclonal
HXB2 Location HIV-1
Author Location gp120
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade MN, B clade GNE8 *HIV component:* gp120
Species (Isotype) human
References Gilbert *et al.* 2005
Keywords neutralization, vaccine antigen design

- Antibody responses against recombinant gp120 in a first efficacy trial were assessed in correlation to incidence of HIV-1 infection. Peak Ab levels were inversely correlated with HIV-1 incidence. The correlation was shown not to depend on the V3 loop tip sequence. Antibody responses were significantly higher for women and non-white volunteers, however, Ab responses were similar in high-, medium-, and low-risk subpopulations. Gilbert *et al.* [2005] (**neutralization**, **vaccine antigen design**)

No. 1693
MAb ID polyclonal
HXB2 Location HIV-1
Author Location Env
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Frost *et al.* 2005
Keywords escape

- Rate of escape from neutralizing antibodies was strongly correlated with the rate of amino acid substitutions. The total number of glycosylation sites or the number of changes in the glycosylation sites did not differ between individuals with high and individuals with low rates of escape from NAbs. There were also no significant associations between the rate of viral escape and the length or the change in length of the V1-V2 or V4 region. Frost *et al.* [2005] (**escape**)

No. 1694
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Forthal *et al.* 2005
Keywords antibody interactions, neutralization

- IgG from HIV-1 infected patients had greater neutralizing activity in monocyte-depleted PBMCs as target cells for virus growth, than in CD4+ lymphocytes. It was shown that the enhanced neutralizing activity in PBMCs was abrogated when they were depleted of NK-cells, which express Fc receptors for IgG. The enhanced neutralizing activity in PBMCs correlated with augmented β-chemokine production but it had rather small effect, indicating that the enhanced neutralization also depends on additional mechanisms. It is suggested that the virus inhibition is more effective in PBMC due to the interaction between the Fc segment on the antibody and the Fc-receptors on the NK cells. Part of the neutralization is due to β-chemokine production triggered by the Fc-receptor activation. Forthal *et al.* [2005] (**antibody interactions**, **neutralization**)

No. 1695
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype B, C
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Cavacini *et al.* 2005
Keywords neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- HIV-1 antibodies in sera from patients infected with subtype B reacted in greater extent with R5 clade B primary isolates than with R5X4 and X4 subtype B primary isolates. Serum IgG from these patients also showed less reactivity to subtype C isolates than to subtype B isolates. On the other hand, HIV-1 antibodies in sera from patients infected with subtype C reacted equally well with B and C primary isolates. In neutralization assays, subtype B sera neutralized only subtype B virus isolates, while subtype C sera neutralized subtype B isolates and 40% of subtype C isolates. Thus, antibodies from subtype C infected individuals have broader cross-reactivity in both binding and neutralization copmared to antibodies from subtype B infected individuals. Cavacini *et al.* [2005] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1696
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Brown *et al.* 2005
Keywords assay standardization/improvement, neutralization, subtype comparisons

- A panel of 60 HIV-1 isolates, with complete genome sequences available, was formed for neutralization assay standardization. It comprises of 10 isolates from each of the subtypes A, B, C, D, CRF01_AE and CRF02AG, with majority

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of the viruses being of R5 phenotype and few of X4 phenotype. Neutralization profile of each isolate was assessed by measuring neutralization by sCD4, a coctail of MAbs, and a large pool of sera collected from HIV-1 positive patients. The polyclonal Abs from pooled patient sera neutralized with >50%: 2 subtype A isolates, 8 subtype B isolates, 7 subtype C isolates, 9 subtype D isolates, 6 CRF-01_AE isolates, and 9 CRF_02AG isolates. Brown *et al.* [2005] (**neutralization**, **subtype comparisons**, **assay standardization/improvement**)

No. 1697
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Burrer *et al.* 2005
Keywords antibody binding site definition and exposure, binding affinity, neutralization

- Four primary isolates (PIs), Bx08, Bx17, 11105C and Kon, were tested for binding and neutralization by IgG from HIV-1 infected patients. IgG bound Bx08 and Bx17 with similar efficiency, but with lower efficiency for 11105C and Kon. IgG neutralization of the PIs varied between patients, but no correlation between neutralization and binding efficiency was found. Virus capture by polyclonal IgG was not decreased in the presence of V3 peptide, but was significantly decreased in the presence of principal immunodominant domain (PID), and somewhat decreased in the presence of gp160 depleted of PID, indicating that the virus capture is mainly attributed to Abs directed against PID peptides. Burrer *et al.* [2005] (**antibody binding site definition and exposure**, **neutralization**, **binding affinity**)

No. 1698
MAb ID polyclonal
HXB2 Location HIV-1
Author Location gp120
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: Con A-NS *Strain:* B clade IIIB *HIV component:* heat-inactivated virus *Adjuvant:* concavalin A-immobilized polystyrene nanospheres
Species (Isotype) mouse (IgA, IgG)
References Akagi *et al.* 2005
Keywords genital and mucosal immunity, vaccine antigen design

- Sera from mice immunized inranasally or inravaginally with HIV-NS of differing sizes contained levels of anti-HIV-1 gp120 IgG Abs that did not differ between NS size or route of immunization. The immunizations also elicited HIV-1 gp120-specific IgG and IgA responses at genital mucosal sites, also with no significant differences between individual particle sizes or route of immunization. Akagi *et al.* [2005] (**genital and mucosal immunity**, **vaccine antigen design**)

No. 1699
MAb ID polyclonal
HXB2 Location HIV-1
Author Location Env
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Beddows *et al.* 2005b
Keywords binding affinity, neutralization

- The major infectivity and neutralization differences between a PBMC-derived HIV-1 W61D strain and its T-cell line adapted counterpart were conferred by the interactions of three Env amino acid substitutions, E440G, D457G and H564N. E440G mutation reduced infectivity and increased neutralization sensitivity to polyclonal Ig, D457G and H564N also increased neutralization sensitivity. Binding of the polyclonal HIVIg to gp120 was, however, not affected by any of these amino acid substitutions. Beddows *et al.* [2005b] (**neutralization**, **binding affinity**)

No. 1700
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Aasa-Chapman *et al.* 2005
Keywords acute/early infection, complement, neutralization

- In all patients studied, IgG antibody-mediated complement inactivation (CMI) appeared at or shortly after the peak in viremia, 6 to 28 days after the onset of symptomatic primary HIV-1 infection (PHI). The CMI was effective on both autologous and heterologous HIV-1 isolates. In contrast, autologous and heterologous NAbs developed more than 200 days after symptomatic PHI. Activation of the classical complement pathway was largely responsible for the observed antiviral effects. Aasa-Chapman *et al.* [2005] (**complement**, **neutralization**, **acute/early infection**)

No. 1701
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype CRF01_AE
Neutralizing L
Immunogen vaccine
Vector/Type: canarypox *Strain:* B clade LAI, CRF01 92TH023 *HIV component:* gp120, gp41, Protease
Species (Isotype) human
References Thongcharoen *et al.* 2007
Keywords neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

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- Immunization of volunteers with ALVAC-HIV vaccine following boosting with oligomeric gp160 or bivalent gp120 resulted in development of CRF01_AE Env- binding Abs in all subjects. Neutralization of homologous and heterologous laboratoty-adapted HIV-1 strains was observed for most vaccine recipients. In addition, recipients of ALVAC-HIV with gp160 boost displayed cross-neutralization of SF2 HIV-1 strain. Thongcharoen *et al.* [2007] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1702
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG, IgG3)
References Verity *et al.* 2007
Keywords autologous responses, co-receptor, kinetics, neutralization, rate of progression

- Antibody responses in eight individuals infected from a single source with nef-attenuated HIV-1 differed considerably between the individuals. Total strength of IgG responses was associated with viral load and virus replication kinetics, with strongest Ab responses observed for individuals with low but detectable viral-load set points. Stronger neutralizing Ab responses were also associated with better replicating viral strains, higher viral loads, and better strength of antiviral IgG responses. The presence of strong neutralizing Ab responses did not prevent disease progression. Verity *et al.* [2007] (**autologous responses**, **co-receptor**, **neutralization**, **kinetics**, **rate of progression**)

No. 1703
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype C
Neutralizing
Immunogen vaccine
Vector/Type: DNA, modified vaccinia Ankara (MVA), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* C clade consensus *HIV component:* Gag, gp120, Protease
Species (Isotype) mouse
References Kumar *et al.* 2006b
Keywords binding affinity, vaccine antigen design

- Mice were immunized with either heterologous rDNA-prime rMVA-boost vaccine expressing env and gagprotease genes from HIV-1 subtype C, or homologous vaccines rDNA-prime rDNA-boost, rMVA-prime rMVA-boost. It was shown that rMVA/rMVA and rDNA/rMVA vaccines induced higher gag- and gp120-specific Ab responses than rDNA/rDNA vaccine. Furthermore, priming and boosting with rMVA (rMVA/rMVA) produced significantly higher Ab levels compared to rDNA/rMVA immunization. Kumar *et al.* [2006b] (**vaccine antigen design**, **binding affinity**)

No. 1704
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Lu 2006
Keywords antibody binding site definition and exposure, antibody generation, neutralization, review, vaccine antigen design

- This review gives an overview of DNA-prime protein-boost vaccines, their improvement of induced magnitude and quality of Ab responses, their role in construction of modified Env antigens and polyvalent HIV vaccines, and their future perspectives. Lu [2006] (**antibody binding site definition and exposure**, **antibody generation**, **neutralization**, **vaccine antigen design**, **review**)

No. 1705
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA, fowlpoxvirus, virus-like particle (VLP) *Strain:* B clade 89.6P, SIV *HIV component:* Env, Gag-Pol
Species (Isotype) mouse
References Radaelli *et al.* 2007
Keywords enhancing activity, neutralization, SIV

- Mice primed with DNA and/or fowlpox virus (FP) recombinants and boosted with VLP-SHIV were shown to generate a specific anti-p27 gag and anti-gp120 env response. VLP-SHIV boosts were also shown to increase the humoral response. Neutralizing activity against SHIV89.6P was raised by all of the regimens used, but the most effective one was immunization with DNA followed by FP recombinants. Radaelli *et al.* [2007] (**enhancing activity**, **neutralization**, **SIV**)

No. 1706
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Subtype A
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Rainwater *et al.* 2007
Keywords mother-to-infant transmission, neutralization

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- Neutralization sensitivity of maternal and infant viruses to maternal Abs close to transmission timepoint was assessed. It was found that viruses transmitted to infants were poorly neutralized by maternal Abs. Viruses from the mothers were also found to be relatively insensitive to maternal Abs but there was a statistical trend for infant viruses to be more resistant to neutralization by maternal Abs than viruses from the mothers. Rainwater *et al.* [2007] (**neutralization**, **mother-to-infant transmission**)

No. 1707
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype) human (IgA, IgG, IgM)
References Metlas *et al.* 2007
Keywords neutralization

- Ig of healthy HIV-uninfected individuals were collected from sera based on their reactivity with human IgG and labeled anti-IgG. It was demonstrated that these anti-IgG can prevent infection of PBMCs by HIV-1. For one of the HIV-1 strains, the neutralization efficacy of anti-IgG was comparable to IgG1b12. This suggests that the most important HIV-1 neutralizing epitopes may share complementary structures with pre-existing V-regions already used by lymphocytes. Metlas *et al.* [2007] (**neutralization**)

No. 1708
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection, in vitro stimulation or selection
Species (Isotype) human, scid-hu mouse (IgG)
References Steyaert *et al.* 2007b
Keywords antibody generation, assay development, assay standardization/improvement

- PBMC from HIV-infected individuals were engrafted into SCID-mice and the functionality of the human B-cells in mice was demonstrated by early and strong antibody response. Strong and multispecific HIV antibody response (gp120, gp41, p31, p24, p17) was observed after transfer of PBMC from untreated viremic patients (mainly directed to env gp120 and gp41) and natural supressors (mainly directed against gag p24 and p17). Antibody responses after transfer from patients recieving HAART were, however, weak and pauci-specific (gp120, gp41, p24). These differences were not observed in human plasma. Large numbers of IgG producing hybridoma cells were generated. Isolation of monoclonal hybridoma was limited. Steyaert *et al.* [2007b] (**antibody generation**, **assay development**, **assay standardization/improvement**)

No. 1709
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgA, IgG)
References Quayle *et al.* 2007
Keywords genital and mucosal immunity, mucosal immunity

- Endocervical and peripheral blood antibody profiles were compared between HIV infected and uninfected women. It was found that IgG predominated over IgA in endocervix and that HIV-1 infected women with uncontrolled viremia had elevated IgG levels in endocervix and serum compared to uninfected women. No differences in IgA concentrations were found. Slow-progressing HIV-1 positive women were also shown to have greater IgG HIV-specific activity in serum but not endocervix than women with uncontrolled viremia. A significant positive correlation was found between the peripheral CD4+ T-cell count and serum IgG HIV specific activity. Quayle *et al.* [2007] (**genital and mucosal immunity**, **mucosal immunity**)

No. 1710
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade BH10, B clade LAI, B clade W61D *HIV component:* gp120, Nef, Tat *Adjuvant:* AS02A (oil-in-water emulsion, 3D-monophosphoryl lipid A, QS21)
Species (Isotype) human
References Goepfert *et al.* 2007
Keywords ADCC, neutralization, vaccine antigen design

- HIV uninfected patients were immunized with recombinant proteins NefTat and gp120. Nef, Tat and gp120 specific antibodies were induced 2 weeks after immunization and maintained for 9 months. All individuals had antibodies that neutralized the laboratory adapted virus strain but no neutralization of primary isolates was observed. The majority of gp120 recipients had detectable ADCC responses that correlated with binding Ab titers. Goepfert *et al.* [2007] (**ADCC**, **neutralization**, **vaccine antigen design**)

No. 1711
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Subtype A, B, C, CRF01_AE
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG)
References Steyaert *et al.* 2007a

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Keywords immunotherapy, neutralization, subtype comparisons

- Plasma and purified IgG Abs from patients infected with different HIV-1 clades showed broad and more narrow neutralization activities. When the purified IgG from different patients was administered to SCID-mice, which were subsequently challenged with primary viruses of clades A, B and CRF01_AE, some inhibition of viral replication was observed. In several cases, the Ab-mediated inhibition was not restricted to the virus belonging to the same clade a subject was infected with. Results from in vitro neutralization assays and the in vivo passive immunization experiments did not correlate. Steyaert *et al.* [2007a] (**neutralization**, **immunotherapy**, **subtype comparisons**)

No. 1712
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen
Species (Isotype) humanized mouse (IgG, IgM)
References Viau *et al.* 2007
Keywords memory cells

- Injection of humanized mice with soluble gp120 induced an inversion in the B-1a/B-1b cell ratios without substantially affecting B2- or T-cells. Treatment with virions resulted in dramatically depressed B-1a cells, which are thought to be functionally equivalent to human IgM memory B cells, suggesting that gp120 may have a direct deleting activity on B cell memory. The observed B cell changes resulted in functional alteration of the humoral response to tetanus toxoid. Viau *et al.* [2007] (**memory cells**)

No. 1713
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: virus-like particle (VLP) *HIV component:* gp41, Other *Adjuvant:* E. coli heat labile enterotoxin
Species (Isotype) guinea pig
References Kim *et al.* 2007
Keywords binding affinity, neutralization, vaccine antigen design

- Guinea pigs were immunized with gp41 derivatives in a prefusion state expressed on the surface of immature VLPs. The sera were shown to contain high levels of anti-VLP Abs, however, no neutralizing Abs were detected and the level of the specific anti-gp41 Ab responses was low. The anti-gp41 response was preferentially directed to the C-helical domain, away from the MPER region. Kim *et al.* [2007] (**neutralization**, **vaccine antigen design**, **binding affinity**)

No. 1714
MAb ID polyclonal
HXB2 Location HIV-1
Author Location Env
Epitope
Neutralizing
Immunogen HIV-1 infection, SHIV infection
Species (Isotype) human, macaque
References Blay *et al.* 2007
Keywords neutralization

- Pseudoviruses derived from gp120 env variants that evolved in multiple macaques infected with SHIV 89.6P displayed a range of degrees of virion-associated Env cleavage. Pseudoviruses with higher amount of cleaved Env were more resistant to neutralization by autologous and heterologous macaque plasma than the wildtype, and also more resistant to neutralization by pooled heterologous HIVIG from HIV-positive donors. Blay *et al.* [2007] (**neutralization**)

No. 1715
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Chen *et al.* 2007b
Keywords antibody binding site definition and exposure, neutralization

- Spread of HIV-1 through formation of virological synapses (VS) between infected and uninfected T-cells was shown to require Env-CD4 receptor interactions. The VS transfer of virus was resistant to inhibition by patient-derived antisera that neutralize homologous cell-free virus. Deletion of the Env cytoplasmic tail resulted in partial blocking of the virus by patient neutralizing antisera, and reduced percentage of viral transfer by 40%. Chen *et al.* [2007b] (**antibody binding site definition and exposure**, **neutralization**)

No. 1716
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype A, B, C, D
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgA, IgG)
References

No. 1717
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* Other *HIV component:* Env, Gag, Pol *Adjuvant:* GM-CSF

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Species (Isotype) macaque (IgG)
References Robinson *et al.* 2006
Keywords adjuvant comparison, binding affinity, neutralization

- Macaques were immunized with DNA-prime MVA-boost vaccine with Env, Gag and Pol sequences from SHIV-89.6 in the presence or absence of GM-CSF as an adjuvant, and challenged with the neutralization escape variant SHIV-89.6P. Co-delivery of the vaccine and GM-CSF induced sooner appearance of neutralizing Abs, it broadened the specificity of the neutralizing activity to include SHIV-89.6P, and it elicited higher avidity Ab than the non-adjuvanted vaccine or the infection. The adjuvanted vaccine group also showed a trend towards better infection control. Robinson *et al.* [2006] (**adjuvant comparison**, **neutralization**, **binding affinity**)

No. 1718
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Smith *et al.* 2006
Keywords neutralization, superinfection, variant cross-recognition or cross-neutralization

- This study showed that cross-protective and autologous NAb responses in three individuals identified with HIV-1 superinfection were significantly lower than the responses in non-superinfected individuals, both at baseline and after 6 months of infection, suggesting that NAbs may be crucial in the protection against superinfection. Smith *et al.* [2006] (**neutralization**, **superinfection**, **variant cross-recognition or cross-neutralization**)

No. 1719
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: peptide, ISCOM *HIV component:* mimotopes
Species (Isotype) macaque
References Pahar *et al.* 2006
Keywords neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Macaques immunized with ISCOM vaccines containing HIV- and SHIV-derived Th and CTL single epitopes developed only low levels of neutralizing Abs against HIV-1 IIIB. After challenge with SHIV, these Abs slightly rose in immunized animals. The challenge virus SHIV SF162p4 was shown to be highly sensitive to neutralization by a variety of serum samples from HIV-1 infected individuals. Pahar *et al.* [2006] (**neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1720
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgA, IgG)
References Albert *et al.* 2007
Keywords ADCC, HIV exposed persistently seronegative (HEPS), mucosal immunity, neutralization, review

- This review summarizes data on the mechanisms of HIV-1 neutralizing Abs, including the role of AADCC, viral strategies to avoid neutralizing Abs, and natural resistance against HIV-1 infection. Albert *et al.* [2007] (**ADCC**, **neutralization**, **mucosal immunity**, **HIV exposed persistently seronegative (HEPS)**, **review**)

No. 1721
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Gao *et al.* 2007
Keywords review, vaccine antigen design, variant cross-recognition or cross-neutralization

- This review summarizes data on the development of HIV-1 centralized genes (consensus and ancestral) for induction of neutralizing antibody responses. Both types of genes have been found to elicit better T- and B- cell immune responses than wildtype immunogens, however, they have not been able to achieve the breadth of the human broadly neutralizing Abs. Potential applications and strategies for improvement of centralized Env immunogenicity are also discussed. Gao *et al.* [2007] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **review**)

No. 1722
MAb ID polyclonal
HXB2 Location HIV-1
Author Location
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: DNA, virus-like particle (VLP), HIV infected-cell lysate, polyepitope *HIV component:* Env, Gag, Nef, Pol
Species (Isotype) mouse (IgG)
References Bazhan *et al.* 2008
Keywords vaccine antigen design

- Two immunogens were combined in the CombiHIV vac (VLP-TBI-pcDNATCI) vaccine: artificial polyepitope protein TBI, containing T- and B-cell epitopes from Env and Gag and the DNA vaccine construct pcDNA-TCI, carrying CTL and CD4+ epitopes from Env, Gag, Pol, Nef. Combination of two B- and T-cell immunogens resulted in increase in the antibody response (but not CTL response) to both TBI protein and the

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proteins from HIV-1 lysate, compared to the level of antibodies induced by immunization with either immunogen alone. The synergistic effect in the induction of B-cell-mediated response was explained by the presence of CD4+ T-helper epitopes in TCI, due to stimulation of B-cell proliferation and differentiation. Bazhan *et al.* [2008] (**vaccine antigen design**)

No. 1723
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype B, C
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgA, IgG1, IgG3, IgM, IgG2, IgG4)
References Binley *et al.* 2008
Keywords neutralization, subtype comparisons

- 24 broadly neutralizing plasmas from HIV-1 subtype B an C infected individuals were investigated using a series of mapping methods to identify viral epitopes targeted by NAbs. All plasmas had detectable IgG1 and IgA Abs. A significant but variable fraction of plasma neutralization was directed to gp120, where half of the subtype B plasmas, and a smaller fraction of subtype C plasmas, contained a significant proportion of NAbs directed to the CD4bs. Anti-gp41 neutralizing activity constituted only a minor fraction of the overall neutralizing activity, while V3 and 2G12-like Abs made little or no contribution. A large fraction of the neutralizing activity in many plasmas, particularly subtype C plasmas, could not be attributed to Abs directed toward any of the known epitopes. Binley *et al.* [2008] (**neutralization**, **subtype comparisons**)

No. 1724
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype CRF01_AE
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Utachee *et al.* 2009
Keywords neutralization

- Neutralization susceptibility of CRF01_AE Env-recombinant viruses, derived from blood samples of Thai HIV-1 infected patients in 2006, was tested to pooled plasma from HIV-1 infected patients. The neutralization showed great deal of variation. There was no correlation observed between virus neutralization susceptibility to pooled plasma and viral infectivity or coreceptor usage, while there was negative correlation between neutralization susceptibility and the length of the V1/V2 region and the number of potential N-linked glycosylation sites in the C1/C2/C3 region. Utachee *et al.* [2009] (**neutralization**)

No. 1725
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Polonis *et al.* 2008
Keywords assay standardization/improvement, neutralization, review

- This minireview summarizes data on differences in neutralizing activities of MAbs and pooled human sera using a traditional primary cell neutralization assay and the more standardized TZM-bl reporter cell line assay. Also, suggestions are made on how to improve and standardize neutralization assays for comparable use in different laboratories. A large panel of polyclonal plasma pools from 6-10 pure clade plasmas derived from HIV-1 infected individuals from 6 different countries were tested against a panel of 60 HIV-1 primary isolates (10 each from clades A-D, CRF01_AE and CRF02_AG) in the two assays. Also, MAbs M9, M47, 2F5 and 4E10 were tested. There was 60% concordance in qualitative neutralizing activity measured by both assays where 47% of Ab sources were negative in both assays and 13% were concordant positive. Pooled polyclonal plasma neutralized all but one viruses tested in the TZM-assay while it did not neutralize 11 viruses in the PBMC assay. The assay discordances were shown to be bi-directional and not attributable to assay sensitivity. Polonis *et al.* [2008] (**neutralization**, **review**, **assay standardization/improvement**)

No. 1726
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Braibant *et al.* 2008
Keywords neutralization, subtype comparisons

- Neutralizing activity of sera from 36% of long term non-progressors (LNTPs) displayed no neutralizing activity, while 16% displayed broadly neutralizing activity able to neutralize 4 heterologous primary isolates of different clades. The most susceptible strain was FRO (clade B) and the most resistant one was MBA (CRF01_AE). Plasma HIV-1 RNA levels and DNA viral loads were higher among LNTPs who developed broadly neutralizing Abs than among those who did not. Analysis of env amino acid sequences from 5 LNTPs with broadly NAbs and from 4 LNTPs with no NAbs revealed that NAb+ patients had higher viral diversity and a lower number of defective env clones, suggesting contineous virus replication and evolution in these patients. Development of NAbs was also associated with longer V1 sequences and additional N-gly sites in V1. Braibant *et al.* [2008] (**neutralization**, **subtype comparisons**)

No. 1727
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1

B Cell

Epitope
Subtype multiple
Neutralizing
Immunogen vaccine
Vector/Type: modified vaccinia Ankara (MVA) *Strain:* Other *HIV component:* Env, Gag-Pol, Nef, Tat
Species (Isotype) mouse (IgG1, IgG2a)
References Chen *et al.* 2008c
Keywords Th1, Th2, vaccine antigen design

- Mice were immunized with a multivalent live recombinant vaccinia (MVA) vaccine containing 5 HIV-1 proteins (gag-pol, env, and nef-tat) based on a virus highly related to subtypes C/B', CRF07 and CRF08 predominating in the Yunnan province of China. Ab responses in mice against gp120 and gag were detected after the first vaccination, but a much higher titer of anti-gp120 Abs was elicited after the second immunization. Similar levels of IgG1 and IgG2a Abs were produced, indicating that the vaccine elicited balanced Th1 and Th2 responses. The vaccine was well tolerated. Chen *et al.* [2008c] (**vaccine antigen design**, **Th1**, **Th2**)

No. 1728
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Haynes & Shattock 2008
Keywords review, vaccine antigen design

- This review summarizes the obstacles that stand in the way of making a successful preventive HIV-1 vaccine, such as masked or transiently expressed Ab epitopes, polyclonal B-cell class switching, and inefficient, late, and not sufficiently robust mucosal IgA and IgG responses. It is suggested that for a preventative vaccine to be successful, it needs to work to extinguish the transmitted virus in the short time period between the time of transmission and the establishment of the latent pool of infected CD4+ T cells, overcome the diversity of HIV-1, and induce high levels of long-lived plasma cells making broadly neutralizing Abs to HIV-1 at mucosal surfaces. Haynes & Shattock [2008] (**vaccine antigen design**, **review**)

No. 1729
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: DNA, protein, DNA prime with protein boost *Strain:* B clade W61D *HIV component:* Env, Nef, Tat *Adjuvant:* AS02A (oil-in-water emulsion, 3D-monophosphoryl lipid A, QS21)
Species (Isotype) macaque
References Koopman *et al.* 2008
Keywords neutralization, vaccine antigen design

- Macaques were immunized with DNA, protein, DNA-prime protein-boost, or protein/DNA vaccine containing HIV-1 Env, Nef, Tat, and SIV Nef DNA and protein. Animals immunized with DNA only did not mount any Ab responses while in all other groups, where protein immunization was included, Abs against HIV-1 Env, Tat and Nef were generated. None of the DNA-immunized animals was able to neutralize homologous SHIV, while sera from almost all animals that had received protein immunizations neutralized the homologous strain. There was no neutralization of the heterologous SHIV 89.6p strain that was used as challenge. After the challenge, all animals became infected, however, there was some degree of protection against the challenge virus. The protein/DNA-immunized group had the highest number of animals with undetectable virus load. Koopman *et al.* [2008] (**neutralization**, **vaccine antigen design**)

No. 1730
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Yamamoto & Matano 2008
Keywords review

- Current insights into CTLs and NAbs, and their possible protective mechanisms against establishment of persistent HIV/SIV infection are discussed. Pre- and post-infection sterile and non-sterile protection of NAbs against viral challenge, and potential role of NAbs in antibody-mediated antigen presentation in modification of cellular immunity, are reviewed. Yamamoto & Matano [2008] (**review**)

No. 1731
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype A, B
Neutralizing
Immunogen vaccine
Vector/Type: virus-like particle (VLP), DNA prime with virus-like particle (VLP) boost *Strain:* A clade, B clade *HIV component:* Gag, gp120, gp160, Rev *Adjuvant:* Other
Species (Isotype) mouse (IgA, IgG)
References Buonaguro *et al.* 2007
Keywords adjuvant comparison, mucosal immunity, vaccine antigen design, variant cross-recognition or cross-neutralization

- Mice were immunized intranasally with a homologous prime-boost protocol (VLP prime+VLP boost) or with heterologous protocol (DNA prime + VLP boost) with or without L3 adjuvant. Serum anti-env Ab titers were higher for the non-adjuvanted heterologous protocol than for the homologous protocol, while adjuvanted boost in either of the protocols induced a relevant increase in the serum anti-gag response. Similar results were observed at vaginal and intestinal sites. Serum from mice immunized with homologous and heterologous prime-boost protocols showed neutralizing activity against heterologous A and B clade isolates, although the heterologous protocol resulted in more efficient neutralizing activity against the heterologous B clade isolate. Both prime-boost protocols were comparable in presenting gp120 epitopes to the immune system. Buonaguro *et al.* [2007] (**adjuvant comparison**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**, **mucosal immunity**)

No. 1732
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype A, B, C
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade, B clade, Other *HIV component:* Gag, gp160, Pol, Rev, RT, Other *Adjuvant:* GM-CSF
Species (Isotype) mouse
References Bråve *et al.* 2007
Keywords vaccine antigen design, variant cross-recognition or cross-neutralization

- Mice were immunized with plasmid DNA encoding p37gag of subtypes A and B, gp160 of subtypes A, B and C, and rev and RT of subtype B, where the vaccine plasmids were divided into two entities (one gag- and RT-encoding and one env- and rev-encoding) to avoid interference between the plasmids. The boost was performed using MVA encoding HIV-1 antigens encoding gp160 env of CRF01_AE and p55gag and pol of subtype A. Significantly higher Ab levels were induced in the DNA-prime MVA-boost animals than in MVA alone or DNA alone. The V3-specific response was highest for subtype B and CRF01_AE, while gp41 response was exclusively directed against subtype B. Bråve *et al.* [2007] (**vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

No. 1733
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen
Species (Isotype) human (IgA, IgG)
References Alexander & Mestecky 2007
Keywords genital and mucosal immunity, HIV exposed persistently seronegative (HEPS), review

- This review summarizes data on the IgG and IgA Ab responses at mucosal surfaces. The neutralizing and protective properties of IgG versus IgA responses are discussed, including discrepancies in the role of IgA Abs in protection against HIV infection. The discrepancies and difficulties in the detection of HIV-specific IgA are highlighted. Alexander & Mestecky [2007] (**genital and mucosal immunity**, **HIV exposed persistently seronegative (HEPS)**, **review**)

No. 1734
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Kramer *et al.* 2007
Keywords immunotherapy, mother-to-infant transmission, neutralization, review, vaccine antigen design

- Data on SHIV constructs used for vaccine development and passive immunization studies conducted with polyclonal and monoclonal Abs in SHIV/primate models is reviewed. Human neutralizing monoclonal Abs and their epitopes, and possible mechanisms to explain protection against infection are discussed. Also, differences in neutralization efficacy between the two mostly used neutralization assays, pseudovirus and PBMC, are reviewed. The implications of anti-HIV-1 Ab autoreactivity for active immunization and vaccine development are discussed. Kramer *et al.* [2007] (**neutralization**, **vaccine antigen design**, **immunotherapy**, **mother-to-infant transmission**, **review**)

No. 1735
MAb ID polyclonal
HXB2 Location HIV-1
Author Location Env
Epitope
Neutralizing
Immunogen
Species (Isotype)
References Lin & Nara 2007
Keywords review

- This review summarizes data on monoclonal Ab structure, interactions with env, and possible strategies for vaccine design for elicitation of these Abs. Different ways of focusing immune responses for Ab elicitation, such as removal of immune evading epitopes and immune dampening and refocusing, are discussed. Lin & Nara [2007] (**review**)

No. 1736
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen
Species (Isotype) (IgA, IgG, IgG1, IgG3, IgM)
References Huber & Trkola 2007
Keywords ADCC, complement, enhancing activity, review

B Cell

- This review summarizes current knowledge on the various functional properties of antibodies in HIV-1 infection, in vivo and in vitro activity of neutralizing Abs, the importance and downfalls of non-neutralizing Abs and antibodies that mediate antibody-dependent cellular cytotoxicity and the complement system, and summarizes data on areas tht need future investigation on Ab-mediated immune control. Huber & Trkola [2007] (**ADCC**, **complement**, **enhancing activity**, **review**)

No. 1737
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype A, B, C
Neutralizing
Immunogen vaccine
Vector/Type: DNA prime with Ad5 boost *Strain:* B clade HXB2/Bal, Other *HIV component:* Env
Species (Isotype) macaque
References Seaman *et al.* 2007
Keywords neutralization, variant cross-recognition or cross-neutralization

- The breadth and magnitude of NAb response was examined in macaques immunized with DNA prime-recombinant adenovirus boost vaccines encoding either single (subtypes B or C) or multiple (A+B+C) Envs, and challenged with SHIV-89.6P. Animals immunized with the multiple Env vaccine showed greater breadth and magnitude of NAb response against Tier 1 viruses following both vaccination and challenge compared to animals immunized with single Env only. There was no difference in NAb response in the different animal groups against Tier 2 viruses, with only limited NAb response, nor in the post-challenge NAb response against SHIV-89.6P. Seaman *et al.* [2007] (**neutralization**, **variant cross-recognition or cross-neutralization**)

No. 1738
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype B
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Schweighardt *et al.* 2007
Keywords assay standardization/improvement, autologous responses, neutralization

- A reference panel of recently transmitted Tier 2 HIV-1 subtype B envelope viruses was developed representing a broad spectrum of genetic diversity and neutralization sensitivity. The panel includes viruses derived from male-to-male, female-to-male, and male-to-female sexual transmissions, and CCR5 as well as CXCR4 using viruses. Plasma samples from early infection were unable to neutralize the panel envelopes, while a much higher level of neutralizing activity was detected in plasma derived from chronically infected individuals. The early infection plasmas were also unable to neutralize contemporaneous autologous virus, but were able to neutralize the sensitive reference strains SF162 and NSC. Schweighardt *et al.* [2007] (**autologous responses**, **neutralization**, **assay standardization/improvement**)

No. 1739
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen vaccine
Vector/Type: canarypox prime with gp120 boost, canarypox *Strain:* B clade *HIV component:* Env, Gag, gp120, Pol
Species (Isotype) human
References Cleghorn *et al.* 2007
Keywords neutralization, variant cross-recognition or cross-neutralization

- The safety and immunogenicity of canarypox virus-vectored vaccine alone, and in combination with recombinant envelope boost, was studied in four different regions: Brazil, Haiti, Peru, and Trinidad and Tobago. Anti-gag p24 and anti-gp120 Ab responses were detected in all vaccine groups, with the gp120-boost combination group having significantly higher response rates for gp120. HIV-1 SS1196.1 strain, which is unusually sensitive to neutralization by V3-specific Abs, was neutralized by sera from 12 of 14 vaccine recipients. There was a very weak heterologous neutralizing Ab response in all groups. Cleghorn *et al.* [2007] (**neutralization**, **variant cross-recognition or cross-neutralization**)

No. 1740
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgG, IgG3)
References Gorry *et al.* 2007
Keywords neutralization, rate of progression, review, variant cross-recognition or cross-neutralization

- Studies of viral evolution, pathogenicity, and immune responses to HIV-1 infection in members of the Sydney blood bank cohort (SBBC) infected with a nef-deleted HIV strain are reviewed. There was a good correlation between total IgG responses in the SBBC members and a detectable plasma viral load, where subjects who maintained undetectable RNA numbers had reduced IgG responses, and individuals with low but detectable viral load set points had the strongest Ab responses. Plasma from SBBC members with undetectable viral load was unable to neutralize nef-deleted viruses, and neutralization ability correlated with viral load, replication capacity of the virus, and the strength of IgG responses. Plasma from some SBBC members was able to neutralize a number of laboratory and primary HIV strains, including HIV-1 subtypes A, C, D, and CRF01_AE, indicating that infection with nef-deleted

B Cell

virus can induce cross-neutralizing Ab responses. Gorry *et al.* [2007] (**neutralization**, **variant cross-recognition or cross-neutralization**, **review**, **rate of progression**)

No. 1741
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen in vitro stimulation or selection
Species (Isotype)
References Hammonds *et al.* 2007
Keywords assay development, assay standardization/improvement, neutralization

- Efficiency of several HIV-1 pseudovirion production methods was assessed, and new methods were developed that produce pseudovirions of uniform consistency and enhance pseudovirion production and purification. In addition, two adsorption techniques were evaluated in order to remove anti-cellular neutralizing activity and derive true HIV neutralization titers. Hammonds *et al.* [2007] (**assay development**, **neutralization**, **assay standardization/improvement**)

No. 1742
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen vaccine
Species (Isotype) (IgA, IgG, IgM)
References Hinkula 2007
Keywords mucosal immunity, review, vaccine antigen design

- Role of induced mucosal humoral immunity, including neutralizing IgA and IgG Abs, in protection against HIV infection, is discussed. Different immunization strategies, routes of immunization, use of adjuvants for mucosal immunization, and results of experimental immunizations in animals inducing mucosal immunity, are reviewed. Hinkula [2007] (**vaccine antigen design**, **mucosal immunity**, **review**)

No. 1743
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human (IgA, IgG, IgG1κ, IgG1λ, IgM)
References Konstantinopoulos *et al.* 2007

- The prevalence and nature of immunoglobulin abnormalities were studied in 320 HIV-1 infected patients. The abnormal protein electrophoresis patterns included oligoclonal and monoclonal banding, and were associated with increased viral load, female sex, younger age, and higher CD4 cell counts, indicating that patients with a more robust immune system are more likely to have augmented B-cell responses to HIV-1 infection. The majority of patients with monoclonal banding were receiving HAART. Females had higher average levels of IgG Abs then men, and a higher percentage of females had elevated IgG levels. Konstantinopoulos *et al.* [2007]

No. 1744
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype C
Neutralizing
Immunogen HIV-1 infection
Species (Isotype) human
References Rademeyer *et al.* 2007
Keywords neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- Genetic features of subtype C viruses from HIV-1 infected individuals capable of eliciting cross-reactive neutralizing Abs against a panel of subtype B and C viruses were studied. Viruses genetically more similar to panel viruses were not more likely to elicit neutralizing Abs then genetically more distant viruses. There was also no correlation between the number of glycosylation sites and the capacity of the virus to induce neutralizing sera. However, for subtype C, viruses with shorter variable loops were more likely to induce cross-reactive Abs. This was not observed for subtype B viruses. Another finding supporting subtype-specific differences in neutralizing sensitivity was division of subtypes B and C in a hierarchical neutralization clustering dendogram. Rademeyer *et al.* [2007] (**neutralization**, **variant cross-recognition or cross-neutralization**, **subtype comparisons**)

No. 1745
MAb ID polyclonal
HXB2 Location HIV-1
Author Location HIV-1
Epitope
Subtype B
Neutralizing
Immunogen vaccine
Vector/Type: protein *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Protease, Other
Species (Isotype) human
References Russell *et al.* 2007
Keywords neutralization

- The safety and immunogenicity of the recombinant ALVAC-HIV vCP1452 vaccine was studied in groups of human volunteers, immunized with ALVAC alone or with ALVAC+gp120 boost. Anti-Gag p24 binding Abs were detected in all groups, indicating that administration of gp120 boost did not significantly enhance Gag-specific Ab responses. Neutralizing Ab titer to HIV-1 MN was higher in the groups receiving the gp120 boost. Neutralizing Ab responses to HIV-1 IIIB were less pronounced in all groups, however, the gp120 boost group had greater responses than the ALVAC alone group. There was no NAb activity against primary clade B isolates. Russell *et al.* [2007] (**neutralization**)

No. 1746

B Cell

MAb ID	polyclonal
HXB2 Location	HIV-1
Author Location	Env
Epitope	
Subtype	A, B, C
Neutralizing	
Immunogen	vaccine *Vector/Type:* DNA prime with protein boost, adenovirus type 5 (Ad5) *Strain:* B clade HXB2, B clade HXB2/Bal, B clade NL43, B clade SF2, Other, B clade BaL *HIV component:* Env, Gag, Gag-Pol, Nef, Pol *Adjuvant:* MF59, phosphorothioate oligodeoxynucleotides (ODNs)
Species (Isotype)	guinea pig
References	Shu *et al.* 2007
Keywords	adjuvant comparison, neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Two vaccine products, a multi-gene plasmid DNA and a recombinant adenovirus serotype-5 (rAd5), were tested for elicitation of Ab responses in guinea pigs either with or without gp140 protein boost. Three immunizations with plasmid DNA and one immunization with rAd5 generated moderate levels of Env Ab responses that were boosted by 50-fold upon protein boosting. Moderatly high neutralization activity was observed in sera from immunized animals against BaL, SS1196, SF162 and HxB2 viruses, where the protein only immunized animals had higher neutralization against SF162 and HxB2 than the animals primed with DNA or rAd5. Neutralization activity against a panel of 12 reference clade B isolates showed moderate responses only against one strain, indicating that these immunigens do not elicit broadly reactive Abs. Using class B or C ODN as adjuvant in addition to MF59 did not augment the Ab responses. Shu *et al.* [2007] (**adjuvant comparison**, **neutralization**, **vaccine antigen design**, **variant cross-recognition or cross-neutralization**)

B Cell

B Cell

IV-D

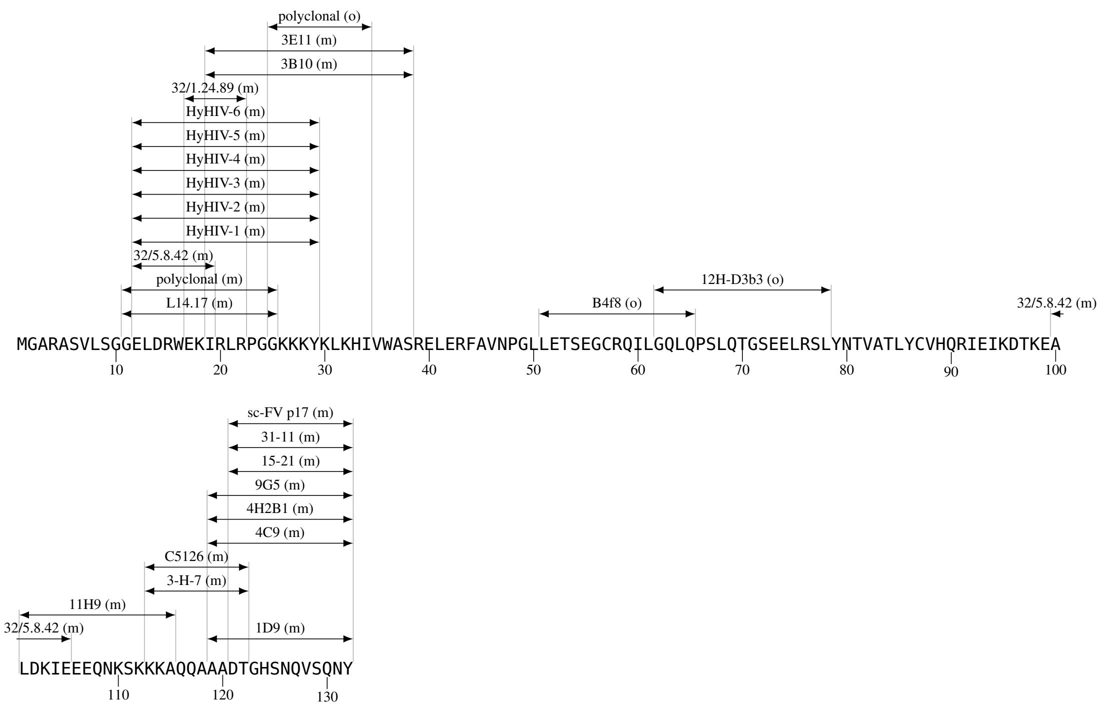
Maps of MAb Locations Plotted by Protein

Linear epitopes less than of 21 amino acids or less are shown with their antibody ID and the experimental species.

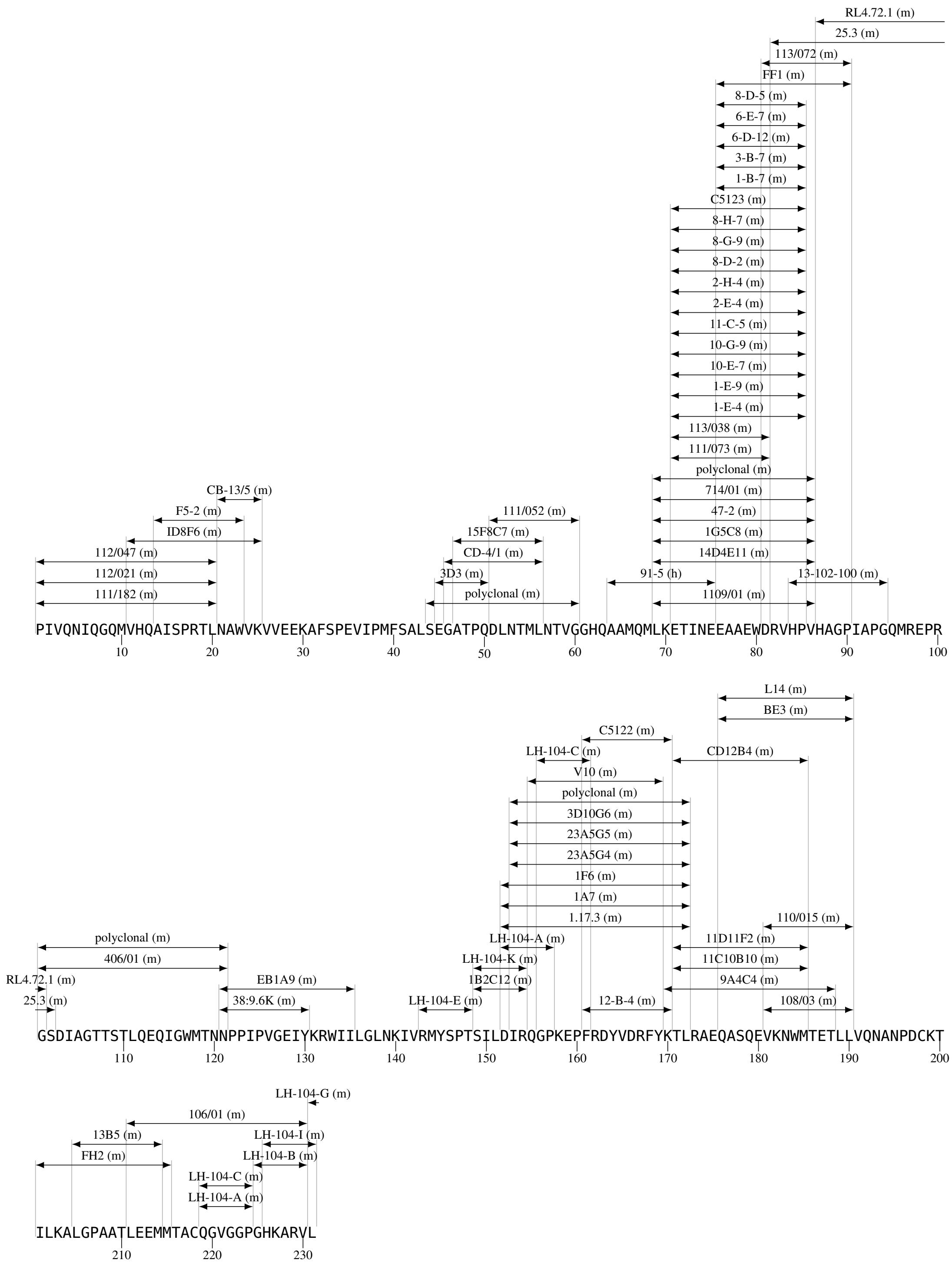
Key	Species
h	human
p	non-human primate
m	murine
o	other

Table IV-D.1: The species that the epitope was generated in and derived from.

IV-D-1 p17 Ab Epitope Map

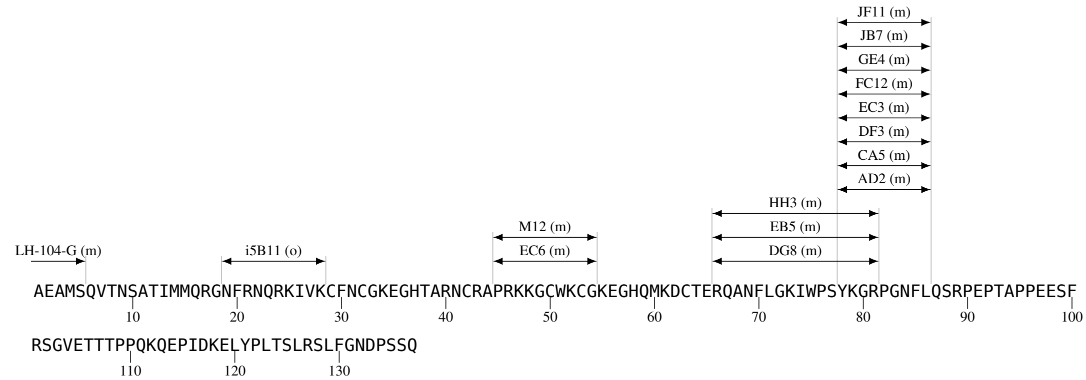


IV-D-2 p24 Ab Epitope Map

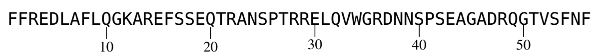


B Cell

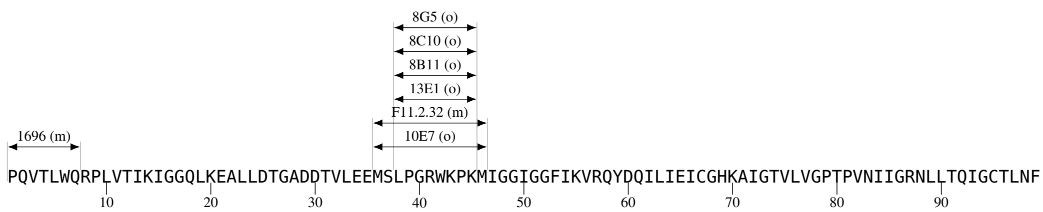
IV-D-3 p2p7p1p6 Ab Epitope Map



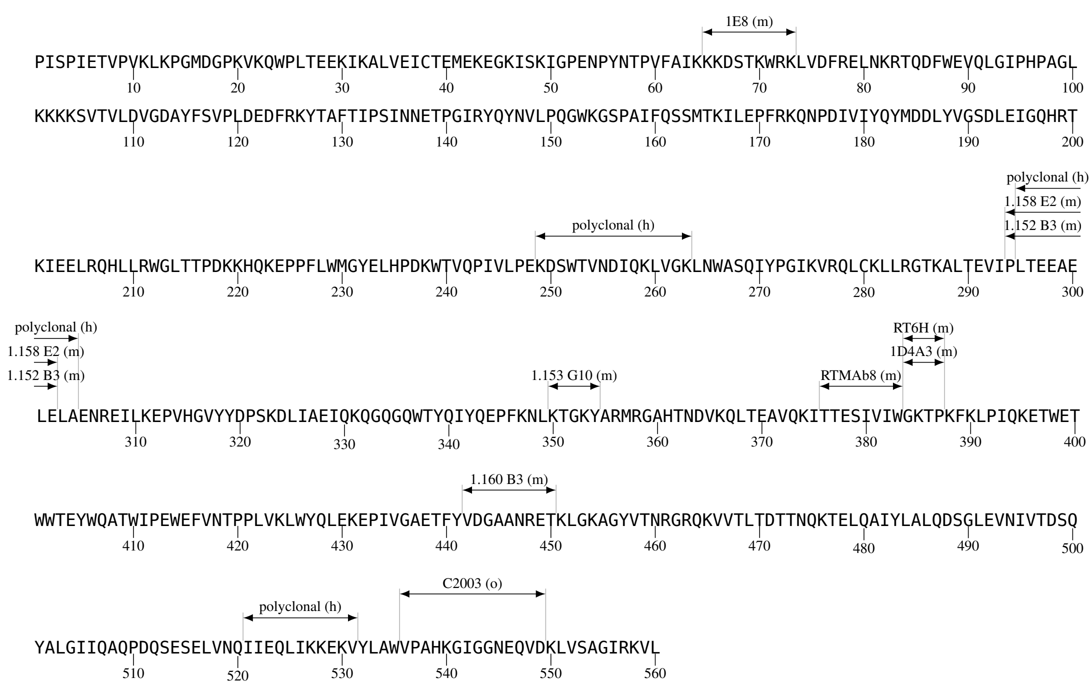
IV-D-4 Gag/Pol TF Ab Epitope Map



IV-D-5 Protease Ab Epitope Map



IV-D-6 RT Ab Epitope Map



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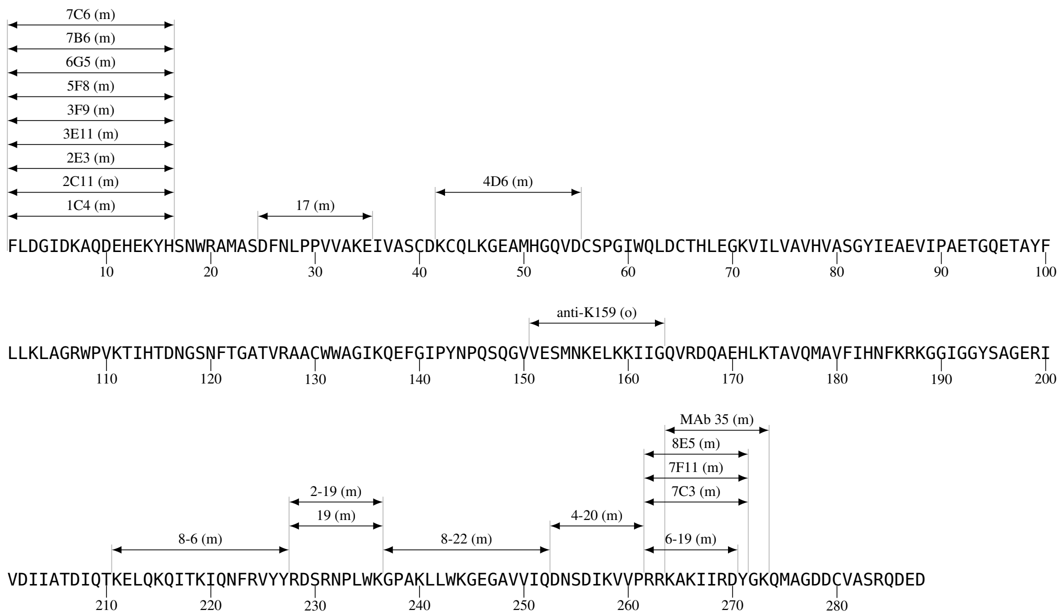
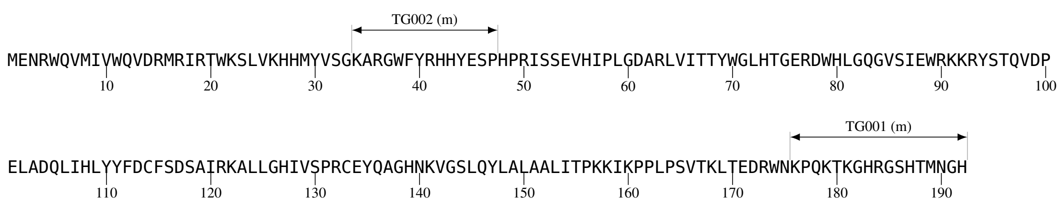
IV-D-7 Integrase Ab Epitope Map



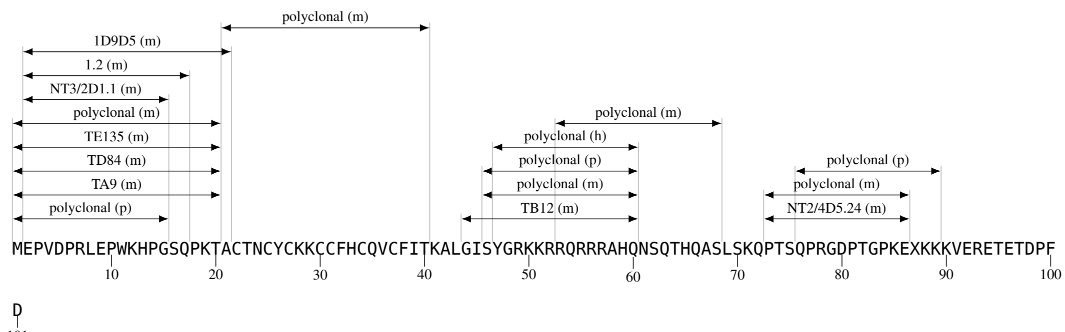
IV-D-8 Vif Ab Epitope Map



IV-D-9 Vpr Ab Epitope Map

MEQAPEDQGPQREPHNEWTLELLEELKNEAVRHFPRIWLHGLGQHIYETYGDTWAGVEAIIRILQQLLFIHFRIGCRHSRIGVTRQRRARNGASRS
10 20 30 40 50 60 70 80 90

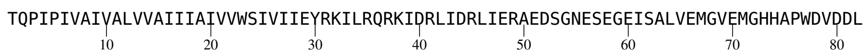
IV-D-10 Tat Ab Epitope Map



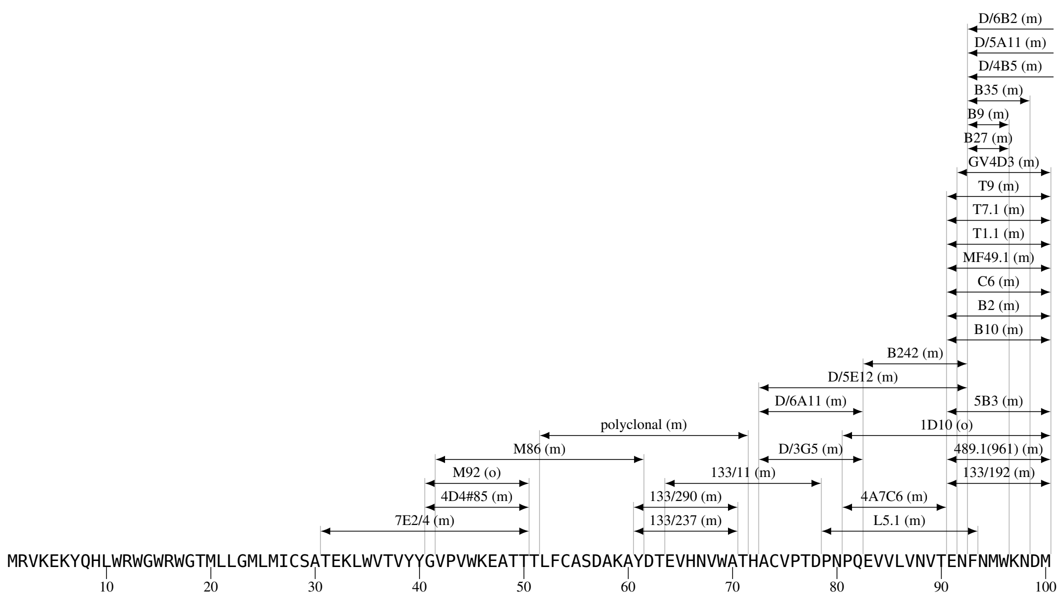
B Cell

IV-D-11 Rev Ab Epitope Map

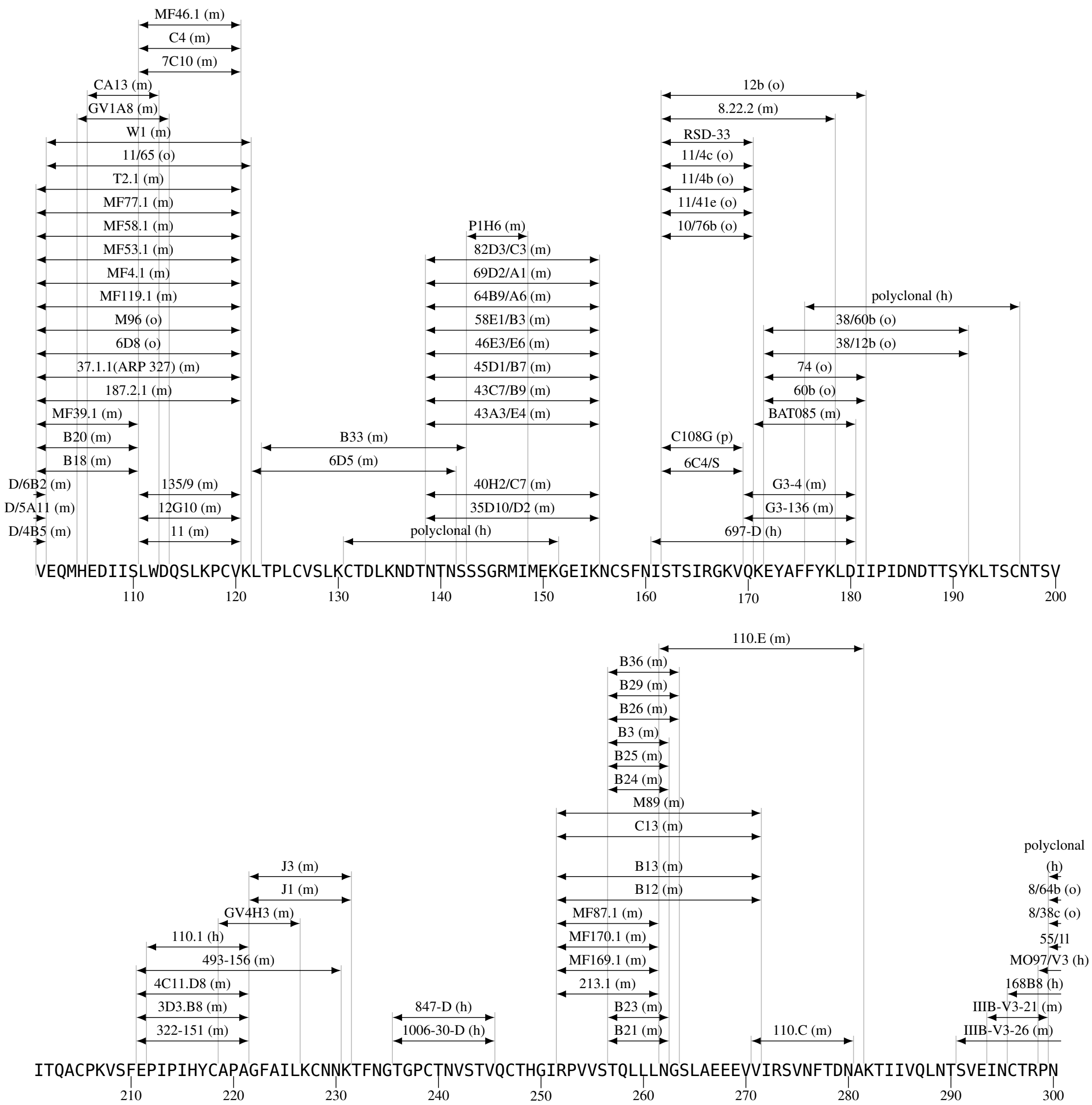
IV-D-12 Vpu Ab Epitope Map



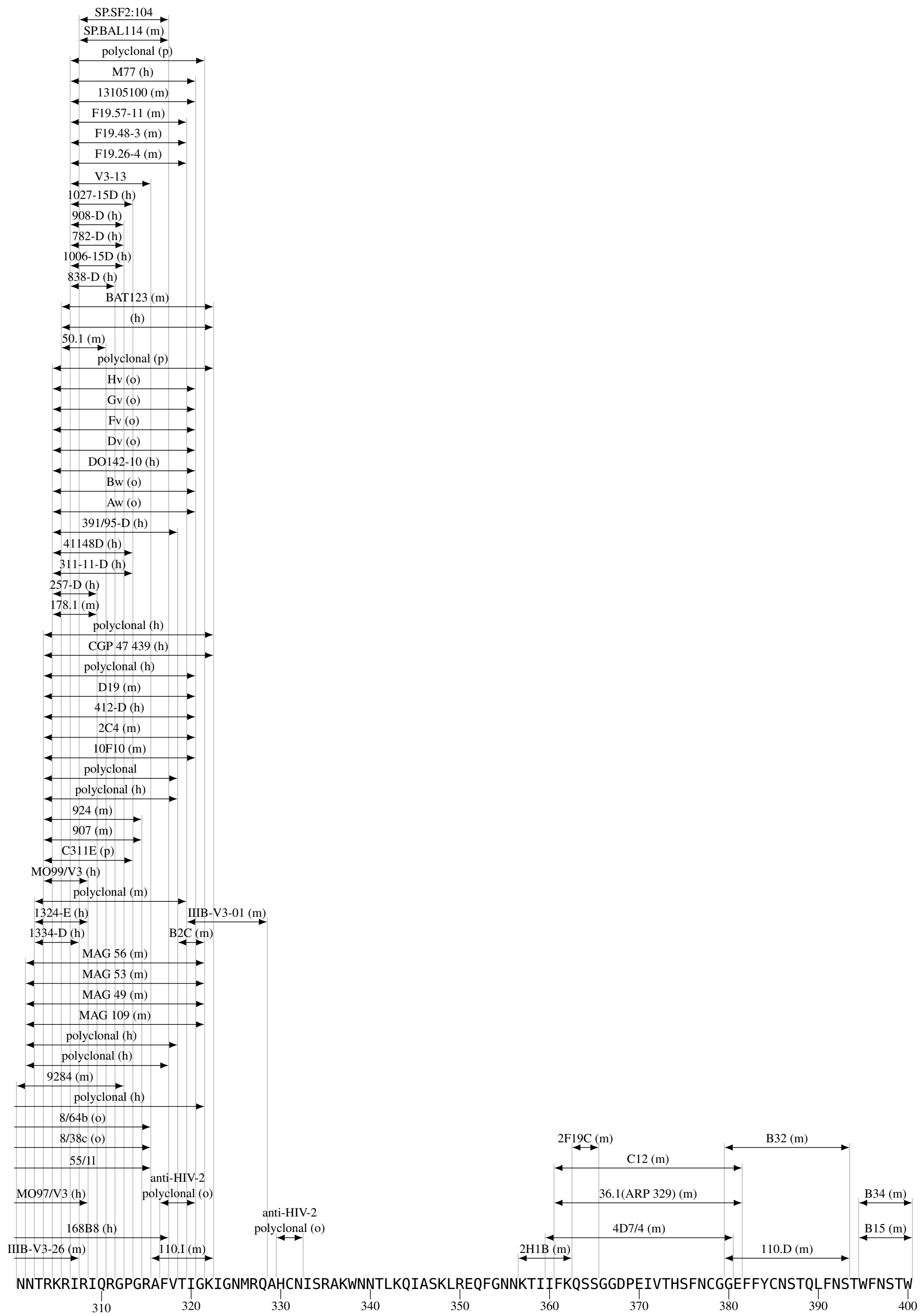
IV-D-13 gp160 Ab Epitope Map



B Cell


MF46.1 (m)
C4 (m)
7C10 (m)
CA13 (m)
GV1A8 (m)
W1 (m)
11/65 (o)
T2.1 (m)
MF77.1 (m)
MF58.1 (m)
MF53.1 (m)
MF4.1 (m)
MF119.1 (m)
M96 (o)
6D8 (o)
37.1.1(ARP 327) (m)
187.2.1 (m)
MF39.1 (m)
B20 (m)
B18 (m)
D/6B2 (m)
D/5A11 (m)
D/4B5 (m)
135/9 (m)
12G10 (m)
11 (m)
B33 (m)
6D5 (m)
polyclonal (h)
P1H6 (m)
82D3/C3 (m)
69D2/A1 (m)
64B9/A6 (m)
58E1/B3 (m)
46E3/E6 (m)
45D1/B7 (m)
43C7/B9 (m)
43A3/E4 (m)
40H2/C7 (m)
35D10/D2 (m)
12b (o)
8.22.2 (m)
RSD-33
11/4c (o)
11/4b (o)
11/41e (o)
10/76b (o)
polyclonal (h)
38/60b (o)
38/12b (o)
74 (o)
60b (o)
BAT085 (m)
C108G (p)
6C4/S
G3-4 (m)
G3-136 (m)
697-D (h)
VEQMHEDIISLWDQSLKPCVKLTPLCVSLKCTDLKNDTNTNSSSGRMIMEKGEIKNCSFNISTSIRGKVQKEYAFFYKLDIIPIDNDTTSYKLTSCNTSV
110 120 130 140 150 160 170 180 190 200
110.E (m)
B36 (m)
B29 (m)
B26 (m)
B3 (m)
B25 (m)
B24 (m)
M89 (m)
C13 (m)
B13 (m)
B12 (m)
MF87.1 (m)
MF170.1 (m)
MF169.1 (m)
213.1 (m)
B23 (m)
B21 (m)
110.C (m)
J3 (m)
J1 (m)
GV4H3 (m)
110.1 (h)
493-156 (m)
4C11.D8 (m)
3D3.B8 (m)
322-151 (m)
847-D (h)
1006-30-D (h)
polyclonal (h)
8/64b (o)
8/38c (o)
55/11
MO97/V3 (h)
168B8 (h)
IIIB-V3-21 (m)
IIIB-V3-26 (m)
ITQACPKVSFEPIPIHYCAPAGFAILKCNNKTFNGTGPCTNVSTVQCTHGIRPVVSTQLLLNGSLAEEEVVIRSVNFTDNAKTIIVQLNTSVEINCTRPN
210 220 230 240 250 260 270 280 290 300

B Cell


SP.SF2:104
SP.BAL114 (m)
polyclonal (p)
M77 (h)
13105100 (m)
F19.57-11 (m)
F19.48-3 (m)
F19.26-4 (m)
V3-13
1027-15D (h)
908-D (h)
782-D (h)
1006-15D (h)
838-D (h)
BAT123 (m)
(h)
50.1 (m)
polyclonal (p)
Hv (o)
Gv (o)
Fv (o)
Dv (o)
DO142-10 (h)
Bw (o)
Aw (o)
391/95-D (h)
41148D (h)
311-11-D (h)
257-D (h)
178.1 (m)
polyclonal (h)
CGP 47 439 (h)
polyclonal (h)
D19 (m)
412-D (h)
2C4 (m)
10F10 (m)
polyclonal
polyclonal (h)
924 (m)
907 (m)
C311E (p)
MO99/V3 (h)
polyclonal (m)
1324-E (h)
IIIB-V3-01 (m)
1334-D (h)
B2C (m)
MAG 56 (m)
MAG 53 (m)
MAG 49 (m)
MAG 109 (m)
polyclonal (h)
polyclonal (h)
9284 (m)
polyclonal (h)
8/64b (o)
8/38c (o)
55/11
anti-HIV-2 polyclonal (o)
MO97/V3 (h)
anti-HIV-2 polyclonal (o)
168B8 (h)
IIIB-V3-26 (m)
110.I (m)
2F19C (m)
B32 (m)
C12 (m)
36.1(ARP 329) (m)
B34 (m)
4D7/4 (m)
B15 (m)
2H1B (m)
110.D (m)
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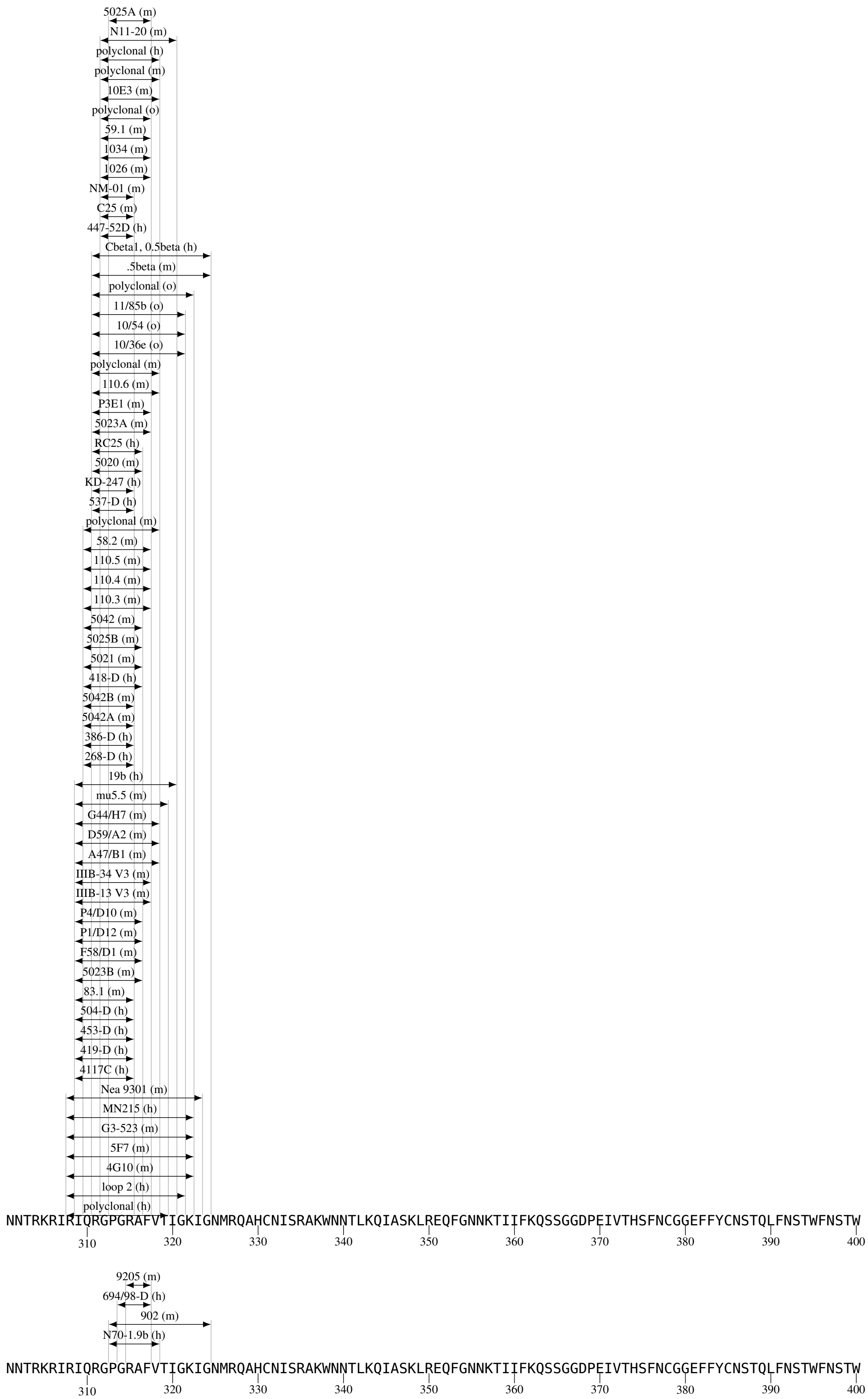
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110.4 (m)
110.3 (m)
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5021 (m)
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5042B (m)
5042A (m)
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268-D (h)
19b (h)
mu5.5 (m)
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A47/B1 (m)
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IIIB-13 V3 (m)
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83.1 (m)
504-D (h)
453-D (h)
419-D (h)
4117C (h)
Nea 9301 (m)
MN215 (h)
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9205 (m)
694/98-D (h)
902 (m)
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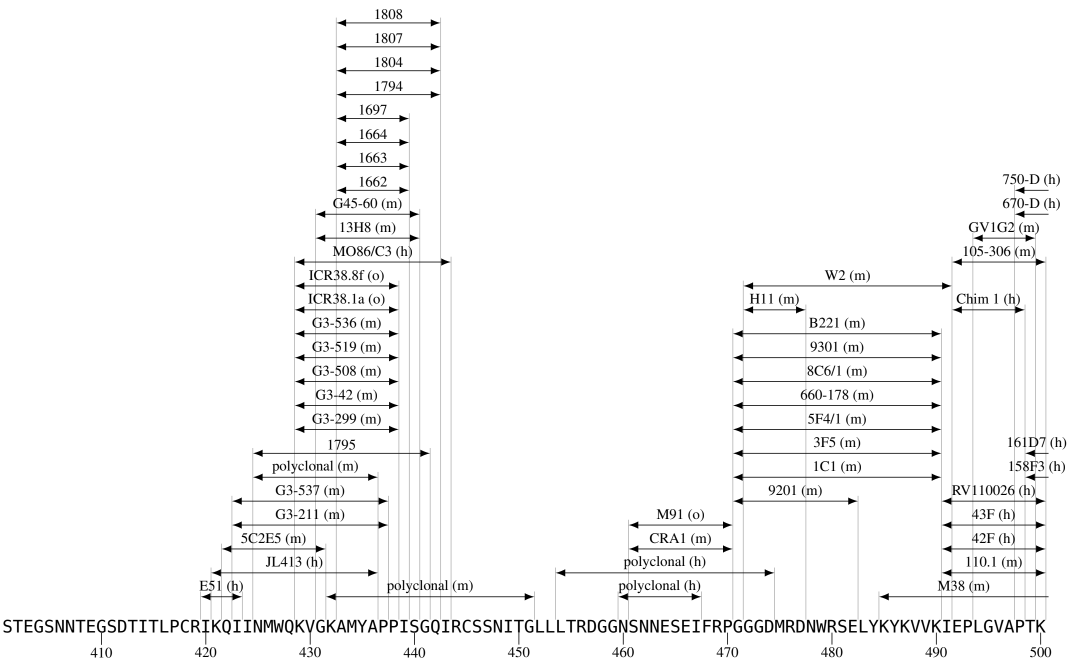
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W2 (m)
H11 (m)
B221 (m)
9301 (m)
8C6/1 (m)
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1C1 (m)
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GV1G2 (m)
105-306 (m)
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158F3 (h)
RV110026 (h)
43F (h)
42F (h)
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M38 (m)
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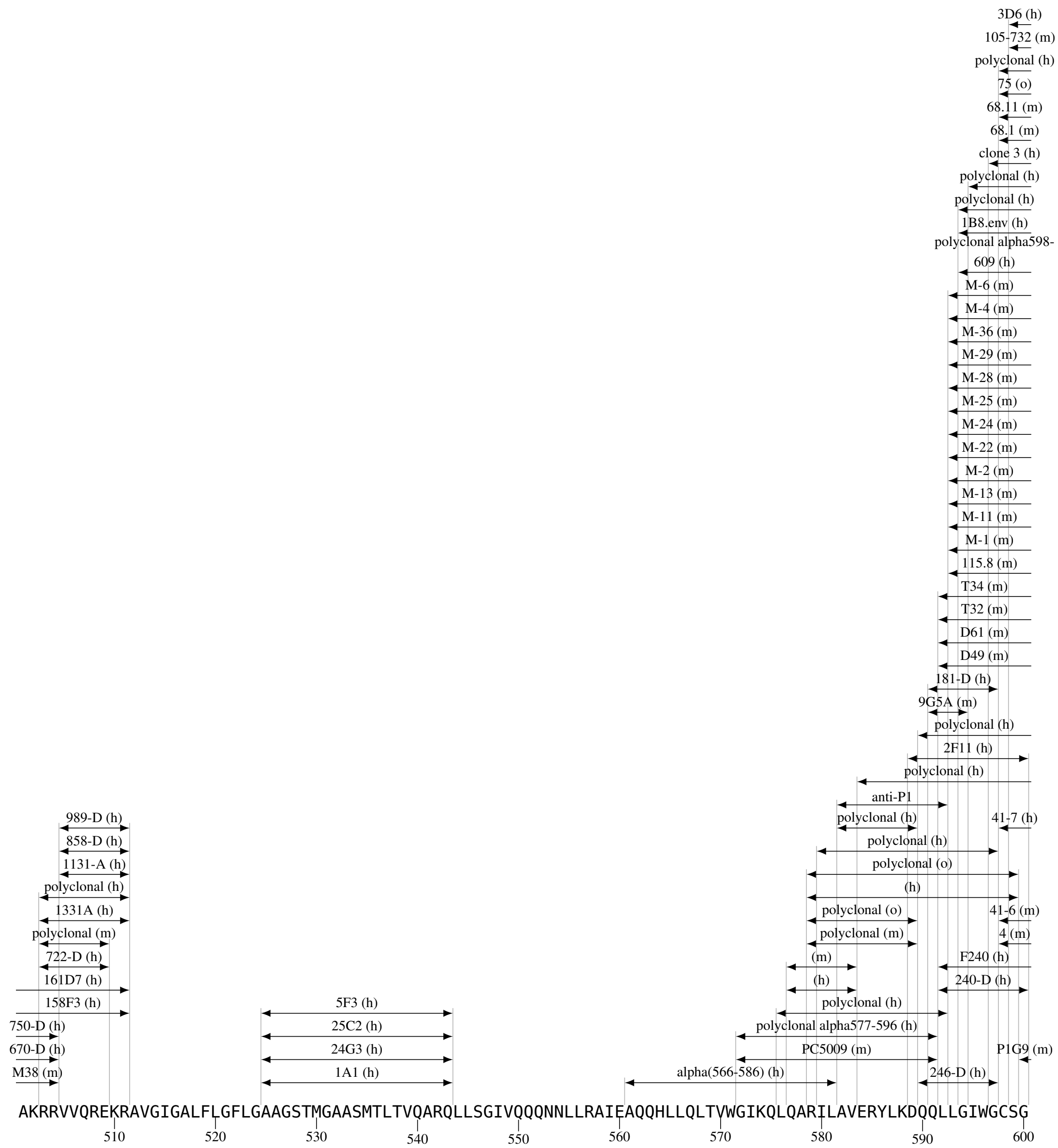
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115.8 (m)
T34 (m)
T32 (m)
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D49 (m)
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9G5A (m)
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(h)
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polyclonal (m)
4 (m)
722-D (h)
(m)
F240 (h)
161D7 (h)
(h)
240-D (h)
158F3 (h)
5F3 (h)
polyclonal (h)
750-D (h)
25C2 (h)
polyclonal alpha577-596 (h)
670-D (h)
24G3 (h)
PC5009 (m)
P1G9 (m)
M38 (m)
1A1 (h)
alpha(566-586) (h)
246-D (h)
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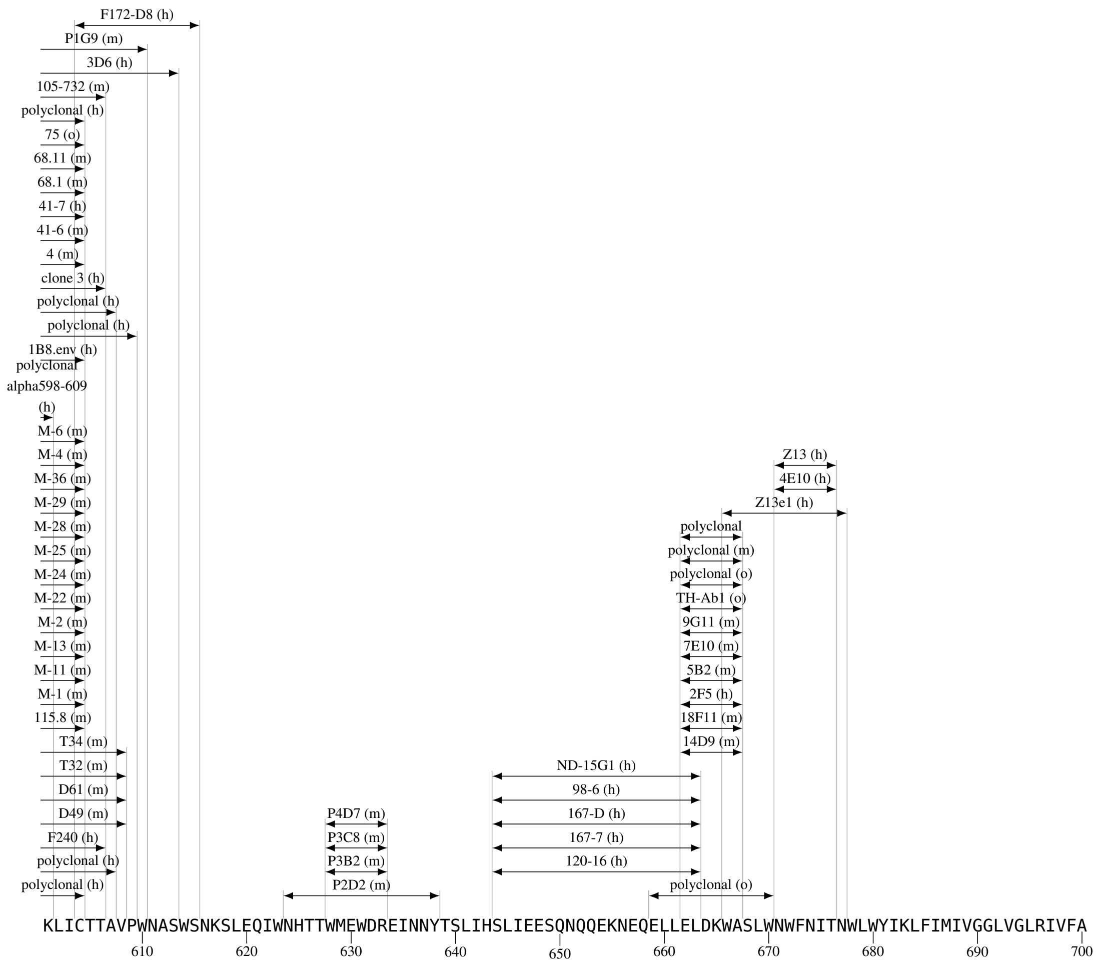
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98-6 (h)
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167-7 (h)
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Z13 (h)
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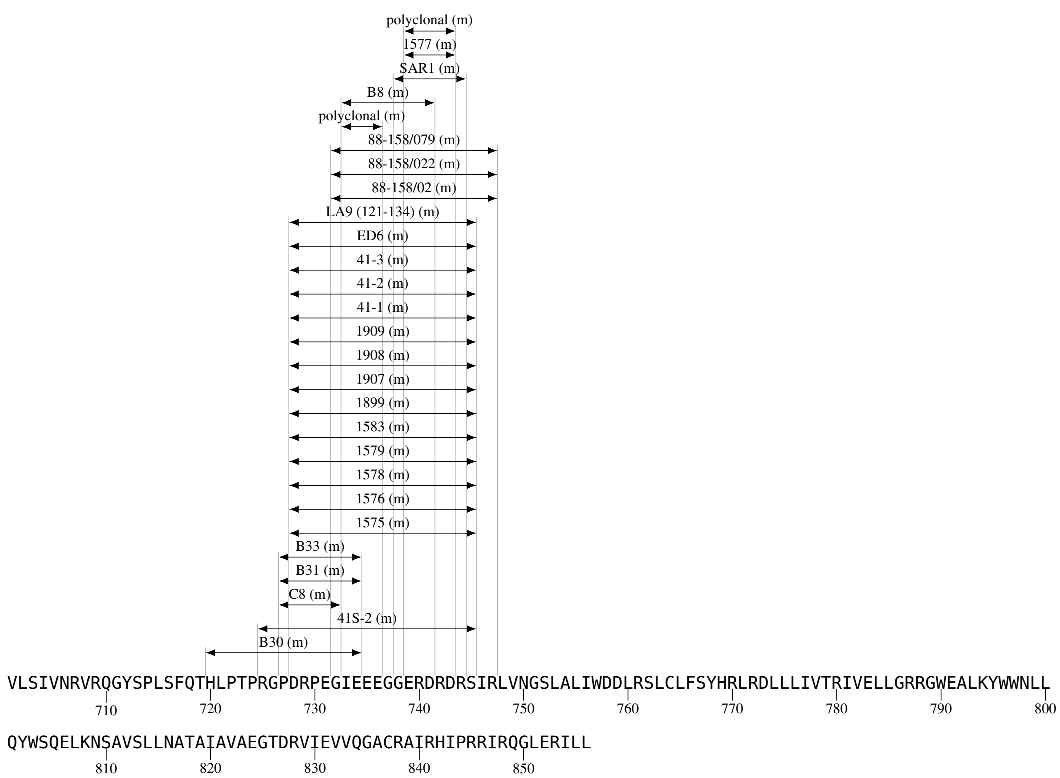
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88-158/02 (m)
LA9 (121-134) (m)
ED6 (m)
41-3 (m)
41-2 (m)
41-1 (m)
1909 (m)
1908 (m)
1907 (m)
1899 (m)
1583 (m)
1579 (m)
1578 (m)
1576 (m)
1575 (m)
B33 (m)
B31 (m)
C8 (m)
41S-2 (m)
B30 (m)
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710 720 730 740 750 760 770 780 790 800
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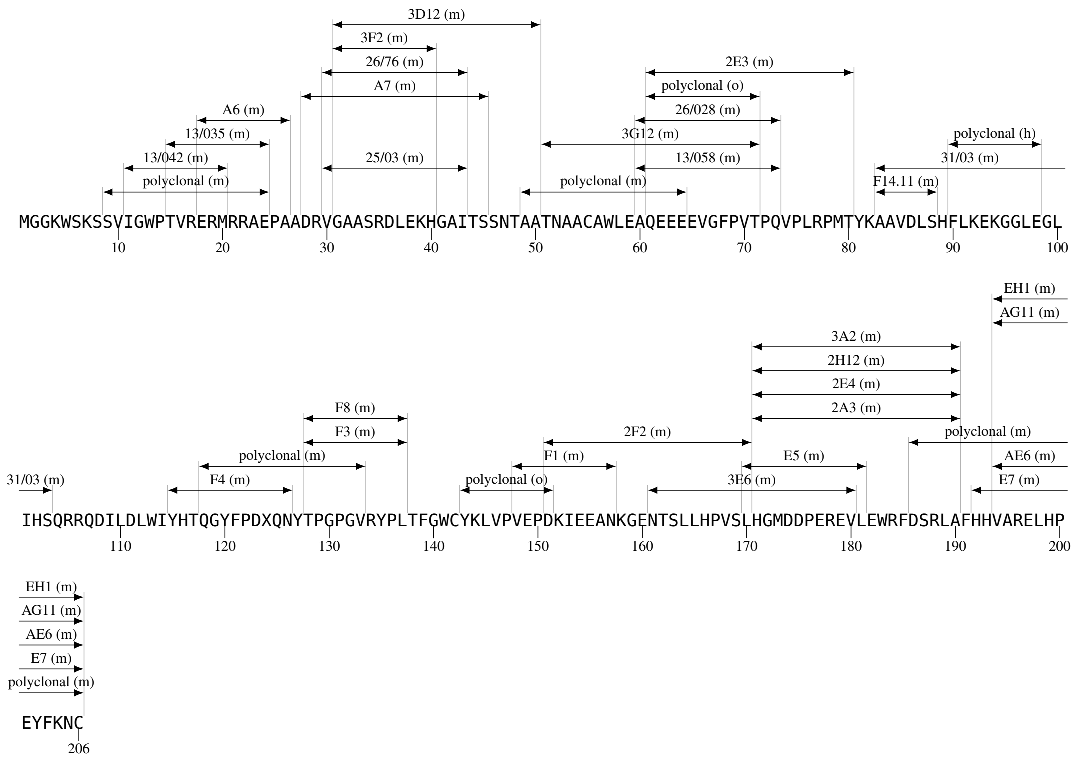
IV-D-14 Nef Ab Epitope Map



B Cell

Part V

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